CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-383

Generic name: Cytarabine Injection, 2 g/20 mL

Sponsor: Faulding Pharmaceutical Co.

Approval Date: November 22, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-383

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	
ANDAs	
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	X
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-383

APPROVAL LETTER

ANDA 75-383

NOV 22 1999

Faulding Pharmaceutical Co.
Attention: Heike Maaser
11 Commerce Drive
Cranford, NJ 07016

Dear Madam:

This is in reference to your abbreviated new drug application dated May 15, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cytarabine Injection, 2 g/20 mL, (100 mg/mL), packaged in a Single-Dose Vial.

Reference is also made to your amendments dated November 24, 1998, and July 6, August 4, September 28, and October 8, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug product, Cytarabine Injection, 2 g/20 mL, (100 mg/mL), can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Please note that as of April 1, 1999, unless this requirement is waived or deferred, all applications for new active ingredients, **new dosage forms**, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe that a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric

studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Sincerely yours,

/S/

11/22/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-383

Final Printed Labeling

Cytarabine Injection

SAMPLE

Rx only

Faulding

For intravenous, Intrathecal and Subcutaneous Use Only

WARNING

Only physicians experienced in cancer chemotherapy should use Cytarabine Injection.

For induction therapy patients should be treated in a facility with laboratory and supportive resources sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The main toxic effect of cytarabine injection is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction.

The physician must judge possible benefit to the patient against known toxic effects of this drug in considering the advisability of therapy with Cytarabine Injection. Before making this judgement or beginning treatment, the physician should be familiar with the following text.

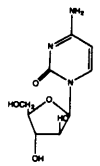
DESCRIPTION

Cytarabine Injection, an antineoplastic, is a sterile solution of cytarabine for intravenous, intrathecal or subcutaneous administration. Each mL contains 20 mg Cytarabine in 100mg (20mg/mL) single dose vial and 100 mg Cytarabine in 2 g (100 mg/mL) single dose vial.

Cytarabine Injection 100mg/5mL is a sterile solution for intravenous, intrathecal or subcutaneous administration. Each mL contains 20 mg Cytarabine, USP, and the following inactive ingredients: sodium chloride 6.8mg and water for injection q.s. When necessary the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a pH of 7.4. Each vial contains approximately 0.58mEq sodium.

Cytarabine Injection 2g/20mL is a sterile solution for intravenous, intrathecal or subcutaneous administration. Each mL contains 20 mg Cytarabine, USP, and the following inactive ingredients: water for injection q.s. When necessary the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a pH of 7.7.

Cytarabine is chemically 1-β-D-Arabinofuranosylcytosine. The structural formula is:



$C_9H_{13}N_3O_5$

M.W. 243.22

APPROVED NOV 22 1994

Cytarabine is an odorless, white to off-white crystalline powder which is freely soluble in water and slightly soluble in alcohol and in chloroform.

CLINICAL PHARMACOLOGY

Cell Culture Studies

Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. Extensive chromosomal damage, including chromatoid breaks, have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Deoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

Cellular Resistance and Sensitivity

Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase; it is inactivated by a pyrimidine nucleoside deaminase, which converts it to the non-toxic uracil derivative. It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine.

Human Pharmacology

Cytarabine is rapidly metabolized and is not effective orally; less than 20 percent of the orally administered dose is absorbed from the gastrointestinal tract.

Following rapid intravenous injection of cytarabine labeled with tritium, the disappearance from plasma is biphasic. There is an initial distributive phase with a half-life of about 10 minutes, followed by a second elimination phase with a half-life of about 1 to 3 hours. After the distributive phase, more than 80 percent of plasma radioactivity can be accounted for by the inactive metabolite 1-β-D-arabinofuranosyluracil (ara-U). Within 24 hours about 80 percent of the administered radioactivity can be recovered in the urine, approximately 90 percent of which is excreted as ara-U.

Relatively constant plasma levels can be achieved by continuous intravenous infusion.

After subcutaneous or intramuscular administration of cytarabine labeled with tritium, peak-plasma levels of radioactivity are achieved about 20 to 60 minutes after injection and are considerably lower than those after intravenous administration.

Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous injection. However, in one patient in whom cerebrospinal fluid levels are examined after 2 hours of constant intravenous infusion, levels approached 40 percent of the steady state plasma level. With intrathecal administration, levels of cytarabine in the cerebrospinal fluid declined with a first order half-life of about 2 hours. Because cerebrospinal fluid levels of deaminase are low, little conversion to ara-U was observed.

Immunosuppressive Action

Cytarabine injection is capable of obliterating immune responses in man during administration with little or no accompanying toxicity. Suppression of antibody responses to E-coli-VI antigen and tetanus toxoid have been demonstrated. This suppression was obtained during both primary and secondary antibody responses.

Cytarabine injection also suppressed the development of cell-mediated immune responses such as delayed hypersensitivity skin reaction to dinitrochlorobenzene. However, it had no effect on already established delayed hypersensitivity reactions.

Following 5-day courses of intensive therapy with cytarabine injection the immune response was suppressed, as indicated by the following parameters: macrophage ingress into skin windows; circulating antibody response following primary antigenic stimulation; lymphocyte blastogenesis with phytohemagglutinin. A few days after termination of therapy there was a rapid return to normal.

INDICATIONS AND USAGE

Cytarabine Injection in combination with other approved anti-cancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients. It has also been found useful in the treatment of acute non-lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of Cytarabine Injection (preservative free preparations only) is indicated in the prophylaxis and treatment of meningeal leukemia.

CONTRAINDICATIONS

Cytarabine Injection is contraindicated in those patients who are hypersensitive to the drug.

WARNINGS (See boxed WARNING)

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leucocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia). One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine injection.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine injection) has been reported following some experimental dose schedules for cytarabine injection. These reactions include reversible corneal toxicity, and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with experimental high dose therapy than with standard treatment programs using cytarabine injection. If experimental high dose therapy is used, do not use a preparation containing benzyl alcohol.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia from one institution in 16/72 patients. The outcome of this syndrome can be fatal.

Two patients with childhood acute myelogenous leukemia who received intrathecal and intravenous cytarabine injection at conventional doses (in addition to a number of other concomitantly administered drugs) developed delayed progressive ascending paralysis resulting in death in one of the two patients.

Use in Pregnancy (Category D)

Cytarabine Injection can cause fetal harm when administered to a pregnant woman. Cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant.

A review of the literature has shown 32 reported cases where cytarabine injection was given during pregnancy, either alone or in combination with other cytotoxic agents:

Eighteen normal infants were delivered. Four of these had first trimester exposure. Five infants were premature or of low birth weight. Twelve of the 18 normal infants were followed up at ages ranging from six weeks to seven years, and showed no abnormalities. One apparently normal infant died at 90 days of gastroenteritis.

Two cases of congenital abnormalities have been reported, one with upper and lower distal limb defects, and the other with extremity and ear deformities. Both of these cases had first trimester exposure.

There were seven infants with various problems in the neonatal period, including pancytopenia, transient depression of WBC, hematocrit or platelets; electrolyte abnormalities; transient eosinophilia; and one case of increased IgM levels and hyperpyrexia possibly due to sepsis. Six of the seven infants were also premature. The child with pancytopenia died at 21 days of sepsis.

Therapeutic abortions were done in five cases. Four fetuses were grossly normal, but one had an enlarged spleen and another showed Trisomy C chromosome abnormality in the chorionic tissue.

Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on cytarabine should be apprised of the potential risk to the fetus and the advisability of pregnancy continuation. There is a definite, but considerably reduced risk if therapy is initiated during the second or third trimester. Although normal infants have been delivered to patients treated in all three trimesters of pregnancy, follow-up of such infants and children [illegible]

termination of therapy there was a lab [illegible]

INDICATIONS AND USAGE
Cytarabine Injection in combination with other approved anti-cancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients. It has also been found useful in the treatment of acute non-lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of Cytarabine Injection (preservative free preparations only) is indicated in the prophylaxis and treatment of meningeal leukemia.

CONTRAINDICATIONS
Cytarabine Injection is contraindicated in those patients who are hypersensitive to the drug.

WARNINGS (See boxed WARNING)
Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leucocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia). One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine injection.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine injection) has been reported following some experimental dose schedules for cytarabine injection. These reactions include reversible corneal toxicity, and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with experimental high dose therapy than with standard treatment programs using cytarabine injection. If experimental high dose therapy is used, do not use a preparation containing benzyl alcohol.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia from one institution in 16/72 patients. The outcome of this syndrome can be fatal.

Two patients with childhood acute myelogenous leukemia who received intrathecal and intravenous cytarabine injection at conventional doses (in addition to a number of other concomitantly administered drugs) developed delayed progressive ascending paralysis resulting in death in one of the two patients.

