CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 77-524

Name: Fluorouracil Cream, USP
5%

Sponsor: Spear Pharmaceuticals, Inc.

Approval Date: April 11, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-524

Spear Pharmaceuticals, Inc.
Attention: K.L. Spear, M.D.
President,
14882 Belleza Lane
Naples, FL 34110

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 22, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluorouracil Cream USP, 5 %.

Reference is also made to your amendments dated July 11, 2005, August 2, 2005, August 18, 2005, January 9, 2006, January 16, 2006, January 26, 2007 and March 14, 2007.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Fluorouracil Cream USP, 5 % to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Efudex Topical Cream, 5%, of Valeant Pharmaceuticals International.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these

submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Gary Buehler
4/11/2008 10:08:06 AM

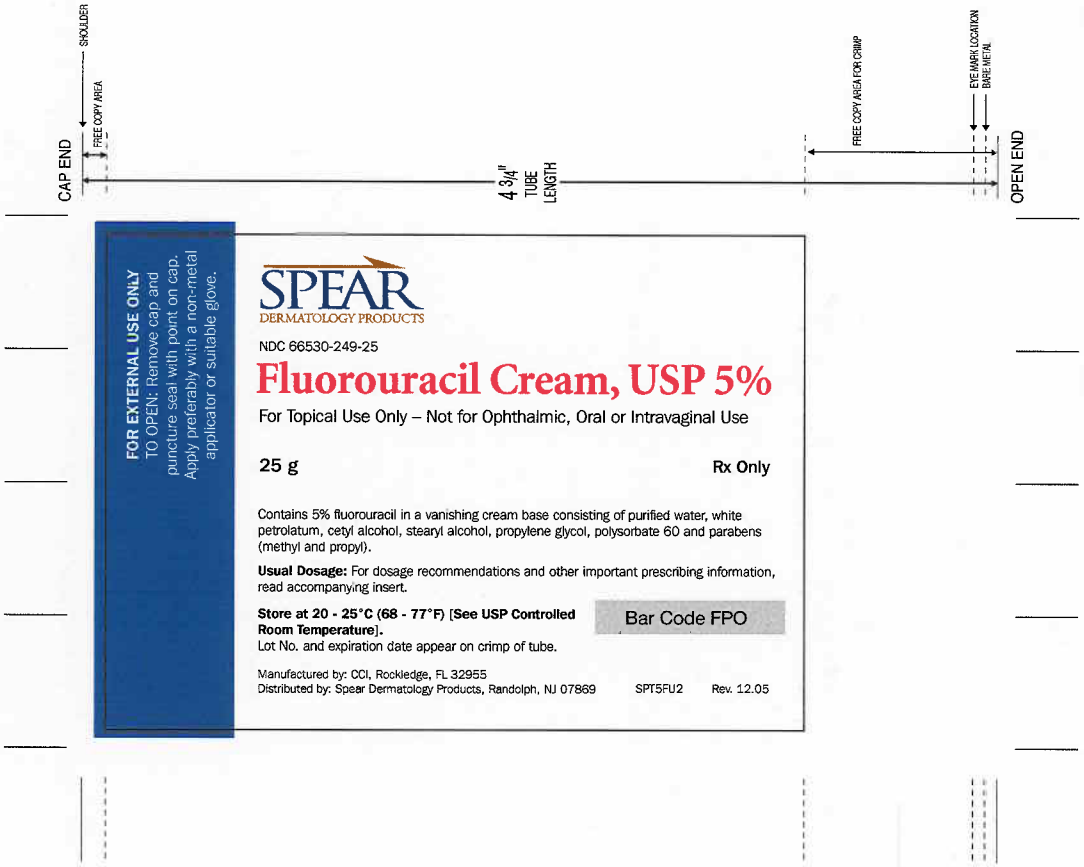
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

LABELING

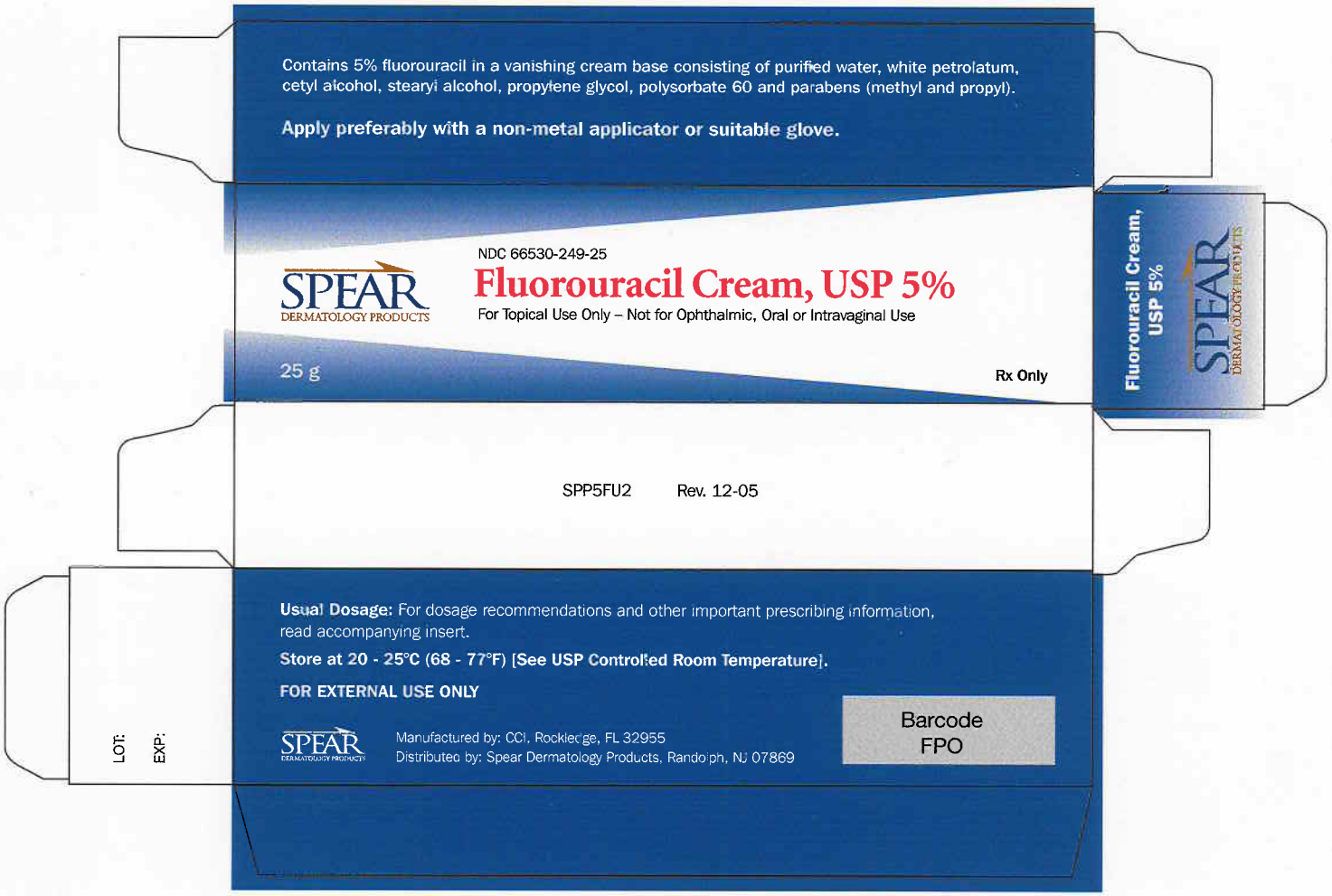
SP-2841
Fluorouracil Cream, USP 5%
25g Tube
12.20.05



PMS (b) (4)
PMS
PMS
PMS

2841-SP
Fluorouracil Cream, USP 5%
25g Carton
12.20.05

25g CARTON (b) (4)



PMS (b) (4)
PMS
PMS
PMS

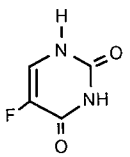
Fluorouracil Cream, USP 5%

For Topical Use Only –
Not for Ophthalmic, Oral or Intravaginal Use

DESCRIPTION: Fluorouracil Cream, USP 5% is a topical preparation containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Fluorouracil Cream contains 5% fluorouracil in a vanishing cream base consisting of purified water, white petrolatum, cetyl alcohol, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Chemically, fluorouracil is 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white to practically white, crystalline powder which is sparingly soluble in water and slightly soluble in alcohol. One gram of fluorouracil is soluble in 100 mL of propylene glycol. The molecular weight of 5-fluorouracil is 130.08 and the structural formula is:



CLINICAL PHARMACOLOGY: There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and take up fluorouracil at a more rapid rate. The catabolic metabolism of fluorouracil results in degradation products (eg, CO_2, urea, α-fluoro-β-alanine) which are inactive.

Systemic absorption studies of topically applied fluorouracil have been performed on patients with actinic keratoses using tracer amounts of ^{14}C-labeled fluorouracil added to a 5% preparation. All patients had been receiving nonlabeled fluorouracil until the peak of the inflammatory reaction occurred (2 to 3 weeks), ensuring that the time of maximum absorption was used for measurement. One gram of labeled preparation was applied to the entire face and neck and left in place for 12 hours. Urine samples were collected. At the end of 3 days, the total recovery ranged between 0.48% and 0.94% with an average of 0.76%, indicating that approximately 5.98% of the topical dose was absorbed systemically. If applied twice daily, this would indicate systemic absorption of topical fluorouracil to be in the range of 5 to 6 mg per daily dose of 100 mg. In an additional study, negligible amounts of labeled material were found in plasma, urine and expired CO_2 after 3 days of treatment with topically applied ^{14}C-labeled fluorouracil.

INDICATIONS AND USAGE: Fluorouracil Cream is recommended for the topical treatment of multiple actinic or solar keratoses. In the 5% strength it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Safety and efficacy in other indications have not been established.

The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%. The success rate with Fluorouracil Cream is approximately 93%, based on 113 lesions in 54 patients. Eighty-eight lesions treated with the cream produced 7 failures.

CONTRAINDICATIONS: Fluorouracil Cream may cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies in pregnant women with either the topical or the parenteral forms of fluorouracil. One birth defect (cleft lip and palate) has been reported in the newborn of a patient using Fluorouracil Cream as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when Fluorouracil Cream was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Fluorouracil Cream. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses equivalent to the usual human intravenous dose; however, the amount of fluorouracil absorbed systemically after topical administration to actinic keratoses is minimal (see CLINICAL PHARMACOLOGY). Fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10 to 40 mg/kg on Day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12 to 37 mg/kg given to rats between Days 9 and 12 of gestation and intramuscular doses of 3 to 9 mg/kg given to hamsters between Days 8 and 11 of gestation were teratogenic and/or embryotoxic (ie, resulted in increased resorptions or embryolethality). In monkeys, divided doses of 40 mg/kg given between Days 20 and 24 of gestation were not teratogenic. Doses higher than 40 mg/kg resulted in abortion.

Fluorouracil Cream should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the DPD enzyme. DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Fluorouracil Cream is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Fluorouracil Cream is also contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS: Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Fluorouracil Cream was applied to mucous membrane areas during pregnancy.

Occlusion of the skin with resultant hydration has been shown to increase percutaneous penetration of several topical preparations. If any occlusive dressing is used in treatment of basal cell carcinoma, there may be an increase in the severity of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.

Exposure to ultraviolet rays should be minimized during and immediately following treatment with Fluorouracil Cream because the intensity of the reaction may be increased.

Patients should discontinue therapy with Fluorouracil Cream if symptoms of DPD enzyme deficiency develop (see CONTRAINDICATIONS section).

Rarely, life-threatening toxicities such as stomatitis, diarrhea, neutropenia, and neurotoxicity have been reported with intravenous administration of fluorouracil in patients with DPD enzyme deficiency. One case of life-threatening systemic toxicity has been reported with the topical use of Fluorouracil Cream in a patient with DPD enzyme deficiency. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

PRECAUTIONS: *General:* There is a possibility of increased absorption through ulcerated or inflamed skin.

Information for Patients: Patients should be forewarned that the reaction in the treated areas may be unsightly during therapy and, usually, for several weeks following cessation of therapy. Patients should be instructed to avoid exposure to ultraviolet rays during and immediately following treatment with Fluorouracil Cream because the intensity of the reaction may be increased. If Fluorouracil Cream is applied with the fingers, the hands should be washed immediately afterward. Fluorouracil Cream should not be applied on the eyelids or directly into the eyes, nose or mouth because irritation may occur.

Laboratory Tests: Solar keratoses which do not respond should be biopsied to confirm the diagnosis. Follow-up biopsies should be performed as indicated in the management of superficial basal cell carcinoma.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Fluorouracil Cream, 5-fluorouracil, have shown positive effects in in vitro tests for mutagenicity and on impairment of fertility.

5-Fluorouracil was positive in three in vitro cell neoplastic transformation assays. In the C3H/10T ½ clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

While no evidence for mutagenic activity was observed in the Ames test (3 studies), fluorouracil has been shown to be mutagenic in the survival count rec-assay with *Bacillus subtilis* and in the Drosophila wing-hair spot test. Fluorouracil produced petite mutations in *Saccharomyces cerevisiae* and was positive in the micronucleus test (bone marrow cells of male mice). Fluorouracil was clastogenic in vitro (ie, chromatid gaps, breaks and exchanges) in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and has been shown to increase sister chromatid exchange in vitro in human lymphocytes. In addition, 5-fluorouracil has been reported to produce an increase in numerical and structural chromosome aberrations in peripheral lymphocytes of patients treated with this product.

Doses of 125 to 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil was inactive at oral doses of 5 to 80 mg/kg/day. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis significantly reduced the incidence of fertile matings, delayed the development of preimplantation and postimplantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos. Single dose intravenous and intraperitoneal injections of 5-fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes (at 500 mg/kg) and to produce abnormalities in spermatids (at 50 mg/kg) in mice.

Pregnancy: **Teratogenic Effects: Pregnancy Category X:**
See CONTRAINDICATIONS section.

Nursing Mothers: It is not known whether Fluorouracil Cream is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration (see CLINICAL PHARMACOLOGY), because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions to Fluorouracil Cream occur locally and are often related to an extension of the pharmacological activity of the drug. These include burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness and ulceration. Ulcerations, other local reactions, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Fluorouracil Cream was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect. Although a causal relationship is remote, other adverse reactions which have been reported infrequently are:

Central Nervous System: Emotional upset, insomnia, irritability.

Gastrointestinal: Medicinal taste, stomatitis.

Hematological: Eosinophilia, thrombocytopenia, toxic granulation.

Integumentary: Alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticaria, skin rash.

Special Senses: Conjunctival reaction, corneal reaction, lacrimation, nasal irritation.

Miscellaneous: Herpes simplex.

OVERDOSAGE: There have been no reports of overdosage with Fluorouracil Cream.

The oral LD_{50} for the 5% topical cream was 234 mg/kg in rats and 39 mg/kg in dogs. These doses represented 11.7 and 1.95 mg/kg of fluorouracil, respectively. The topical application of the 5% cream to rats yielded an LD_{50} of greater than 500 mg/kg.

DOSAGE AND ADMINISTRATION: When Fluorouracil Cream is applied to a lesion, a response occurs with the following sequence: erythema, usually followed by vesiculation, desquamation, erosion and reepithelialization.

Fluorouracil Cream should be applied preferably with a nonmetal applicator or suitable glove. If Fluorouracil Cream is applied with the fingers, the hands should be washed immediately afterward.