Use in Pregnancy (Category D)
Cytarabine Injection can cause fetal harm when administered to a pregnant woman. Cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant.

A review of the literature has shown 32 reported cases where cytarabine injection was given during pregnancy, either alone or in combination with other cytotoxic agents:

Eighteen normal infants were delivered. Four of these had first trimester exposure. Five infants were premature or of low birth weight. Twelve of the 18 normal infants were followed up at ages ranging from six weeks to seven years, and showed no abnormalities. One apparently normal infant died at 90 days of gastroenteritis.

Two cases of congenital abnormalities have been reported, one with upper and lower distal limb defects, and the other with extremity and ear deformities. Both of these cases had first trimester exposure.

There were seven infants with various problems in the neonatal period, including pancytopenia, transient depression of WBC, hematocrit or platelets; electrolyte abnormalities; transient eosinophilia; and one case of increased IgM levels and hyperpyrexia possibly due to sepsis. Six of the seven infants were also premature. The child with pancytopenia died at 21 days of sepsis.

Therapeutic abortions were done in five cases. Four fetuses were grossly normal, but one had an enlarged spleen and another showed Trisomy C chromosome abnormality in the chorionic tissue.

Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on cytarabine should be apprised of the potential risk to the fetus and the advisability of pregnancy continuation. There is a definite, but considerably reduced risk if therapy is initiated during the second or third trimester. Although normal infants have been delivered to patients treated in all three trimesters of pregnancy, follow-up of such infants would be advisable.

PRECAUTIONS

1. **General Precautions**
   Patients receiving Cytarabine Injection must be monitored closely. Frequent platelet and leucocyte counts and bone marrow examinations are mandatory. Consider suspending or modifying therapy when drug-induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear granulocyte count under 1000/mm³. Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped and reach lowest values after drug-free intervals of 12 to 24 days. When indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose drug is withheld until "normal" peripheral blood values are attained may escape from control.

   When large intravenous doses are given too quickly, patients are frequently nauseated and may vomit for several hours post-injection. This problem tends to be less severe when the drug is infused.

   The human liver apparently detoxifies a substantial fraction of an administered dose. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose cytarabine injection treatment. Use the drug with caution and possibly at reduced dose in patients whose liver or kidney function is poor.

   Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine injection.

   Like other cytotoxic drugs, Cytarabine Injection may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

   Acute pancreatitis has been reported to occur in a patient receiving Cytarabine Injection by continuous infusion and in patients being treated with Cytarabine Injection who have had prior treatment with L-asparaginase.

2. **Information for patient**
   Not applicable

3. **Laboratory tests**
   See General Precautions

4. **Drug interactions**
   Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine injection or procarbazine. Steady-state plasma digitoxin concentrations did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilization of digitoxin for such patients may be considered as an alternative.

   An *in vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. This study suggests that in patients on cytarabine being treated with gentamicin for a *K. pneumoniae* infection, the lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

   Clinical evidence in one patient showed possible inhibition of fluorocytosine efficacy during therapy with cytarabine injection. This may be due to potential competitive inhibition of its uptake.

5. **Carcinogenesis, mutagenesis, impairment of fertility**
   Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported.

6. **Pregnancy**
   Pregnancy Category D. See WARNINGS.

7. **Labor and delivery**
   Not applicable.

8. **Nursing mothers**
   It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cytarabine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

9. **Pediatric use**
   See INDICATIONS AND USAGE

ADVERSE REACTIONS
Expected Reactions
Because cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of administration with Cytarabine Injection. The severity of these reactions are dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Following 5-day constant infusions or acute injections of 50 mg/m² to 600 mg/m², white cell depression follows a biphasic course. Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7-9. This is followed by a brief rise which peaks around the twelfth day. A second and deeper fall reaches nadir at days 15-24. Then there is a rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at 5 days with a peak depression occurring between days 12-15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

Infectious Complications
Injection: Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body may be associated with the use of cytarabine injection alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

XXXXXX

The Cytarabine (Ara-C) Syndrome
A cytarabine syndrome has been described by Castleberry. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with Cytarabine Injection.

Most Frequent Adverse Reactions

Anorexia	oral and anal inflammation	rash
Nausea	or ulceration	thrombophlebitis
Vomiting	hepatic dysfunction	bleeding (all sites)
Diarrhea	fever	

Nausea and vomiting are most frequent following rapid intravenous injection.

Less Frequent Adverse Reactions

Sepsis	sore throat	conjunctivitis (may occur with rash)
pneumonia	esophageal ulceration	dizziness
cellulitis at injection site	esophagitis	alopecia
skin ulceration	chest pain	anaphylaxis (see Warning)
urinary retention	pericarditis	allergic edema
renal dysfunction	bowel necrosis	pruritis
neuritis	abdominal pain	shortness of breath
neural toxicity	pancreatitis	urticaria
	freckling	headache
	jaundice	

Experimental Doses

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine injection) has been reported following some experimental dose schedules of cytarabine injection. These reactions include reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with experimental high dose therapy than with standard treatment programs using cytarabine. If experimental high dose therapy is used, do not use a preparation containing benzyl alcohol.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation. **This cardiac toxicity may be schedule dependent.**

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia from one institution in 16/72 patients. The outcome of this syndrome can be fatal.

Two patients with adult acute non-lymphocytic leukemia developed peripheral motor and sensory neuropathies after consolidation with high-dose cytarabine, daunorubicin, and asparaginase. Patients treated with high-dose cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Ten patients treated with experimental intermediate doses of cytarabine (1 g/m²) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, etoposide) at various dose regimes developed a diffuse interstitial pneumonitis without clear cause that may have been related to the cytarabine.

Two cases of pancreatitis have been reported following experimental doses of cytarabine injection and numerous other drugs. Cytarabine injection could have been the causative agent.

OVERDOSAGE

There is no antidote for overdosage of Cytarabine Injection. Doses of 4.5 g/m² by intravenous infusion over 1 hour every 12 hours for 12 doses have caused an unacceptable increase in irreversible CNS toxicity and death.

Single doses as high as 3 g/m² have been administered by rapid intravenous infusion without apparent toxicity.

DOSAGE AND ADMINISTRATION

Cytarabine Injection is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine Injection may be given by intravenous infusion or injection, subcutaneously, or intrathecally (preservative free preparation only).

Thrombophlebitis has occurred at the site of drug injection or infusion in some patients, and rarely patients have noted pain and inflammation at subcutaneous injection sites. In most instances, however, the drug has been well tolerated.

Patients can tolerate higher total doses when they receive the drug by rapid intravenous injection as compared with slow infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells seem to respond in somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

In the induction therapy of acute non-lymphocytic leukemia, the usual cytarabine dose in combination with other anti-cancer drugs is 100 mg/m²/day by continuous IV infusion (Days 1-7) or 100 mg/m² IV every 12 hours (Days 1-7).

The literature should be consulted for the current recommendations for use in acute lymphocytic leukemia.

Intrathecal Use in Meningeal Leukemia

Cytarabine injection has been used intrathecally in acute leukemia in doses ranging from 5 mg/m² to 75 mg/m² of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days. The most frequently used dose was 30 mg/m² every 4 days until cerebrospinal fluid findings were normal, followed by one additional treatment. The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy.

Cytarabine injection given intrathecally may cause systemic toxicity and careful monitoring of the hematopoietic system is indicated. Modification of other anti-leukemia therapy may be necessary. Major toxicity is rare. The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever; these reactions are mild and self-limiting. Paraplegia has been reported. Necrotizing leukoencephalopathy occurred in 5 children; these patients had also been treated with intrathecal methotrexate and hydrocortisone, as well as by central nervous system radiation. Isolated neurotoxicity has been reported. Blindness occurred in two patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic central nervous system radiation and intrathecal cytarabine injection.

When cytarabine injection is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity, however, in serious life-threatening disease, concurrent use of intravenous and intrathecal Cytarabine Injection is left to the discretion of the treating physician.

Focal leukemic involvement of the central nervous system may not respond to intrathecal cytarabine injection and may better be treated with radiotherapy.

Chemical Stability of Infusion Solutions

Chemical stability studies were performed by ultraviolet assay on Cytarabine Injection in infusion solutions. These studies showed that when Cytarabine Injection was added to Water for Injection, 5% Dextrose in Water or Sodium Chloride Injection, 94 to 98 percent of the cytarabine was present after 192 hours storage at room temperature.

Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Cytarabine Injection is available as follows:

100 mg/5 mL in a single dose flip top vial (cool green cap) packaged individually. NDC No.: 61703-304-09

2 g/20 mL in a single dose flip top vial (green cap) packaged individually. NDC No.: 61703-319-22

STORAGE CONDITIONS

Protect from light. Retain in carton until time of use.

Store the product at controlled room temperature 15° to 30° C (59° to 86° F).

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publications No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office, Washington, D.C. 20402.
2. AMA Council Report, Guidlines for Handling Parenteral Antineoplastics, JAMA, 1985; 2.53 (11): 1590-1592.
3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal of Clinicians, 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp. Pharm. 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work Practice Guidelines), Am J. Health- Syst Pharm, 1996; 53:1669-1685.

Manufactured in Australia by:
F H Faulding & Co Limited
1-23 Lexia Place
Mulgrave Victoria 3170 Australia

For:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth, NJ 07207 USA

Revision June 1999.

Chloride injection, 94 to 96 percent of the cytarabine was stable.

Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Cytarabine Injection is available as follows:

100 mg/5 mL in a single dose flip top vial (cool green cap) packaged individually. NDC No.: 61703-304-09

2 g/20 mL in a single dose flip top vial (green cap) packaged individually. NDC No.: 61703-319-22

STORAGE CONDITIONS

Protect from light. Retain in carton until time of use.

Store the product at controlled room temperature 15° to 30° C (59° to 86° F).

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publications No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office. Washington, D.C. 20402.
2. AMA Council Report. Guidilines for Handling Parenteral Antineoplastics, JAMA, 1985; 2.53 (11): 1590-1592.
3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia. 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal of Clinicians, 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp. Pharm, 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work Practice Guidelines), Am J. Health- Syst Pharm, 1996; 53:1669-1685.

Manufactured in Australia by:
F H Faulding & Co Limited
1-23 Lexia Place
Mulgrave Victoria 3170 Australia

For:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth, NJ 07207 USA

Revision June 1999.

xxxxxx

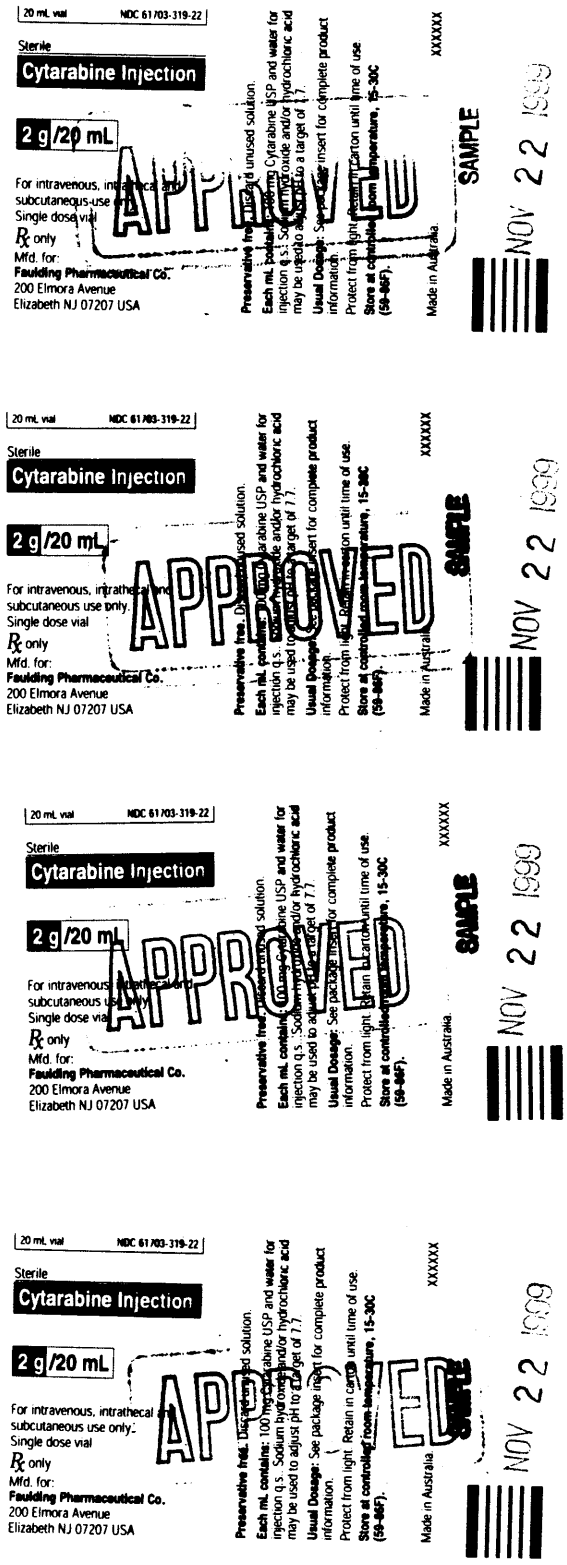
CYTARABINE INJECTION
ANDA 75-383
100 mg/mL, 20 mL vial

Faulding
A World of Health

REVISED CARTON LABEL

Faulding **artwork**

Customer: Faulding Pharmaceutical Co.
Container(s): 1 x 20 mL tall vial
Size: 32.5 x 32.5 x 80.5 mm
Colours: 295 C (dark blue), 575 C (olive)
Drafted: 30 October 1998 mf


20 mL vial
NDC 61703-319-22
Sterile
Cytarabine Injection
2 g/20 mL
For intravenous, intrathecal and subcutaneous use only.
Single dose vial
℞ only
Mfd. for:
Faulding Pharmaceutical Co.
200 Elmora Avenue
Elizabeth NJ 07207 USA
Preservative free. Discard unused solution.
Each mL contains: 100 mg Cytarabine USP and water for injection q.s. Sodium hydroxide and/or hydrochloric acid may be used to adjust pH to a target of 7.7.
Usual Dosage: See package insert for complete product information.
Protect from light. Retain in carton until time of use.
Store at controlled room temperature, 15-30C (59-86F).
Made in Australia.
XXXXXX
APPROVED
SAMPLE
NOV 22 1999

1269

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-383

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 1

2. **ANDA #:** 75383

3. **NAME AND ADDRESS OF APPLICANT:**
Faulding Pharmaceutical Co.
Attention: Heike Maaser
200 Elmora Avenue
Elizabeth, NJ 07207

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
505 j

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:** Cytarabine Injection

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Faulding:
05/15/98 Submission of ANDA (received on 05/18/98)

FDA:
06/10/98 Acknowledgment letter
07/14/98 Labeling review completed (Deficiencies).
08/26/98 bioequivalent WAI Granted.

10. **PHARMACOLOGICAL CATEGORY:**
Acute non-lymphocytic leukemia

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
Innovator: Pharmacia & Upjohn (NDA 16793)
100 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial

ANDA 71868(Faulding)-Cytarabine USP, 20 mg/ML, 5 mL,(single dose)
ANDA 72168(Faulding)-Cytarabine USP, 20 mg/ML, 50 mL (bulk package)
ANDA 72945(Faulding)-Cytarabine USP, 20 mg/mL, 25 mL(multi- dose)

DMF —

DMF —

13. **DOSAGE FORM:**
Solution for Injection

14. **POTENCY:**
2 g/20 mL (100mg/mL)

15. **CHEMICAL NAME AND STRUCTURE:**
4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

[redacted]

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (Major Amendment).

19. **REVIEWER:**	**DATE COMPLETED:**	**DATE Revised:**
Bing Cai, Ph.D.	10/08/98	10/19/98

APPEARS THIS WAY ON ORIGINAL

Redacted 28

pages of trade secret and/or confidential commercial information

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 2

2. **ANDA #:** 75-383

3. **NAME AND ADDRESS OF APPLICANT:**
Faulding Pharmaceutical Co.
Attention: Heike Maaser
200 Elmora Avenue
Elizabeth, NJ 07207

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
505 j

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:** Cytarabine Injection

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**

Faulding:

05/15/98	Submission of ANDA (received on 05/18/98)
11/24/98	Major Amendment.
11/25/98	Petition to change Major to minor amend.

FDA:

06/10/98	Acknowledgment letter
07/14/98	Labeling review completed (Deficiencies).
08/26/98	bioequivalent WAI Granted.
12/03/99	Telecon-Petition denied.
11/24/98	Labeling review (2nd round) completed with Deficiencies.

10. PHARMACOLOGICAL CATEGORY:
Acute non-lymphocytic leukemia

11. Rx or OTC: Rx

12. **RELATED IND/NDA/DMF(s):**
Innovator: Pharmacia & Upjohn (NDA 16793)
100 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial

ANDA 71868(Faulding)-Cytarabine USP, 20 mg/ML, 5 mL,(single dose)
ANDA 72168(Faulding)-Cytarabine USP, 20 mg/ML, 50 mL (bulk package)
ANDA 72945(Faulding)-Cytarabine USP, 20 mg/mL, 25 mL(multi- dose)

DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM:**
Solution for Injection

14. **POTENCY:**
2 g/20 mL (100mg/mL)

15. **CHEMICAL NAME AND STRUCTURE:**
4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

[redacted]

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (FAX Amendment).