Actinic or Solar Keratosis: Apply cream twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion stage, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following cessation of Fluorouracil Cream therapy.

Superficial Basal Cell Carcinomas: **Only the 5% strength is recommended.** Apply cream twice daily in an amount sufficient to cover the lesions. Treatment should be continued for at least 3 to 6 weeks. Therapy may be required for as long as 10 to 12 weeks before the lesions are obliterated. As in any neoplastic condition, the patient should be followed for a reasonable period of time to determine if a cure has been obtained.

HOW SUPPLIED: Fluorouracil Cream, USP 5% is available in 25-gm tubes containing 5% fluorouracil (NDC 66530-249-25) in a vanishing cream base consisting of purified water, white petrolatum, cetyl alcohol, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

Manufactured by:
CCI
Rockledge, FL 32955

Distributed by:
SPEAR DERMATOLOGY PRODUCTS
Spear Dermatology Products
Randolph, NJ 07869

FPO Barcode

SPI5FU2 Rev. 12-05

09

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING - #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-524

Date of Submission: December 22, 2004

Applicant's Name: Spear Pharmaceuticals, Inc.

Established Name: Fluorouracil Cream, USP, 5%

Labeling Deficiencies:

1. **GENERAL COMMENT [ALL LABELING]**

   Inactive Ingredients – Include "Purified Water" in your inactive ingredients, to be consistent with your "components and composition" statement.

2. **CONTAINER** (25 gram tube)
   - See GENERAL COMMENT
   - Please assure that your container labels are of actual size, color and clarity when submitting in final print. In addition, assure all text is clear and readable.

3. **CARTON** (25 gram)
   - See GENERAL COMMENT
   - The white text on the blue background is difficult to read. Increase readability by changing background and/or printing color.

4. **INSERT**
   - See GENERAL COMMENT
   - Revise to use "USP" with the established name only in the TITLE, DESCRIPTION, and HOW SUPPLIED sections.

Please revise your labeling, as instructed above, and submit each labeling piece in final print.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. In order to keep your ANDA current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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.

John G Gurgol

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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	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?		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).		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.		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)?		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?		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?		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	

NOTES/QUESTIONS TO THE CHEMIST: NONE

FOR THE RECORD:

1. **MODEL LABELING**
   This review was based on the labeling for Efudex Topical Cream, 5% by Valeant International, Inc., formerly ICN Pharmaceuticals, Inc., (NDA 16-831/S-047): Approved June 24, 2004).

2. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Component	% w/w	Quantity per Gram of Product (mg)	Quantity per bio batch (b) (4) kg	Quantity per commercial batch (b) (4) kg	Function
Fluorouracil, USP	5.00	50			Active
Purified Water, USP			(b) (4)		
Propylene Glycol, USP					
White Petrolatum, USP					

Polysorbate 60, NF		(b) (4)
Stearyl Alcohol, NF		
Cetyl Alcohol, NF		
Methylparaben, NF		
Propylparaben, NF		
Total	100.0	

The firm has included Cetyl Alcohol, NF and Purified Water, USP in their formulation which are not present in the innovator's formulation (page 1060). Per chemistry, the amount of Cetyl Alcohol, NF is below the FDA inactive ingredients database level for topical drug products and is therefore considered safe (page 1059).

3. PATENTS/EXCLUSIVITIES

Patent Data – NDA 16-831

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE	NONE	NONE	NONE	II	NONE

Exclusivity-Data – NDA 16-831

Code	Reference	Expiration	Labeling Impact
NONE	NONE	NONE	NONE

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers, and store at controlled room temperature.
- RLD: Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F).
- ANDA: Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

5. CONTAINER/CLOSURE

Component	Description	Manufacturer
25 gram tube	Aluminum sealed tube 7/8" x 4 ¾" (b) (4) External coating: white (b) (4)	**Tube:** (b) (4)
Cap	Black puncture screw cap (b) (4) Black HDPE (b) (4) (b) (4)	**Cap:** (b) (4)

6. PACKAGE CONFIGURATION

- RLD: Packaged in 25 gram tubes.
- ANDA: Packaged in 25 gram line aluminum tubes with HDPE screw caps.

7. FINISHED DOSAGE FORM

- RLD: Topical cream, 5% supplied in 25 gram tubes
- ANDA: White, smooth, homogeneous cream

8. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
CCI
417 Richard Rd.
Rockledge, FL 32955

Date of Review: **Date of Submission:** December 22, 2004

Primary Reviewer: Beverly Weitzman **Date:** 06/27/2005

S. Weitzman

Team Leader: **Date:** 6/28/05

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cc:
ANDA: 77-524
DUP/DIVISION FILE
HFD-613/Jgrace (no cc) .
V:\FIRMSNZ\SPEAR\LTRS&REV\77524NA1.L.doc
Review

APPROVAL SUMMARY

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

ANDA Number: 77-524

Date of Submission: **August 2, 2005**

Applicant's Name: Spear Pharmaceuticals, Inc.

Established Name: Fluorouracil Cream, 5%

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 Label (25 g tube): Satisfactory in FPL as of **August 2, 2005** paper submission. [Vol. 3.1]
- Carton Labeling (25 g carton): Satisfactory in FPL as of **August 2, 2005** paper submission. [Vol. 3.1]
- Professional Package Insert Labeling: Satisfactory in FPL as of **August 2, 2005** electronic submission \\Cdsesubogd1\n77524\N_000\2005-08-02\Fluorouracil PI.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Efudex Cream, 5%
- NDA Number: 16-831
- NDA Drug Name: Fluorouracil Cream, 5%
- NDA Firm: Valeant International, Inc., formerly ICN Pharmaceuticals, Inc.,
- Date of Approval of NDA Insert: NDA 16-831/S-047: Approved June 24, 2004
- 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
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 16-831

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE	NONE	NONE	NONE	II	NONE

Exclusivity-Data – NDA 16-831

Code	Reference	Expiration	Labeling Impact
NONE	NONE	NONE	NONE

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	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?		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).		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.		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)?		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?		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?		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	

NOTES/QUESTIONS TO THE CHEMIST: NONE

FOR THE RECORD:

1. **MODEL LABELING**
   This review was based on the labeling for Efudex Cream, 5% by Valeant International, Inc., formerly ICN Pharmaceuticals, Inc., (NDA 16-831/S-047): Approved June 24, 2004).

2. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Component	% w/w	Quantity per Gram of Product (mg)	Quantity per bio batch (b) (4) kg	Quantity per commercial batch (b) (4) kg	Function
Fluorouracil, USP	5.00	50			Active
Purified Water, USP	(b) (4)				
Propylene Glycol, USP					

White Petrolatum, USP	(b) (4)	
Polysorbate 60, NF		
Stearyl Alcohol, NF		
Cetyl Alcohol, NF		
Methylparaben, NF		
Propylparaben, NF		
Total	100.0	

The firm has included Cetyl Alcohol, NF and Purified Water, USP in their formulation which are not present in the innovator's formulation (page 1060). Per chemistry, the amount of Cetyl Alcohol, NF is below the FDA inactive ingredients database level for topical drug products and is therefore considered safe (page 1059).

3. PATENTS/EXCLUSIVITIES

Patent Data – NDA 16-831

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE	NONE	NONE	NONE	II	NONE

Exclusivity-Data – NDA 16-831

Code	Reference	Expiration	Labeling Impact
NONE	NONE	NONE	NONE

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers, and store at controlled room temperature.
- RLD: Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F).
- ANDA: Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

5. CONTAINER/CLOSURE

Component	Description	Manufacturer
25 gram tube	Aluminum sealed tube 7/8" x 4 ¾" (b) (4) External coating: white (b) (4)	**Tube:** (b) (4)
Cap	Black puncture screw cap (b) (4) Black HDPE (b) (4) (b) (4)	**Cap:** (b) (4)

6. PACKAGE CONFIGURATION

- RLD: Packaged in 25 gram tubes.
- ANDA: Packaged in 25 gram line aluminum tubes with HDPE screw caps.

7. FINISHED DOSAGE FORM

- RLD: Topical cream, 5% supplied in 25 gram tubes
- ANDA: White, smooth, homogeneous cream

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

CCI
417 Richard Rd.
Rockledge, FL 32955

Date of Review: **Date of Submission:** August 2, 2005

Primary Reviewer: Beverly Weitzman **Date:** 8/10/2005

Team Leader: **Date:** 8/10/05

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cc:

ANDA: 77-524
DUP/DIVISION FILE
HFD-613/Jgrace (no cc) .
V:\FIRMSNZ\SPEAR\LTRS&REV\77524AP.L.doc
Review

APPROVAL SUMMARY #2

SUPERCEDES APPROVAL SUMMARY
FROM AUGUST 2, 2005 SUBMISSION

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

ANDA Number: 77-524

Date of Submission: **January 9, 2005**

Applicant's Name: Spear Pharmaceuticals, Inc.

Established Name: Fluorouracil Cream, 5%

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

1. **Container Label** (25 g tube): Satisfactory in FPL as of **January 9, 2005** paper submission. [Vol. 5.1; code SPT5FU2; Revised 12-05]
2. **Carton Labeling** (25 g carton): Satisfactory in FPL as of **January 9, 2005** paper submission. [Vol. 5.1; code SPP5FU2; Revised 12-05]
3. **Professional Package Insert Labeling:**
   - Satisfactory in FPL as of **January 9, 2005** paper submission. [Vol 5.1; code SPI5FU2; Revise 12-05]
   - Satisfactory in SPL as of **January 9, 2005** electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Efudex Cream, 5%
- NDA Number: 16-831
- NDA Drug Name: Fluorouracil Cream, 5%
- NDA Firm: Valeant International, Inc., formerly ICN Pharmaceuticals, Inc.,
- Date of Approval of NDA Insert: NDA 16-831/S-049: Approved October 13, 2005
- 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
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Basis of Approval for the insert: Side by side comparison with SPL and RLD.
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 16-831

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE	NONE	NONE	NONE	II	NONE

Exclusivity-Data – NDA 16-831

Code	Reference	Expiration	Labeling Impact
NONE	NONE	NONE	NONE

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	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?		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).		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.		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)?		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?		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?		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	

NOTES/QUESTIONS TO THE CHEMIST: NONE

FOR THE RECORD:

1. **MODEL LABELING**

This review was based on the labeling for Efudex Cream, 5% by Valeant International, Inc., formerly ICN Pharmaceuticals, Inc., (NDA 16-831/S-049): Approved October 13, 2005).

2. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Component	% w/w	Quantity per Gram of Product (mg)	Quantity per bio batch (b) (4) kg	Quantity per commercial batch (b) (4) kg	Function

Fluorouracil, USP	5.00	50	[redacted]	Active
Purified Water, USP	[redacted] (b) (4)			
Propylene Glycol, USP				
White Petrolatum, USP				
Polysorbate 60, NF				
Stearyl Alcohol, NF				
Cetyl Alcohol, NF				
Methylparaben, NF				
Propylparaben, NF				
Total	100.0	[redacted]		

The firm has included Cetyl Alcohol, NF and Purified Water, USP in their formulation which are not present in the innovator's formulation (page 1060). Per chemistry, the amount of Cetyl Alcohol, NF is below the FDA inactive ingredients database level for topical drug products and is therefore considered safe (page 1059).

3. PATENTS/EXCLUSIVITIES

Patent Data – NDA 16-831

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE	NONE	NONE	NONE	II	NONE

Exclusivity-Data – NDA 16-831

Code	Reference	Expiration	Labeling Impact
NONE	NONE	NONE	NONE

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers, and store at controlled room temperature.
- RLD: Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F).
- ANDA: Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

5. CONTAINER/CLOSURE

Component	Description	Manufacturer
25 gram tube	Aluminum sealed tube 7/8" x 4 ¾" [redacted] (b) (4) External coating: white [redacted] (b) (4)	**Tube:** [redacted] (b) (4)
Cap	Black puncture screw cap [redacted] (b) (4) Black HDPE (b) (4) [redacted] (b) (4)	**Cap:** [redacted] (b) (4)

6. **PACKAGE CONFIGURATION**
   - RLD: Packaged in 25 gram tubes.
   - ANDA: Packaged in 25 gram line aluminum tubes with HDPE screw caps.

7. **FINISHED DOSAGE FORM**
   - RLD: Topical cream, 5% supplied in 25 gram tubes
   - ANDA: White, smooth, homogeneous cream

8. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
   CCI
   417 Richard Rd.
   Rockledge, FL 32955

Date of Review: **Date of Submission: January 9, 2005**

Primary Reviewer: Beverly Weitzman **Date:** 1/25/06

B Weitzman

Team Leader: John Grace **Date:** 1.26.2006

John Grace

cc:

ANDA: 77-524
DUP/DIVISION FILE
HFD-613/Jgrace (no cc) .
V:\FIRMSNZ\SPEAR\LTRS&REV\77524AP.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

CHEMISTRY REVIEWS

Chemistry Review Data Sheet

ANDA 77-524

Fluorouracil Cream USP, 5%

Spear Pharmaceuticals, Inc.

Susan Pittinger
Division 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-524

2. REVIEW #: 1

3. REVIEW DATE: April 15, 2005

4. REVIEWER: Susan Pittinger

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	December 22, 2004
Accepted for Filing	January 6, 2005
Fax Amendment	February 28, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Spear Pharmaceuticals, Inc.
Address:	13100 Ponderosa Way Fort Myers, FL 33907
Representative:	Robert Sarrio
Telephone:	(321) 543 - 7039

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fluorouracil

9. LEGAL BASIS FOR SUBMISSION: The basis for this ANDA is Efudex® (Fluorouracil Topical Cream) Cream, 5% w/w. The NDA, 16-831, is held by Valeant International, Inc. (formerly ICN Pharmaceuticals, Inc.). The firm filed a Paragraph II patent certification for the drug product stating that no unexpired patents exist for the reference listed drug (page 20). Also, there are no exclusivities for the reference listed drug (page 21).

10. PHARMACOLOGICAL CATEGORY: Treatment of actinic keratoses

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

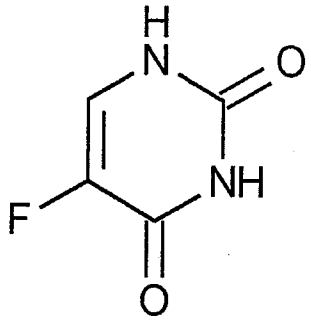
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-Fluorouracil. 2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-. $C_4H_3FN_2O_2$. MW 130.08.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Inadequate	4/08/05	
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-524

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable at this point.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: The drug substance is manufactured by (b) (4) (b) (4). DMF (b) (4) describes the synthesis of the drug substance. The DMF was reviewed by S. Pittinger on April 8, 2005 and was found to be inadequate.

Drug product: Fluorouracil Cream, USP, 5% is a multiple dose cream for treatment of actinic keratoses. Inactive ingredients present in the formulation are Purified Water, USP, Propylene Glycol, USP, White Petrolatum, USP, Polysorbate 60, NF, Stearyl Alcohol, NF, Cetyl Alcohol, NF, Methylparaben, NF, and Propylparaben, NF. The product is filled into 25 gram lined aliminum tubes. An expiration date of 24 months has been requested based on 6-months of accelerated stability data. In addition to the accelerated stability data, the firm has also submitted 6 months of room temperature stability data. The stability data support the requested expiration date of 24 months.