19. **REVIEWER:** Bing Cai, Ph.D. **DATE COMPLETED:** 05/20/98 **DATE Revised:** 05/21/99

Redacted 13

pages of trade secret and/or

confidential

commercial

information

D W

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #:** 75-383

3. **NAME AND ADDRESS OF APPLICANT:**
Faulding Pharmaceutical Co.
Attention: Heike Maaser
200 Elmora Avenue
Elizabeth, NJ 07207

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
505 j

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:** Cytarabine Injection

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**

Faulding:

05/15/98	Submission of ANDA (received on 05/18/98)
11/24/98	Major Amendment.
11/25/98	Petition to change Major to minor amend.
07/06/99	**Amendment (CMC & Labeling)**
07/14/99	**New Correspondence.(labeling)**
08/04/99	**Amendment (Labeling)**

FDA:

06/10/98	Acknowledgment letter
07/14/98	Labeling review(1st round) w/ Deficiencies.
08/26/98	Bioequivalent WAI Granted.
10/26/98	CMC NA-Major
12/03/99	Telecon-Petition denied.
11/24/98	Labeling review (2nd round) w/ Deficiencies.
06/07/99	CMC NA-FAX
08/06/99	Labeling review (3rd round)-acceptable.
08/10/99	Micro review completed w/ Deficiencies.

10. **PHARMACOLOGICAL CATEGORY:**
Acute non-lymphocytic leukemia

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
Innovator: Pharmacia & Upjohn (NDA 16793)
100 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial

ANDA 71868(Faulding)-Cytarabine USP, 20 mg/ML, 5 mL,(single dose)
ANDA 72168(Faulding)-Cytarabine USP, 20 mg/ML, 50 mL (bulk package)
ANDA 72945(Faulding)-Cytarabine USP, 20 mg/mL, 25 mL(multi- dose)

DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM:**
Solution for Injection

14. **POTENCY:**
2 g/20 mL (100mg/mL)

15. **CHEMICAL NAME AND STRUCTURE:**
4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

[redacted]

18. **CONCLUSIONS AND RECOMMENDATIONS:**
NA, MINOR

19. **REVIEWER:** Bing Cai, Ph.D. **DATE COMPLETED:** 08/03/99 **DATE Revised:** 08/16/99

Redacted 8

pages of trade secret and/or confidential commercial information

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 4

2. **ANDA #:** 75-383

3. **NAME AND ADDRESS OF APPLICANT:**
Faulding Pharmaceutical Co.
Attention: Heike Maaser
200 Elmora Avenue
Elizabeth, NJ 07207

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Cytarabine Injection

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Faulding:

05/15/98	Submission of ANDA (received on 05/18/98)
11/24/98	Major Amendment.
11/25/98	Petition to change Major to minor amendmnet
07/06/99	Amendment (CMC & Labeling)
07/14/99	New Correspondence (labeling)
08/04/99	Amendment (Labeling)
09/28/99	**FAX Amendment (CMC/Microbiology)**
10/08/99	Telephone Amendment (Micro)

FDA:

06/10/98	Acknowledgment letter
07/14/98	Labeling review(1st round) w/ Deficiencies.
08/26/98	Bioequivalent WAI Granted.
10/26/98	CMC NA-Major
12/03/99	Telecon-Petition denied.
11/24/98	Labeling review (2nd round) w/ Deficiencies.
06/07/99	CMC NA-FAX
08/06/99	Labeling review (3rd round)-acceptable.
08/10/99	Micro review completed w/ Deficiencies.
08/30/99	NA, FAX
10/04/99	CMC completed/satisfactory, pending Micro.
10/14/99	Micro review completed-acceptable

10. **PHARMACOLOGICAL CATEGORY:**
Acute non-lymphocytic leukemia

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
Innovator: Pharmacia & Upjohn (NDA 16793)
100 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial

ANDA 71868(Faulding)-Cytarabine USP, 20 mg/ML, 5 mL,(single dose)
ANDA 72168(Faulding)-Cytarabine USP, 20 mg/ML, 50 mL (bulk package)
ANDA 72945(Faulding)-Cytarabine USP, 20 mg/mL, 25 mL(multi- dose)

DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM:**
Solution for Injection

14. **POTENCY:**
2 g/20 mL (100mg/mL)

15. **CHEMICAL NAME AND STRUCTURE:**
4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

[redacted]

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Approvable

19. **REVIEWER:** Bing Cai, Ph.D. **DATE COMPLETED:** 09/30/99 **DATE Revised:** 11/02/99

Redacted 5

pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-383

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #1
July 28, 1999

A. 1. **ANDA: 75-383**

APPLICANT: Faulding Pharmaceuticals Company
200 Elmore Ave.
Elizabeth, NJ 07207

2. PRODUCT NAME: Cytarabine Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
100mg/mL in 20mL vials (2g/20mL), single dose vial, for intravenous, intrathecal and subcutaneous use only.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: acute non-lymphocytic leukemia

B. 1. DATE OF INITIAL SUBMISSION: **May 15, 1998**
Subject of this Review (Received May 18, 1998)

2. DATE OF AMENDMENTS:
11/24/98 - major chemistry & labeling amendment

3. RELATED DOCUMENTS:
NDA 16793 - Innovator
ANDA 71868 - Faulding - Cytarabine, 20 mg/mL (5 mL, single dose)
ANDA 72168 - Faulding - Cytarabine, 20 mg/mL (50 mL, bulk package)
ANDA 72945 - Faulding - Cytarabine, 20 mg/mL (25 mL, multi-dose)

4. ASSIGNED FOR REVIEW: July 1, 1999

C. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process and associated sterilization processes are provided in "D. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

/S/ 7/28/99
Lynne A. Ensor, Ph. D.

7/28/99

cc: Original **ANDA 75-383**
Duplicate ANDA
Division Copy
Field Copy
Drafted by L. Ensor, HFD 620 v:wp\microrev\75383
Initialed by M. Fanning, P. Cooney

Redacted 9

pages of trade secret and /or confidential commercial information

should be considered.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. [redacted]

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #2
October 8, 1999

A. 1. **ANDA: 75-383**

APPLICANT: Faulding Pharmaceuticals Company
200 Elmore Ave.
Elizabeth, NJ 07207

2. PRODUCT NAME: Cytarabine Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
100mg/mL in 20mL vials (2g/20mL), single dose vial, for intravenous, intrathecal and subcutaneous use only.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: acute non-lymphocytic leukemia

B. 1. DATE OF INITIAL SUBMISSION: May 15, 1998

2. DATE OF AMENDMENTS:
Facsimile Amendment: September 28,1999
Subject of this Review (Received Sept. 29, 1999)

Telephone Amendment: October 8,199
Subject of this Review (Received Oct.8, 1999)

3. RELATED DOCUMENTS:
NDA 16793, ANDA 71868, ANDA 72168, ANDA 72945

4. ASSIGNED FOR REVIEW: October 5, 1999

C. REMARKS: The amendment provides for the response to the microbiology and chemistry deficiencies in the fax dated August 30,1999.

Telecons were held with the applicant on 10/5/99 and 10/8/99 to discuss the [redacted] The firm's commitment, set during the 10/8/99 telecon, was submitted via a telephone amendment (10/8/99), which is included as part of this review.

D. CONCLUSIONS: The submissions **are recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process and associated sterilization processes are provided in "E. Review Notes".

/S/ 10/8/99
Lynne A. Ensor, Ph. D.

10/14/99

cc: Original **ANDA 75-383a**
Duplicate ANDA
Division Copy
Field Copy

Drafted by L. Ensor, HFD 620 v:wp\microrev\75383a
Initialed by A. High and/or M. Fanning

Redacted 3

pages of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-383

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # 75-383 SPONSOR: Faulding Pharmaceuticals, Inc.

DRUG & DOSAGE FORM: Sterile Cytarabine Injection

STRENGTH (S): 2 g/vial

TYPE OF STUDY: SD SDF MULT OTHER X

STUDY SUMMARY: N/A

Formulation is acceptable, waiver is granted

PRIMARY REVIEWER: Carol Y. Kim BRANCH: 3
INITIAL: /S/ DATE: 8/20/98

TEAM LEADER: Barbara M. Davit BRANCH: 3
INITIAL: /S/ DATE: 8/21/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: DATE: 8/26/98

DIRECTOR /S/
OFFICE OF GENERIC DRUGS
INITIAL: DATE:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-383

APPLICANT: Faulding Pharmaceuticals, Inc.