B. Description of How the Drug Product is Intended to be Used

The drug product is a multiple dose topical cream for the treatment of actinic keratoses. The labeling states to apply the drug product in an amount sufficient to cover the lesions and to use for 2 – 4 weeks. The maximum dose is 12.5 grams of drug product per week, so the maximum daily dose is 1.79 grams of drug product (89 mg of the drug substance). (b) (4) (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The deficiencies are related to drug substance and drug product specifications.

III. Administrative

A. Reviewer's Signature

Susan Pittinger

B. Endorsement Block

HFD-627/S.Pittinger/ smp 6/17/05
HFD-627/J.Fan, Team Leader/ 6/22/05

C. CC Block

ANDA 77-524
ANDA DUP 77-524
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Field Copy

Following this page, 13 pages withheld in full-(b)(4) Chemistry review #1

(b) (4)

30. MICROBIOLOGY

Review status: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

N/A

32. LABELING

Review status: Pending

Labeling review is pending.

33. ESTABLISHMENT INSPECTION

Review status: Pending

34. BIOEQUIVALENCE

Review status: Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review status: Satisfactory

The firm requests a categorical exclusion from the requirement of an environmental assessment because the drug product will not be administered at higher dosage levels, for longer duration, or for different indications than the RLD (page 1695). The firm also states that they are in compliance with all local, State, and Federal environmental regulations or codes (page 1696).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-524 APPLICANT: Spear Pharmaceuticals, Inc.

DRUG PRODUCT: Fluorouracil Cream USP, 5%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

Following this page, 1 page withheld in full- (b)(4) Chemistry Review #1

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

1. Please provide all available drug product room temperature stability data.

2. Bioequivalence and labeling information you have provided is pending review. After the reviews are completed, any deficiencies found will be communicated to you separately.

3. All facilities referenced in your ANDA should be in compliance with CGMP at the time of approval. We have requested an evaluation from the Office of Compliance.

4. The USP methods for the drug substance and the drug product are the regulatory methods and they will prevail in the event of any dispute.

Sincerely yours,

6/23/05

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-524
ANDA DUP 77-524
DIV FILE
Field Copy

Endorsements:

HFD-627/S.Pittinger /6/1/05 6/17/05

HFD-627/J.Fan, Team Leader/6/1/05 6/22/05

HFD-617/A.Vu, PM/

V:\FIRMSNZ\SPEAR\LTRS&REV\77524REV01.doc

F/T by: gp/6/9/05

TYPE OF LETTER: NOT APPROVABLE - MINOR

Chemistry Review Data Sheet

ANDA 77-524

Fluorouracil Cream USP, 5%

Spear Pharmaceuticals, Inc.

Susan Pittinger
Division 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-524

2. REVIEW #: 2

3. REVIEW DATE: August 5, 2005

4. REVIEWER: Susan Pittinger

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original Submission	December 22, 2004
Accepted for Filing	January 6, 2005
Fax Amendment	February 28, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	July 11, 2005
Telephone Amendment	August 18, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Spear Pharmaceuticals, Inc.
Address:	13100 Ponderosa Way Fort Myers, FL 33907
Representative:	David J. Christ
Telephone:	(631) 476 5860

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fluorouracil

9. LEGAL BASIS FOR SUBMISSION: The basis for this ANDA is Efudex® (Fluorouracil Topical Cream) Cream, 5% w/w. The NDA, 16-831, is held by Valeant International, Inc. (formerly ICN Pharmaceuticals, Inc.). The firm filed a Paragraph II patent certification for the drug product stating that no unexpired patents exist for the reference listed drug (page 20). Also, there are no exclusivities for the reference listed drug (page 21).

10. PHARMACOLOGICAL CATEGORY: Treatment of actinic keratoses and superficial basal cell carcinoma.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

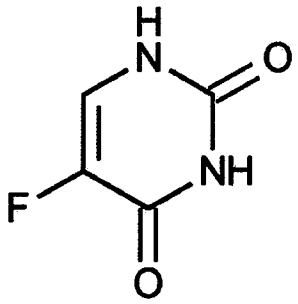
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-Fluorouracil. 2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-. $C_4H_3FN_2O_2$. MW 130.08.

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	11/27/06	Reviewed by E. Schafer
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/06/05	
Methods Validation	N/A		
Labeling	Acceptable	01/26/06	B. Weitzman
Bioequivalence	Acceptable	03/30/07	C. Kim
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-524

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: The drug substance is manufactured by (b) (4) (b) (4) DMF (b) (4) describes the synthesis of the drug substance. The DMF was reviewed by E. Schafer on November 27, 2006 and was found to be adequate.

Drug product: Fluorouracil Cream, USP, 5% is a multiple dose cream for treatment of actinic keratoses. Inactive ingredients present in the formulation are Purified Water, USP, Propylene Glycol, USP, White Petrolatum, USP, Polysorbate 60, NF, Stearyl Alcohol, NF, Cetyl Alcohol, NF, Methylparaben, NF, and Propylparaben, NF. The product is filled into 25 gram lined aliminum tubes. An expiration date of 24 months has been requested based on 6-months of accelerated stability data. In addition to the accelerated stability data, the firm has also submitted 12 months of room temperature stability data. The stability data support the requested expiration date of 24 months.

B. Description of How the Drug Product is Intended to be Used

The drug product is a multiple dose topical cream for the treatment of actinic keratoses and superficial basal cell carcinoma. The labeling states to apply the drug product in an amount sufficient to cover the lesions and to use for 2 – 4 weeks. The maximum dose is 12.5 grams of drug product per week, so the maximum daily dose is 1.79 grams of drug product (89 mg of the drug substance). (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable

Following this page, 15 pages withheld in full- (b)(4) Chemistry review #2

(b) (4)

30. MICROBIOLOGY
Review status: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
N/A

32. LABELING
Review status: Acceptable on January 26, 2006 by B. Weitzman

33. ESTABLISHMENT INSPECTION
Review status: Acceptable on December 6, 2005

34. BIOEQUIVALENCE
Review status: Acceptable on March 30, 2007

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Review status: Satisfactory per review #1

cc: ANDA 77-524
ANDA DUP 77-524
DIV FILE
Field Copy

Endorsements:

HFD-627/S.Pittinger /

HFD-627/J.Fan, Team Leader/

HFD-617/R. Adigun, PM/

V:\FIRMSNZ\SPEAR\LTRS&REV\77524REV02.doc

F/T by:

TYPE OF LETTER: APPROVABLE

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

/s/

Susan Levine
4/11/2008 12:22:14 PM
CHEMIST

Rosalyn Adigun
4/14/2008 11:08:18 AM
CSO

James Fan
4/16/2008 08:47:12 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

BIOEQUIVALENCE REVIEWS

Clinical Review Section

Review of A Bioequivalence Study with a Clinical Endpoint

ANDA # 77-524 Spear Pharmaceuticals, Inc.

Fluorouracil Cream, USP 5%

Carol Kim, Pharm.D.
Clinical Review Team

Submission dates reviewed:
1/6/05, 1/16/06

Date of Review: 3/30/07

CLINICAL REVIEW

Clinical Review Section

Table of Contents

Review of A Bioequivalence Study with a Clinical Endpoint for ANDA 77-524

Executive Summary

This double-blind, randomized, single-center, parallel-group study, carried out in patients with Actinic Keratosis (AK), demonstrates that Spear's Fluorouracil Cream, USP 5%, is bioequivalent to the approved Efudex® 5% Topical Cream. The FDA's statistical review concludes that the 90% Confidence Interval (CI) of the difference in success rate (complete clearing of actinic keratosis lesions) between the test and reference products at the 4-week follow-up (Visit 4, Week 6) is (-0.087, 0.062), within the bioequivalence limits of (-0.20 and + 0.20). A total of 318 patients were randomized and treated with the study drugs. Based on the FDA's statistical review, 309 patients were included in the Intent-to-Treat (ITT)[1] population, and 297 were included in the Per Protocol (PP) Population[2].

I. Recommendation on Approval

The data submitted to ANDA 77-524, using the primary endpoint of success (complete clearing of AK lesions) rate at week 6 (Visit 4, 4 weeks post-treatment visit), are adequate to demonstrate bioequivalence of Spear Pharmaceuticals, Inc.'s Fluorouracil Cream, USP 5%, with the reference listed drug, ICN Pharmaceuticals, Inc. 's (currently known as Valeant Pharmaceutical Intl.) Efudex® 5% Topical Cream. Therefore, the test product is recommended for approval.

II. Summary of Clinical Findings

The data presented in this ANDA 77-524 demonstrate that Spear Pharmaceuticals, Inc.'s Fluorouracil Cream, USP 5%, is bioequivalent to the reference listed drug, Efudex® (fluorouracil) Topical Cream, 5%.

A. Brief Overview of Clinical Program

The study #SPR00-5FU-01 was a randomized, double-blind, comparative study of Spear Pharmaceuticals, Inc.'s Fluorouracil Cream, USP 5%, versus the reference listed drug, Efudex® (fluorouracil) Topical Cream, 5%, in the treatment of AK. Three hundred eighteen (318)

[1] Included patients randomized, applied at least one dose of study medication, and returned for at least one post-baseline efficacy visit (visit 4).

[2] Included all randomized patients who applied at least 75% to 125% of the expected 28 applications (21 to 35 applications) or discontinued the trial due to a lack of treatment effect, completed the final evaluation visit within the designated visit window of 6 weeks (± 4 days), and did not have a significant protocol violation (s) that would affect the clinical evaluations such as use of a prohibited concomitant medication.

patients with presence of at least 3 AK lesions on the face were randomized in a 4:4:1 ratio to receive the test, reference, or placebo/vehicle cream twice daily for 2 weeks.

B. Comparative Efficacy

The primary endpoint of this study is the proportion of patients with success (complete clearing of AK lesions) at the week 6 visit (Visit 4, 4 weeks follow-up) after completion of 2 weeks of treatment. Success was defined by the sponsor as complete clearing of AK lesions. Clearing of AK was defined by the sponsor as either no evidence of the lesion, or only residual smooth flat redness present without elevation above the skin.

According to the FDA's statistical analysis, the success rate in the Per Protocol (PP) Population at Visit 4 was 86.9% in the test group and 88.1% in the reference group. The 90% CI of the difference in success rate between the two active products was (-0.087, 0.062), which is within the bioequivalence limits of (-0.20 and +0.20).

C. Comparative Safety

The safety data submitted in this ANDA confirm that the test product did not cause worse adverse events compared to the reference product in the treatment of AK. Of 318 patients randomized in this study, 273 patients reported skin irritation at the application site, 131 (93%), 136 (96%), and 6 (17%) patients in the test, reference, and vehicle groups, respectively. Skin irritation was evidenced by erythema, redness and dermatitis. Other adverse events not related to skin irritation occurred in 33 patients (15 in the test, 16 in the reference, and 2 in the vehicle group) and most of these events were considered not related to study treatment.

Two patients (#89: Test and 99: Reference) discontinued the study medication due to an adverse event not related to the study treatment. Patient #70 (Test) reported an application site reaction (bleeding on face) and discontinued the study within the first week. Patient #241 (Reference) complained of increasing erythema in the treated area and requested to withdraw from the study within 10 days. This patient was then excluded by the investigator due to non-compliance.

Clinical Review

I. Introduction and Background

Efudex® Topical Cream, 5%, is an antineoplastic metabolite that is approved for topical treatment of actinic or solar keratosis. It is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. For treatment of actinic keratosis, Efudex cream is applied twice daily to the affected area. The approved labeling states that the medication should be continued until the inflammatory response reaches the erosion stage and then terminated. The recommended duration of therapy is 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following discontinuation of Efudex therapy. For treatment of superficial basal cell

carcinoma, the medication should be applied twice daily for at least 3 to 6 weeks. For this indication, the therapy may be required for 10 to 12 weeks before the lesions are obliterated.

The most frequent adverse reactions reported with Efudex cream occur locally and include burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness and ulceration. Ulcerations, other local reactions, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas. Leukocytosis is the most frequent hematologic side effect.

A. Drug Established Name, Drug Class,

Drug Established Name: 5-Fluorouracil Cream 5%
Drug Class: Anti-neoplastic agent

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug (NDA number): Efludex® Cream (NDA 16831), Valeant Pharmaceutical Intl. (formerly known as ICN Pharmaceuticals, Inc.)
Date of approval: 7/29/70
Approved indication(s): Topical treatment of multiple actinic or solar keratoses. It is also useful in the treatment of superficial basal cell cacinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites.
Recommended dosing regimens: For treatment of actinic or solar keratosis, the cream should be applied twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion stage, at which time the use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks but complete healing of the lesions may not be evident for 1 to 2 months following cessation of Efudex therapy.

For treatment of superficial basal cell carcinoma, the cream should be applied twice daily for at least 3 to 6 weeks. The therapy may be required for up to 12 weeks before the lesions are obliterated.

C. Regulatory Background

The following submissions have been reviewed by the OGD for 5-fluorouracil cream:

1. INDs, Protocols, and/or Control Documents submitted by Spear

Submission	Submission date	Name of the Product
P# 99-022	6/4//99	5-fluorouracil cream, 5%
IND#69813	5/6/04	5-fluorouracil cream, 5%
CD# 06-0349	3/9/06 (pending review)	5-fluorouracil, cream, 0.5% ((b) (4) Cream)

2. INDs, Protocols, and/or Control Documents submitted by other sponsors

Submission	Submission date	Name of the Product/Sponsor
CD# 03-151	3/7/03	5-fluorouracil, 5% (b) (4)
CD# 03-043	7/25/03	5-fluorouracil, 5%
IND# (b) (4)	12/10/04	5-fluorouracil, 5%
CD# 05-0727	6/9/05 (pending review)	5-fluorouracil, 5%

3. Previous ANDA submissions for same or related product

None

D. Other Relevant Information

A citizen petition (docket number 2004-P-0057) was submitted by Valeant Pharmaceuticals International (Valeant) on December 21, 2004 that questions the reliability of a single BE study in the treatment of actinic keratosis (AK) given that this product is indicated for treatment of both AK and superficial basal cell carcinomas (sBCC). The petition requests that the FDA refrain from approving an ANDA for a generic version of Efudex Cream, unless the ANDA contains data from an adequately designed comparative clinical study conducted in patients with superficial basal cell carcinomas (sBCC). The response to this citizen petition is currently pending.

II. Description of Clinical Data and Sources

Study Centers/Investigators: The study was performed by a single investigator.

Site	Investigator	Address	Number of patients eligible for randomization
1	Shari Skinner, M.D.	SFBCFM 3745 Broadway, Suite 100, Fort Myers, FL	342

Study Period: June 7, 2004 to September 7, 2004

Enrollment: A total of 318 patients were enrolled into this study (141 in the test, 142 in the reference, 35 in the vehicle group).

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: ANDA 77-524, Vol. 1.1-1.2, submitted on 1/6/05

Study Amendment: On 1/6/06, the sponsor was requested to provide source documents and clarify blinding procedures. The information submitted in the study amendment dated 1/16/06 was adequate to complete the review.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) Report:

A DSI inspection was not requested for this study due to an acceptable inspection history of the same clinical site (ANDA 76-498, Spear's Tretinoin Emollient Cream, 0.05%).

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor declared that the study was conducted according to principles of Good Clinical Practices (GCP), FDA regulations and SFBCFM standard operating procedures reflecting those guidelines/regulations. The sponsor's original protocol and consent forms were reviewed and approved by the IRB prior to initiation of the study.