DRUG PRODUCT: Sterile Cytarabine Injection, 2 g/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Sterile Cytarabine Injection
2 g/vial
ANDA #75-383
Reviewer: Carol Y. Kim
x:\new\firmsam\faulding\ltrs&rev\75383w.598.doc

Faulding Pharmaceuticals, Inc.
Elizabeth, New Jersey
Submission Date:
May 15, 1998

REVIEW OF A WAIVER REQUEST

I. Background

1. The firm has requested a waiver of an in vivo bioequivalence study requirement for its proposed product, Sterile Cytarabine Injection, 2 g/20 ml, single dose vial. The reference listed product is Cytosar-U^R (Sterile Cytarabine, USP) Injection, 2 g/vial, by The UpJohn Company. Faulding's Sterile Cytarabine Injection is a ready-to-use product solution but Cytosar-U^R requires reconstitution prior to use. The proposed

2. The Sterile Cytarabine Injection is an antineoplastic agent indicated for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients. It has also been found useful in the treatment of acute non-lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration is used in the prophylaxis and treatment of meningeal leukemia.

3. The test and the reference listed product are both administered by intravenous infusion or injection, subcutaneously, and intrathecally (preservative free preparation only).

II. Formulation Comparison

The test and reference formulations are compared as shown below:

Ingredient	Test product	UpJohn's Cytosar-U^R
Cytarabine	2 g/20 ml	2 g/vial
Dosage Form	Ready-to-use solution (single use)	Sterile powder for injection
Concentration per ml	100 mg	100 mg*
NaOH and/or HCl	pH adjusting	pH adjusting
Water for Injection, USP	QS 1 ml	QS 1 ml

*Upon reconstitution with 20 ml Bacteriostatic Water for Injection

III. Comments

1. The test product, Sterile Cytarabine Injection, 2 g/20ml, contains active and inactive ingredients at the same concentrations as the reference product, Cytosar-U[R] (Sterile Cytarabine, USP) Injection, 2 g/vial.

2. The change in dosage form (from a dry sterile powder to a ready-to-use solution) is authorized under section 505 (j) (2) (C) (i) of the Food Drug and Cosmetic Act.

3. ———— is not known to affect the bioavailability of the proposed parenteral product, nor to have any adverse influence on the therapeutic efficacy of the active ingredient.

4. A waiver is granted.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Faulding Pharmaceuticals, Inc. on its drug product, Sterile Cytarabine Injection, 2 g/vial, falls under 21 CFR section 320.24 (b) (6) of the Bioavailability/Bioequivalence Regulations. The waiver of an in vivo bioequivalence study for the drug is granted. The Division of Bioequivalence deems the test product, Sterile Cytarabine Injection, USP, 2 g/vial, bioequivalent to the reference product, Cytosar-U[R] (Sterile Cytarabine, USP) Injection, 2 g/vial, manufactured by The UpJohn Company.

The firm should be informed of the recommendation.

/S/

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

/S/ 8/24/98
/S/

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT Date: 8/21/98

Concur: /S/ Date: 8/26/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

CC: ANDA #75-383
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ C. Kim

X:\NEW\FIRMSam\faulding\ltrs&rev\75383w.598.doc
Printed in final on 8/20/98

Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim /S/ 8/20/98
HFD-658/ Bio team Leader B. Davit /S/ 8/21/98
HFD-617/ Project Manager
HFD-650/ D. Conner /S/ 8/26/98

BIOEQUIVALENCY-ACCEPTABLE Submission date: 05/15/98

1. WAIVER (WAI) **Strength: 2 g/vial**
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments: A waiver is granted

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-383

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-383

FIRM: Faulding Pharmaceutical Co.

DOSAGE FORM: Injection

STRENGTH: 2 g/20 mL (100 mg/mL)

DRUG: Cytarabine Injection

cGMP STATEMENT/EIR UPDATED STATUS:
EER is acceptable per 10/29/99.

BIO STUDY:
Acceptable per bio letter to the firm dated 08-26-98.
Bio waiver is granted.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Waived. The [redacted] methods are the same as those used in their two other previous approved ANDAs (See comments in CR#1).

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

Expiration dating period of 18 months for the drug product is acceptable per CR #3.

LABELING:
Satisfactory per T. Watkins' review completed on 08/06/99.

STERILIZATION VALIDATION (IF APPLICABLE):
Acceptable per Lynn A. Ensor review dated 10-08-99.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
N/A. Bio waiver is requested.

NDS Source: Referenced DMF [redacted] is adequate per B. Cai's review completed on 05/20/99. No new submission has been received since then (per 11/02/99).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Size of stability Batch(lot #7022016): [redacted]

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Production batch size post-approval of the application is ~~~~

Bing Cai
Review Chemist

Mike Smela
Team Leader

Division of Chemistry I
OGD/CDER

cc: ANDA 75-383
Division File
Field Copy

Endorsements:
HFD-625/BCai/11/02/99
HFD-625/M.Smela/
V:\FIRMSAM\FAULDING\LTRS&REV\75383.SUM.BBC.DOC
FT\njg/11/3/99

11/8/99

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-383 **Date of Submission:** July 6, 1999 and August 4, 1999

Applicant's Name: Faulding Pharmaceutical Company
Established Name: Cytarabine Injection, 2 g/20 mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (20 mL) Satisfactory as of November 24, 1998 submission.

Carton Labeling: (1 x 20 mL) Satisfactory as of July 14, 1999 submission (New Correspondence to July 6, 1999 submission).

Professional Package Insert Labeling: Satisfactory as of August 4, 1999 submission

Revisions needed post-approval:
BASIS OF APPROVAL:
Was this approval based upon a petition? Yes Suitability Petition was approved July 26, 1996.

What is the RLD on the 356(h) form: CYTOSAR-U (sterile cytarabine, USP) sterile powder

NDA Number: 16-793/S-059
NDA Drug Name: Sterile Cytarabine Powder, USP
NDA Firm: Pharmacia & Upjohn Company

Date of Approval of NDA Insert and supplement #: October 15, 1998/S-059
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side by side comparison with Cytosar-U labels in file.
Basis of Approval for the Carton Labeling: Side by side comparison with Cytosar-U cartons in file.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23, page 448.	X		
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns? See note to chemist about USP requirements Stability, light sensitivity	X		
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).The company name is too prominent in comparison to the established name on the insert and carton labeling..	X		
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. See note to chemist.	X		
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			

Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? Benzyl alcohol used in the 500mg/25ml strength only.	X		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? See note to chemist	X		
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? See note to chemist.	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

1. Does the container(20 mL, 2 mm clear Type I glass vial) meet the USP requirement for well-closed,lightresistantcontainer?
2. The innovator's product is only stable for 48 hours once reconstituted. The applicant's product is already in solution. Is there any concern about the stability of the applicant's product beyond 48 hours once the vial is opened?
3. The USP requires a pH between 4.0 and 6.0 in a solution containing the equivalent of 10 mg Cytarabine per mL. The applicant's product concentration is 100 mg Cytarabine/ mL. It is adjusted to a pH of 7.5 to 7.9 with either 1 N Sodium Hydroxide, NF or 1 N Hydrochloric Acid, NF. Does this meet the USP requirement?

These questions were answered on T[illegible] first review /S/ 1/[illegible]/99

FOR THE RECORD:

1. The reference listed drug for this application is Cytosar-U® by Upjohn. (NDA#16-793 S-059, Approved 10-15-98). The applicant filed a petition for a different dosage form which was approved 7/26/96 for a 100 mg/mL injection.

2. The Orange Book name is Cytarabine Injectable; Injection. The USP name is Sterile Cytarabine.

3. The USP requirements are:
-well-closed, light resistant container.
-Preserve in containers for Constituted Solutions under Injections.
-not more than 0.07 USP Endotoxin Unit per mg of cytarabine.
-pH between 4.0 and 6.0 in a solution containing the equivalent of 10 mg Cytarabine per mL. See USP 23, pages 448-449.

4. Patent/Exclusivity Certification:

   The applicant certifies that no patents or exclusivities exist for this product. See Vol. 1.1, page 11.

5. Manufacturing:

   The product is Manufactured by F.H.Faulding & Co. Limited, 1-23 Lexia Place, Mulgrave, Victoria 3170, Australia for shipment to Faulding Pharmaceutical Co. 200 Elmora Avenue, Elizabeth, NJ 07207. See Vol. 1.1, page 161.

6. Outside Firms:

   Outside firms are utilized for testing only. See Vol. 1.1, page 247.

7. Container/Closure Statement:

   Container= 20 mL, 20 mm clear Type I glass vial.
   Closure= 20 mm, ——— closure.
   Seals= 20 mm ——— with plastic color coded flip-off cap.
   See Vol. 1.2, page 592.

8. Finished Product:

   The finished product is described as a clear, colorless solution, free from visible particles. See Vol. 1.2, page 628.