Reviewer's Comment: *The sponsor's study appears to be in compliance with the accepted ethical standards.*

D. Evaluation of Financial Disclosure: The sponsor submitted a signed financial disclosure document certifying that the principal investigator (Dr. Skinner) has not entered into any financial arrangement with the sponsor that could be affected by the outcome of the study and declared that she has not received significant payment of other sorts as defined in 21 CFR Part 54.

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

The sponsor's study confirms the bioequivalence of the test product with the reference product.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol #SPR00-5FU-01) was reviewed to determine bioequivalence of the test product and the reference product. The primary endpoint of this study is the proportion of patients with complete clearing of actinic keratosis (success) at Week 6 (4 weeks after the end of treatment). The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

Protocol Review (SPR00-5FU-01):

1. The sponsor's original protocol (#P99-022) was submitted on 6/4/99.

2. Following review of Spear's protocol, the OGD asked the sponsor to add a placebo arm in the proposed study design on December 10, 1999. The OGD also asked the sponsor to provide the classification schema for severity of lesions.
3. Spear's letters of 12/27/99, 1/18/00, and 3/1/00 questioned the need for a placebo arm because the study drug is treating a pre-cancerous condition. The sponsor provided literature data to support their ethical concern for the use of a placebo arm in this study.
4. On 6/20/00, the OGD confirmed that a placebo arm is necessary for this study. The OGD recognized that actinic keratosis may develop into squamous cell carcinoma and the treatment is necessary but disagreed with the sponsor regarding the urgency of active intervention. It has been reported that in some instances, actinic keratosis may spontaneously regress.
5. In Spear's letters of 7/4/00, the sponsor stated that they incorporated the FDA comments in their protocol and a placebo arm was also included in their study design.
6. Based on the consult comments received from the Division of Dermatologic and Dental Products (DDDP) for the bioequivalence study design of 5-fluorouracil on December 14, 2003, the OGD notified Spear on January 14, 2004 that patients with known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency should be excluded from the study. The treatment duration was recommended as 2 weeks and the primary endpoint was to be evaluated at Week 6 (4 weeks after the end of treatment). The primary endpoint was defined as the proportion of patients with complete clearing of AK lesions.
7. On January 21, 2004 and February 17, 2004, Spear requested further clarification regarding the duration of treatment and an acceptable treatment compliance rate to be included in the PP population.
8. On March 8, 2004, OGD medical officer responded that 2 weeks duration of treatment is recommended for a bioequivalence study and commented that the sponsor's proposed completion of 70% of the total intended doses of the study drug is an acceptable treatment compliance rate for inclusion in the PP population.
9. Spear filed an IND #69-813 for this study on 5/6/04.
10. Spear's protocol with revision was approved by the IRB on 5/17/04.
11. The first patient was enrolled on 6/7/04.
12. The OGD responded to the sponsor's IND #69-813 on 9/1/04.
13. The sponsor's study was completed on 9/7/04.
14. On October 18, 2004, the OGD Clinical Review Team had a T-con with Spear and clarified the following items regarding the review of IND #69-813: 1) it is acceptable to conduct the stratified randomization as long as the sponsor ensures that they have a balance between all three treatment arms. 2) it is acceptable to have a minimum treatment period of 10 days (70% treatment compliant), 3) the sponsor's proposed minimum lesion count for enrollment may not be adequate to show superiority over the placebo. The DDDP recommended a minimum lesion count of 5 but the sponsor proposed to enroll patients with mild severity (3-6 lesions).
15. The sponsor completed the study report on 12/14/04.

Sponsor's protocol#: SPR00-5FU-01

Title: A Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Clinical Bioequivalence of 5-Fluorouracil (Spear Pharmaceuticals) and Efudex ®

Objectives: The Primary purpose of this study was to evaluate bioequivalence of Efudex® cream, 5%, and Spear Pharmaceutical's 5-fluorouracil cream, 5%. The secondary objective was to assess the statistical superiority of Efudex® Cream and Spear Pharmaceutical's 5-Fluorouracil Cream 5% to Vehicle.

The safety objective was to compare the severity of irritation (as evidenced by erythema, redness and dermatitis) and incidence of adverse events in treated patients in all treatment groups.

Study Design: This was a randomized, double-blind, parallel-group, placebo-controlled study design comparing the following products:

1. Test: Fluorouracil Cream, 5%, Spear Pharmaceuticals Inc., applied topically twice daily for 2 weeks; lot # 4A09A
2. Reference: Efudex® Cream (Fluorouracil), 5%, ICN Pharmaceuticals, applied topically twice daily for 2 weeks; lot # C0273
3. Vehicle/Placebo: Spear's vehicle, applied topically twice daily for 2 weeks; lot # 4A19A

Prior to randomization, the patients were stratified by number of actinic keratoses and gender, and a restricted randomization procedure was employed to balance the treatment group with these stratifying variables. In this restricted randomization procedure, four cells were employed. They were mild female, mild male, moderate female and moderate male. Patients with 3-6 total AK lesions were considered mild and patients with 7-12 total AK lesions were considered moderate.

Blinding:

The test and vehicle creams were supplied to SFBCFM in unlabeled aluminum tubes. Efudex® Cream 5% was purchased commercially. To prevent accidental unblinding by a patient, the customary labeling on tubes of Efudex® Cream 5% was removed. All tubes were then coated with an epoxy covering to blind. Tubes were labeled by SFBCFM in an identical blinded fashion. Upon dispensing, patient number, initials, and date were recorded on the study medication. In order to maintain blinding at SFBCFM, the individuals responsible for patient randomization also labeled and dispensed the study drugs.

At the conclusion of the study, a summary of study drug disposition was provided to the sponsor and all empty containers were returned to the sponsor.

Study Population: Patients at least 45 years of age or older with clinical signs and symptoms of actinic keratosis. Patients who met the following criteria were eligible for the study:

Inclusion Criteria

1. Men and women with the presence of actinic keratosis
2. Aged 45-85 years
3. Women who had surgical sterilization or were post-menopausal (absence of menses for at least one year). Women of child-bearing potential who were non-pregnant and non-nursing, and willing to avoid pregnancy during the course of the study and during the menstrual cycle following completion of their participation in the study (adequate contraception was defined as regular use of condoms, diaphragm, IUD, or systemic contraceptives - if used for at least three months prior to enrollment in the study, or abstinence)
4. Presence of at least 3 total actinic keratosis lesions on the face
5. Able to refrain from the use of all other topical medications to the facial area during the treatment period
6. Considered reliable and capable of understanding their responsibility and role in the study
7. Provided written informed consent

Exclusion Criteria

1. History of allergy or hypersensitivity to 5-fluorouracil
2. Known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency
3. More than 12 lesions total on the face (Lesions that were hyperkeratotic, thicker than 1mm (a piece of paper) or larger than 9 mm, or lesions suspicious for squamous cell carcinoma were not included in lesion counts.)
4. Clinical evidence of severe, uncontrolled auto-immune, cardiovascular, gastrointestinal, hematological, hepatic, neurological, pancreatic, pulmonary or renal disease
5. Abnormal pre-existing dermatologic condition which could have affected the normal course of the disease (e.g., albinism, or chronic vesiculobullous disorders)
6. Positive urine pregnancy test in women of child-bearing potential
7. Serious psychological illness
8. Significant history (within the past year) of alcohol or drug abuse
9. Participation in any clinical research study during the 30 day period preceding study initiation
10. Medical history which, based on the clinical judgment of the investigator, implied an unlikelihood of successful completion of the study
11. Any systemic chemotherapy at least 4 weeks before study
12. Treatment for actinic keratoses in last month with topical 5-fluorouracil
13. Use of sun lamps or sun tanning beds or booths during the 2 weeks prior to first application until Day 42 visit

Criteria for discontinuation of study:

Patients were discontinued from the study after randomization for any of the following reasons:

- Adverse reaction, including drug-induced irritation of such severity that the patient stopped use of the study drug before completing 2 weeks of treatment
- Non-compliant with study requirements
- Decision by the patient not to continue
- Judgment by the investigator that it was not in the patient's best interest to continue

Dropouts were not replaced.