9. Components/Composition Statement;
   Innovator:
   Active: Cytarabine, USP 2 gram powder.
   Inactive: Bacteriostatic water for injection
   Hydrochloric Acid to adjust pH when necessary
   Sodium Hydroxide to adjust pH when necessary

Applicant:
Active: Cytarabine, USP 100 mg/ml (2 gram/ 20 mL)
Inactive: Water for Injection, BP/USP
1 N Hydrochloric Acid to adjust pH into range of 7.5-7.9.
1 N Sodium Hydroxide to adjust pH into range of 7.5-7.9

10. Storage Conditions:
Innovator: Controlled Room Temperature 15-30°C (59-86°F).
Applicant: Controlled Room Temperature 15-30°C (59-86°F).

11. Product Line:

Innovator: 100 mg vial 20 mg/mL, 500mg vial 50 mg/mL, 1 gram vial 100 mg/mL, 2 gram vial 100 mg/mL.

Applicant: 100 mg/5mL single dose flip top vial (cool green cap),
2gram/20mL in a single dose flip top vial (green cap).

Date of Review: August 6, 1999
Date of Submission: July 6, 1999

Reviewer: /S/ **Date:** 8/6/99

Team Leader: /S/ **Date:** Concur 8/6/99

---

cc:
ANDA:
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSAM\FAULDING\LTRS&REV\75383.APL
Review

Concur: M. /S/ 8/6/99

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-383** Date of Submission: **May 15, 1998**

Applicant's Name: **Faulding Pharmaceutical Company**

Established Name: **Cytarabine Injection, 2 g/20 mL**

Labeling Deficiencies:

1. CONTAINER

   a. Revise to read as follows:

      Usual Dosage: See package insert for complete product information.

2. CARTON

   a. See comment (a) under CONTAINER.

   b. Include the following statement on all labels and labeling:

      Protect from light. Retain in carton until time of use.

3. INSERT

   a. Delete reference to the [redacted] vial in the package insert. This product should have separate labeling since it contains [redacted] and should be labeled "Not for intrathecal administration".

   b. The first WARNINGS section should appear in a box. Refer to approved labeling of Cytosar-U and 21 CFR 201.57(e) for guidance.

      i. We note the use of British variants in spelling throughout the text (eg., oesophagitis, foetus,etc). Please revise using the American variants(eg, esophagitis, fetus, etc.).

ii. Delete reference to the [redacted] dose vial in the package insert. This product should have separate labeling since it contains [redacted] and should be labeled "Not for intrathecal administration".

c. DESCRIPTION

i. Revise the second sentence to read as follows:

Each mL contains 100 mg Cytarabine...

ii. Revise the chemical name to read:

1-β-D-Arabinofuranosylcytosine

d. DOSAGE AND ADMINISTRATION (Chemical Stability of Infusion Solutions)

i. Revise the first sentence to read as follows:

Chemical Stability studies were performed by ultraviolet assay...

ii. Revise the second sentence to read as follows:

...Sodium Chloride Injection, 94 to 96 percent...

Please revise your labels and labeling, as instructed above, and submit twelve copies of final printed labels and twelve copies of final printed insert and carton labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes Suitability Petition was approved July 26, 1996.

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? Yes No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23, page 448.	X		
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns? See note to chemist about USP requirements Stability, light sensitivity	X		
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).The company name is too prominent in comparison to the established name on the insert and carton labeling..	X		
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. See note to chemist.	X		
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? Benzyl alcohol used in the 500mg/25ml strength only.	X		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? See note to chemist	X		
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? See note to chemist.	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

see Chem Rev. B. Cai 10/2/98

NOTES/QUESTIONS TO THE CHEMIST:

1. Does the container (20 mL,2 mm clear Type I glass vial) meet the USP requirement for well-closed, light resistant container? ← This is for DS not DP!
2. The innovator's product is only stable for 48 hours once reconstituted. The applicant's product is already in solution. Is there any concern about the stability of the applicant's product beyond 48 hours once the vial is opened? No. This is a SDV.
3. The USP requires a pH between 4.0 and 6.0 in a solution containing the equivalent of 10 mg Cytarabine per mL. The applicant's product concentration is 100 mg Cytarabine/ mL. It is adjusted to a pH of 7.5 to 7.9 with either 1 N Sodium Hydroxide, NF or 1 N Hydrochloric Acid, NF. Does this meet the USP requirement? This product is not a USP item

/S/ 10/14/98

FOR THE RECORD:

1. The reference listed drug for this application is Cytosar-U® by Upjohn. (NDA#16-793 S-058, Approved 1-24-96). The applicant filed a petition for a different dosage form which was approved 7/26/96 for a 100mg/mL injection.

2. The Orange Book name is Cytarabine Injectable; Injection. The USP name is Sterile Cytarabine.

3. The USP requirements are:
   -well-closed, light resistant container.
   -Preserve in containers for Constituted Solutions under Injections.
   -not more than 0.07 USP Endotoxin Unit per mg of cytarabine.
   -pH between 4.0 and 6.0 in a solution containing the equivalent of 10 mg Cytarabine per mL. See USP 23, pages 448-449.

4. Patent/Exclusivity Certification:

   The applicant certifies that no patents or exclusivities exist for this product. See Vol. 1.1, page 11.

5. Manufacturing:

   The product is Manufactured by F.H.Faulding & Co. Limited, 1-23 Lexia Place, Mulgrave, Victoria 3170, Australia for shipment to Faulding Pharmaceutical Co. 200 Elmora Avenue, Elizabeth, NJ 07207. See Vol. 1.1, page 161.

6. Outside Firms:

Outside firms are utilized for testing only. See Vol. 1.1, page 247.

7. Container/Closure Statement:

Container= 20 mL, 20 mm clear Type I glass vial.
Closure= 20 mm, [illegible] closure.
Seals= 20 mm [illegible] color coded flip-off cap.
See Vol. 1.2, page 592.

8. Finished Product:

The finished product is described as a clear, colorless solution, free from visible particles. See Vol. 1.2, page 628.

9. Components/Composition Statement;

Innovator:

Active: Cytarabine, USP 2 gram powder.
Inactive: Bacteriostatic water for injection
Hydrochloric Acid to adjust pH when necessary
Sodium Hydroxide to adjust pH when necessary

Applicant:

Active: Cytarabine, USP 100mg/ml (2 gram/ 20 mL)
Inactive: Water for Injection, BP/USP
1 N Hydrochloric Acid to adjust pH into range of 7.5-7.9.
1 N Sodium Hydroxide to adjust pH into range of 7.5-7.9

10. Storage Conditions:

Innovator: Controlled Room Temperature 15-30°C (59-86°F).

Applicant: Controlled Room Temperature 15-30°C (59-86°F).

11. Product Line:

Innovator: 100mg vial 20 mg/mL, 500mg vial 50 mg/mL, 1 gram vial 100 mg/mL, 2 gram vial 100 mg/mL.

Applicant: 100mg/5mL single dose flip top vial (cool green cap), 2gram/20mL in a single dose flip top vial (green cap).

Date of Review: Date of Submission: May 15, 1998

Primary Reviewer: /S/ Date: 7/13/98

Team Leader: /S/ Date: 7/14/98

cc:

ANDA:
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
x:\new\firmsam\faulding\ltrs&rev\75383.na1.1
Review

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Branch 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE:12/3/98

NAME/TITLE OF INDIVIDUAL(S): Heike Maaser
FIRM:Faulding
PRODUCT NAME:Cytarabine
TEL #: 908-931-3806
Reference:75383

Notes of Conversation:I called in regard to 11/25/95 (IT should be '98) communication and advised that request for conversion of amendment to minor is denied.

I clarified the difference between facsimile/minor/major amendments and advised that 30 day response time is difference between facsimile/minor not minor/major where the difference is 1 hour review time.

I advised that the NA action on this ANDA was somewhat borderline and required a judgement call regarding >1 hour review time. I said I made that call and would not reconsider unless it is shown that we made an error in the review (i.e. deficiencies are not valid). She did not think this was so but wondered about whether the review would take > 1 hour. I said I would not debate this further as it was our judgement call to make.

SIGNATURE OF OGD REPRESENTATIVES: /S/ 12/3/98

Location of Electronic Copy:
X:\new\firmsam\faulding\telecons\120398

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-383** Date of Submission: **November 24, 1998**

Applicant's Name: **Faulding Pharmaceutical Company**

Established Name: **Cytarabine Injection, 2 g/20 mL**

Labeling Deficiencies:

1. CONTAINER (20 mL)

   Satisfactory in final.

2. CARTON (1 x 20 mL)

   Satisfactory in draft.

3. INSERT

   Due to changes in the labeling for the reference listed drug, please revise your insert as follows:

   a. DESCRIPTION

      Please enhance the size of the structural formula, chemical formula, and molecular weight.

   b. PHARMACOLOGY

      i. Revise this section heading to read "CLINICAL PHARMACOLOGY".

      ii. Cell Culture Studies

         Delete the second paragraph of this subsection.

      iii. ~~~~~

         Delete this entire subsection.

      iv. Human Pharmacology

         A. Revise ' ~~~~~ to read "labeled" in

the first sentence of the second paragraph of this subsection and in the first sentence of paragraph five of this subsection.

B. Revise — to read "β" in the chemical name in the last sentence of paragraph two of this subsection.

c. WARNINGS

i. Use in Pregnancy

A. Replace ——————————— in the first paragraph of this subsection with the following:

Cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus.

B. Delete the fourth sentence of the first paragraph of this subsection:

If Cytarabine for Injection...

C. Revise ———— to read "Trisomy" in sixth paragraph.

d. PRECAUTIONS

i. General

A. Replace the first sentence of the last paragraph of this subsection with the following:

Acute pancreatitis has been reported to occur in a patient receiving Cytarabine ——Injection by continuous infusion and in patients being treated with Cytarabine — Injection who have had prior treatment with L-asparaginase.

e. ADVERSE REACTIONS

i. Less Frequent Adverse Reactions

A. Include "pancreatitis" in the second column after "abdominal pain" and before "freckling".

B. Relocate "jaundice" to the bottom of the second column.

C. Relocate "headache" to the bottom of the third column.

f. REFERENCES

Delete all references except for the references that refer to safe handling procedures. The superscripts in the text should also be revised to reflect these changes.

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publications No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 2.53(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.

5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists

Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp. Pharm, 1990; 47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work Practice Guidelines), Am J. Health-Syst Pharm, 1996; 53:1669-1685.

g. _____

Delete this entire section.

Please revise your insert labeling, as instructed above, and submit twelve copies of final printed container labels along with twelve copies each of final printed insert and carton labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

_____

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes Suitability Petition was approved July 26, 1996.

What is the RLD on the 356(h) form: CYTOSAR-U (sterile cytarabine, USP) sterile powder

NDA Number: 16-793/S-059

NDA Drug Name: Sterile Cytarabine Powder, USP

NDA Firm: Pharmacia & Upjohn Company

Date of Approval of NDA Insert and supplement #: October 15, 1998/S-059
Has this been verified by the MIS system for the NDA?
Yes
Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side by side comparison with Cytosar-U labels in file.
Basis of Approval for the Carton Labeling: Side by side comparison with Cytosar-U cartons in file.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23, page 448.	X		
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns? See note to chemist about USP requirements Stability, light sensitivity	X		
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).The company name is too prominent in comparison to the established name on the insert and carton labeling..	X		
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. See note to chemist.	X		

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? Benzyl alcohol used in the 500mg/25ml strength only.	X		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? See note to chemist	X		
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? See note to chemist.	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

APPEARS THIS WAY
ON ORIGINAL

see CR#1. BC

NOTES/QUESTIONS TO THE CHEMIST:

1. Does the container (20 mL, 2 mm clear Type I glass vial) meet the USP requirement for well-closed, light resistant container?
2. The innovator's product is only stable for 48 hours once reconstituted. The applicant's product is already in solution. Is there any concern about the stability of the applicant's product beyond 48 hours once the vial is opened?
3. The USP requires a pH between 4.0 and 6.0 in a solution containing the equivalent of 10 mg Cytarabine per mL. The applicant's product concentration is 100 mg Cytarabine/ mL. It is adjusted to a pH of 7.5 to 7.9 with either 1 N Sodium Hydroxide, NF or 1 N Hydrochloric Acid, NF. Does this meet the USP requirement?

FOR THE RECORD:

1. The reference listed drug for this application is Cytosar-U® by Upjohn. (NDA#16-793 S-059, Approved 10-15-98). The applicant filed a petition for a different dosage form which was approved 7/26/96 for a 100 mg/mL injection.

2. The Orange Book name is Cytarabine Injectable; Injection. The USP name is Sterile Cytarabine.

3. The USP requirements are:
   -well-closed, light resistant container.
   -Preserve in containers for Constituted Solutions under Injections.
   -not more than 0.07 USP Endotoxin Unit per mg of cytarabine.
   -pH between 4.0 and 6.0 in a solution containing the equivalent of 10 mg Cytarabine per mL. See USP 23, pages 448-449.

4. Patent/Exclusivity Certification:

   The applicant certifies that no patents or exclusivities exist for this product. See Vol. 1.1, page 11.

5. Manufacturing:

   The product is Manufactured by F.H.Faulding & Co. Limited, 1-23 Lexia Place, Mulgrave, Victoria 3170, Australia for shipment to Faulding Pharmaceutical Co. 200 Elmora Avenue, Elizabeth, NJ 07207. See Vol. 1.1, page 161.

6. Outside Firms:

   Outside firms are utilized for testing only. See Vol. 1.1, page 247.

7. Container/Closure Statement:

   Container= 20 mL, 20 mm clear Type I glass vial.

Closure= 20 mm, [redacted] closure.
Seals= 20 mm [redacted] with plastic color coded flip-off cap.
See Vol. 1.2, page 592.

8. Finished Product:

The finished product is described as a clear, colorless solution, free from visible particles. See Vol. 1.2, page 628.

9. Components/Composition Statement;

Innovator:

Active: Cytarabine, USP 2 gram powder.
Inactive: Bacteriostatic water for injection
[redacted]
Hydrochloric Acid to adjust pH when necessary
Sodium Hydroxide to adjust pH when necessary

Applicant:

Active: Cytarabine, USP 100 mg/ml (2 gram/ 20 mL)
Inactive: Water for Injection, BP/USP
1 N Hydrochloric Acid to adjust pH into range of 7.5-7.9.
1 N Sodium Hydroxide to adjust pH into range of 7.5-7.9
[redacted]

10. Storage Conditions:

Innovator: Controlled Room Temperature 15-30°C (59-86°F).

Applicant: Controlled Room Temperature 15-30°C (59-86°F).
1

11. Product Line:

Innovator: 100 mg vial 20 mg/mL, 500mg vial 50 mg/mL, 1 gram vial 100 mg/mL, 2 gram vial 100 mg/mL.

Applicant: 100 mg/5mL single dose flip top vial (cool green cap), [redacted] 2gram/20mL in a single dose flip top vial (green cap).

Date of Review: December 8, 1998
Date of Submission: November 24, 1998

Reviewer: /S/ **Date:** 1-4-99

Team Leader: /S/ **Date:** 1-5-99

cc:

ANDA:
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
X:\NEW\FIRMSAM\FAULDING\LTRS&REV\75383NA2.L
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-383

CORRESPONDENCE

Faulding Inc
A World of Health

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc.
11 Commerce Drive
Cranford, New Jersey 07016
Telephone (908) 709 1200
Facsimile (908) 709 4150

TELEPHONE AMENDMENT

October 8, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

Attention: Dr. Lynn Ensor

RE: Telephone Amendment: Microbiology Deficiency
ANDA 75-383 Cytarabine Injection, 2 g/20 mL

Dear Dr. Ensor:

We are, hereby, submitting data in response to your request (telephone contact October 8, 1999) to revise the bioburden limits for our bulk drug solution prior to [redacted] from the limit of [redacted] previously submitted in our amendment dated September 28, 1999.

Based on the data provided in Table 1, the following agreement was reached with the agency:

[redacted]

This amendment is being submitted to you via fax (301 594-0183). Hard copies (archive, review and field copies) are also being forwarded under separate cover.

Faulding would like to thank you for your time and the advice you provided to us during our telephone conversation. Should you have any other comments/questions, please feel free to contact me at the telephone number provided below.

We are looking forward to the approval of our application.

Sincerely,

H. Maaser

Heike Maaser, Ph.D.
Director, Regulatory Affairs
Tel.: 908 931-3806
Fax: 908 709-4150

cc: D. Hui, Project Manager

APPEARS THIS WAY
ON ORIGINAL

Faulding Inc
A World of Health

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc.
11 Commerce Drive
Cranford, New Jersey 07016
Telephone (908) 709 1200
Facsimile (908) 709 4150

FACSIMILE AMENDMENT

September 28, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC to FAX

RE: "RESPONSE TO CHEMISTRY and MICROBIOLOGY DEFICIENCIES"
ANDA 75-383 Cytarabine Injection, 2 g/20 mL

Dear Dr. Patel,

Faulding Pharmaceutical Co. is responding to your deficiency fax dated August 30, 1999 in which you requested the MICROBIOLOGY and CHEMISTRY information.

For ease of review we have arranged the amendment as follows:

1. Form FDA 356h
2. CMC: Agency's comments followed by Faulding's response and any attachment(s) for the response.
3. Microbiology: Agency's comments followed by Faulding's response and any attachment(s) for the responses.
4. Field Copy Certification.

The information in this amendment is being provided to you directly via fax (301) 827-4337. Our complete response, including attachments, is being mailed to the above address under separate cover.

We have provided an archival copy, a review copy and a field copy for this response. Faulding certifies that the field copy is a true copy of the technical sections provided in the review and archival copies of this submission.

If you have any questions concerning this submission, please contact me at (908) 931-3806. We are looking forward to your review of this Amendment.

Sincerely,

H. Maaser

Heike Maaser, Ph.D.
Director, Regulatory Affairs

ORIGINAL

Faulding Inc
A World of Health

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc.
11 Commerce Drive
Cranford, New Jersey 07016
Telephone (908) 709 1200
Facsimile (908) 709 4150

CORRESPONDENCE TO FACSIMILE AMENDMENT

August 4, 1999

FPL
ORIG AMENDMENT
FA

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-383 Cytarabine Injection, 2 g/ 20 mL
(Questions of June 17, 1999)

Dear Dr. Sporn,

This response is to a telephone request made by Teresa Watkins, on July 25, 1999. At that time Faulding was asked to further revise the Cytarabine Package Insert to include the below listed revisions to the final printed package insert. Faulding Pharmaceutical Co. is hereby submitting for your review the revisions requested.

1. **To improve readability in Faulding's Package Insert:**
   - The font size has been increased to 6 pt.
2. **Clinical Pharmacology Section/Cell Culture Studies:**
   - Add the G_1 Phase to the second sentence.
3. **Adverse Reactions Section/Less Frequent Adverse Reactions:**
   - Relocate the word jaundice to the second column under freckling.

Enclosed are twelve (12) copies of the revised package insert with the requested revisions for your review. Also enclosed is a side-by-side comparison with all differences annotated by the use of different color. If this meets with your approval, please consider this as final printed labeling.

Faulding Pharmaceutical Co. looks forward to your review of this Amendment.

Sincerely,

Iris Feliciano
Regulatory Coordinator
Tel: 908-931-3822
Fax: 908-709-4150

pc: Heike Maaser, Director
enc.:.

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc.
11 Commerce Drive
Cranford, New Jersey 07016
Telephone (908) 709 1200
Facsimile (908) 709 4150

Faulding Inc
A World of Health

CORRESPONDENCE TO FACSIMILE AMENDMENT

July 14, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[illegible] CORRECT
NC to [illegible]

RE: ANDA 75-383 Cytarabine Injection, 2 g/ 20 mL
(Questions of June 17, 1999)

Dear Dr. Sporn,

This response is to a telephone request made by Teresa Watkins, on July 9, 1999. At that time Faulding was asked to further revise the Cytarabine labels to include the carton dimensions and color data on the final printed labeling. Faulding Pharmaceutical Co. is hereby submitting for your review the revisions requested.

Enclosed are twelve (12) copies of the revised carton labeling for your review. If this meets with your approval, please consider this as final printed labeling.

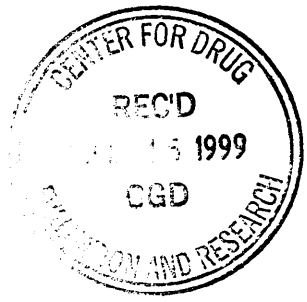
Faulding Pharmaceutical Co. looks forward to your review of this Amendment.

Sincerely,

Iris Feliciano

Iris Feliciano
Regulatory Coordinator
Tel: 908-931-3822
Fax: 908-709-4150

PC: Heike Maaser, Director
enc.:.



Faulding Inc
A World of Health

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc.
11 Commerce Drive
Cranford, New Jersey 07016
Telephone (908) 709 1200
Facsimile (908) 709 4150

FACSIMILE AMENDMENT

July 6,1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

RE: "RESPONSE TO CHEMISTRY and LABELING DEFICIENCIES"
ANDA 75-383 Cytarabine Injection, 2 g/ 20 mL

Dear Dr. Patel,

Faulding Pharmaceutical Co. is responding to your deficiency fax dated June 17, 1999 in which you requested CHEMISTRY information and additional LABELING information.

For ease of review we have arranged the amendment as follows:

1. Form FDA 356h
2. Table of Contents
3. Table of Attachments
4. CMC: Agency's comments printed in bold, followed by Faulding's response and any attachment(s) for the responses
5. Labeling: Agency's comments printed in bold, followed by Faulding's response and any attachment(s) for the responses
6. Field Copy Certification

The information in this amendment is being provided to you directly via fax (301) 827-4337. Our complete response, including attachments, is being mailed to the above address under separate cover.

We have provided an archival copy, a review copy and a field copy for this response. Faulding certifies that the Field Copy is a true copy of the technical sections provided in the Review and Archival copies of this submission.

If you have any questions concerning this submission, please contact me at (908) 931-3821. We are looking forward to your review of this Amendment.

Sincerely,

KPatel

Kala Patel
Sr. Regulatory Affairs Associate
Tel.: (908) 931-3821
Fax: (908) 709-4150

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 07 1999
OGD

ANDA 75-383

JUN 10 1998

Faulding Pharmaceutical Co.
Attention: Heike Maaser
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: ~~[illegible]~~ Cefuroxime Injection 2g/20 mL
2 g/vial

DATE OF APPLICATION: May 15, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 18, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Faulding Inc
A World of Health

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc.
200 Elmora Avenue
Elizabeth, New Jersey 07207
Telephone (908) 527 9100
Facsimile (908) 527 0649

VIA UPS OVERNIGHT COURIER

May 15, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Cytarabine Injection, 2 g/20 mL
Original Application

Dear Mr. Sporn,

In accordance with the regulations as promulgated under Section 505(j) of the Federal Food, Drug and Cosmetic Act, as amended, Faulding Pharmaceutical Co. is submitting this Abbreviated New Drug Application for Cytarabine Injection, 2 g/20 mL vials.

The reference listed drug is Cytosar-U® (brand of sterile cytarabine, USP) manufactured by The Upjohn Company. Cytarabine Injection is a ready-to-use solution intended for intravenous, subcutaneous and intrathecal administration. Its composition is qualitatively and quantitatively the same as the listed drug product.

A suitability petition to file an ANDA for Cytarabine Injection, 100 mg/mL in a 20 mL vial, was reviewed by the FDA and determined suitable for submission as an ANDA (Docket No. 92P-0184/CPI; Approved July 26, 1996).

If you have any questions concerning this submission, please contact me directly at (908) 659-2591.

Yours sincerely,

Faulding Pharmaceutical Co.

H. Maaser

H. Maaser
Director, Regulatory Affairs

EXECUTIVE SUMMARY

Organization of the ANDA; Certification as to Field Copy.

Faulding's Cytarabine Injection ANDA is organized in the manner recommended by the Office of Generic Drugs in its Policy and Procedure Guide 30-91. The ANDA is divided into 21 sections, each of which is designated as a roman numeral. An overall Table of Contents is provided in front of each volume which references each section along with significant sub-sections by providing the actual page number where each section or subsection begins. In addition to the overall Table of Contents, a section specific table of contents is provided for ease of review at the beginning of larger sections. Both a table listing attachment by number and a table listing tables of data are also provided at the beginning of each volume immediately following the overall Table of Contents.

For ease of reference, the entire ANDA is numbered sequentially in the lower right corner of each page. Numbered red tabs identify the beginning of each new section. All attachments, identified by white tabs, are located in back of the appropriate sections and are numbered consecutively throughout the document. A cross-reference to the specific page is provided whenever the text of a section or sub-section refers to any documentation/attachments in the dossier. All documentation/attachments are provided in the submission only once. If reference is made to a document more than once, a cross reference is provided to the page at which it appears in the ANDA.

- **Applicant:**
  Faulding Pharmaceutical Co.

- **Manufacturer of Cytarabine Injection:**
  F. H. Faulding & Co. Limited

F. H. Faulding & Co. also trades under the name of David Bull Laboratories in other countries, hence the abbreviation DBL is sometimes used.

Faulding is submitting an archival copy of the ANDA that contains all the information required in an ANDA. Faulding confirms that the information in the review copy is identical to the information provided to the agency in the archival copy. Although the proposed product, Cytarabine Injection, is not an USP article, it is identical at the time of use to the reconstituted Sterile Cytarabine, USP. Therefore, separately bound copies of the analytical methods are not provided. This application does contain a bioequivalency requirement waiver since Cytarabine Injection is a parenteral solution intended for: intravenous infusion or injection; and subcutaneous or intrathecal administration. Cytarabine Injection contains the same active ingredient and the same total drug content per container as the listed drug Cytosar-U®.

As required by the final rule dated September 8, 1993, Faulding, hereby, confirms that the field copy containing (a) the technical section as required by 21 CFR 314.94 (a) (9), (b) a copy of the 356h form, and (c) the certification that the copy of the technical section is identical to the archival and review copies, has been sent under separate cover to the Office of Generic Drugs.

Date: 5/15/98

H. Maaser

Heike Maaser
Director, Regulatory Affairs