Treatment Compliance

Patients were to apply at least 75% to 125% of the expected 28 applications (21 to 35 applications) of study medication to be considered compliant with the treatment regimen. Treatment compliance was verified by use of the patient diaries.

The study tubes were weighed and recorded in a dispensing log by study staff. At the conclusion of the study, patients were asked to return their unused study medication to be returned to the sponsor.

Reviewer's Comment: *Patients who applied a minimum of 21 (75%) and up to 33 (118%) applications were considered treatment compliant and included in the sponsor's analysis.*

Procedures/Observations, and safety measures:

The following procedures were scheduled in this study:

		Visits			
Procedures		**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
	Day -21 to 0	**Day 0**	**Day 7**	**Day 14**	**Day 42**
Screening/informed consent	X				
Comprehensive medical history	X				
Review of Inclusion/Exclusion	X	X			
Pregnancy tests	X				X
Physician evaluation for irritation			X	X	X
Physician evaluation for AK		X			X
Study materials dispensed		X	X	X	
Study materials retrieved			X	X	
Photo-documentation		X			
Diary explanation, review retrieval		X	X	X	
Review con med, AEs compliance		X	X	X	X

Screening may have been performed within 21 days of study enrollment, but could have been combined with Day 0 randomization visit

Screening (-21 to day 0) and Visit 1

The following procedures were performed prior to treatment application:

- Reviewed inclusion/exclusion criteria
- Completed medical history
- Women of childbearing potential performed pregnancy test
- Patients had to complete a 4-week wash-out period if they were treated with any systemic or topical chemotherapeutic agent.
- The face of each patient was examined. The face area were defined from hair line to jaw line. The scalp was not included; an imaginary normal hair line was the upper boundary for bald men.
- All actinic keratoses of the face were counted by the investigator.
- Actinic keratoses of the face was circled in ink and the face was photographed. A copy of the photograph was given to the patient to help identify where to apply the medication

as instructed by the investigator. The baseline photograph was used at the final visit to allow the investigator to accurately compare exactly all the keratoses treated to determine if they were clear, or still present.

- The study medication and diary were dispensed. Patients were instructed to follow all instructions provided.
- The study medication was weighed.

Visit 2 (day 7 +/- 2 days),Visit 3 (day 14 +/- 2 days), and Visit 4 (day 42 +/- 4 days)

- The face of each patient was examined.
- All actinic keratoses of the face were counted on Visit 1 and Visit 4 only.
- Treatment compliance was verified by the use of the patient diaries.
- Skin irritation (as evidenced by erythema, redness and dermatitis) was evaluated at the end of 1 and 2 weeks of treatment, and at the week 6 visit using the following scale.

  0=none
  1=mild
  2=moderate
  3=severe

  Mild, moderate and severe were to be graded consistent with the photographic gallery provided by the sponsor. Patients who had lesions still present at the last visit were advised to see a dermatologist or their general medical doctor for further therapy.

- Patients were instructed to return the study medication and diary at the end of visit 4.
- Patients were questioned concerning possible adverse events and compliance with the protocol. Any adverse events or changes to concomitant medications were documented.

Endpoints:

The primary endpoint was the proportion of patients with complete clearing (success) of AK lesions at week 6 (4 weeks after the end of treatment). Clearing of actinic keratosis lesions was defined as either no evidence of the lesion, or only residual smooth flat redness present without elevation above the skin. Partially cleared lesions were counted as still present in the final count.

Statistical analysis plan

Primary Endpoint: The primary endpoint is the proportion of patients who experience complete clearing (success) of AK lesions at week 6. The sponsor performed descriptive statistics for the proportion of patients with complete clearing of all lesions for each treatment group at week 6 in both the ITT and PP Populations.

Sample Size: The sponsor proposed 152 patients randomized to each active treatment and 38 to the vehicle (4:4:1 ratio). This sample size was proposed based on the sponsor's estimated

calculation of cure rate of 50% for the active treatment groups. A total of 318 patients were randomized into this study.

Analysis: For the bioequivalence analysis, a confidence interval was constructed for the difference in cure rates between the test and the reference products at the week 6 visit. If the 90% confidence limits, using Yate's continuity correction, were within -0.20 and +0.20, the test was considered therapeutically equivalent to the RLD. To ensure that the study was sensitive enough to show a difference between products, the test and reference products were evaluated for their statistical superiority to vehicle cream with regard to the success rate at Week 6, using the ITT study population. The Fisher's Exact test of proportions was used to compare each of the active products against vehicle cream.

Additional descriptive statistics were performed for the percent of lesions cleared for each treatment group at Week 6. The summary was presented for both the ITT and PP Populations.

Demographic characteristics were summarized with descriptive statistics to assess the comparability of the treatment groups.

Study Conduct
Discussion of Safety, ITT and PP populations:

Three analysis populations were defined by the sponsor as follows:

The safety population: all patients enrolled in the study and dispensed study medication.
The intent-to-treat (ITT) population: all patients who were randomized, applied at least one dose of study medication, and returned for at least one post-baseline visit. The ITT population was used in the analysis of superiority.
The per-protocol (PP) population consisted of all patients who:

- applied at least 75 % to 125% of the expected 28 applications (21 to 35 applications). Compliance was verified by the use of the patient diaries.
- discontinued the trial due to a lack of treatment effect.
- completed the final evaluation visit within the designated visit window of 6 weeks (±4 days).
- did not have significant protocol violations that could affect the clinical evaluations such as use of a concomitant medication.

Patients discontinued due to severe irritation were not included in the per-protocol population. Patients discontinued for other reasons (all adverse events) were excluded from the PP population but included in the ITT Population. The per-protocol population was used in the analysis of bioequivalence. Every attempt was made to obtain a final lesion count. Last Observation Carried Forward (LOCF) was used to impute efficacy data (lesion counts) which were missing subsequent to the baseline evaluation.

Reviewer's Comment: *Since lesion counts (efficacy data) were collected at baseline and final visits only, patients missing the final lesion count should be excluded from the PP population.*

Retention of Reserve Samples:

Since detailed explanation for retention sample procedure was not provided in the study report, this reviewer asked the sponsor to provide information regarding the selection of reserved samples. The sponsor responded in the study amendment dated 1/16/06 that the reserved samples were selected randomly from each treatment group.

Demographics

Of the 318 treated patients, 316 (99%) were Caucasian, 1 (1%) was Hispanic, and 1 (1%) was classified as "American Indian/Alaska Native". Baseline demographics, age, and race in the Safety population were similar in all treatment groups. The demographic characteristics for all treated patients are tabulated by the sponsor in Table I.

Table I: Demographic Characteristics for 318 treated patients (per sponsor)

Characteristic		Spear (N=141)	RLD (N=142)	Vehicle (N=35)	P-value
Race	Caucasian	140 (99%)	141 (99%)	35 (100%)	0.791[a]
	Black	0 (0%)	0 (0%)	0 (0%)	
	Hispanic	1 (1%)	1 (1%)	0 (0%)	
	American Indian/Alaska Native	0 (0%)	0 (0%)	0 (0%)	
Age (years)	Mean (Std)	66.89 (10.8)	67.79 (9.68)	63.71 (10.26)	0.109[b]
	Min - Max	45.5-85.3	46.5-84.1	46.5-82.9	
Gender	Male	95 (67%)	94 (66%)	23 (66%)	0.970[b]
	Female	46 (33%)	48 (34%)	12 (34%)	
Lesion Count	Mean (Std)	7.50 (3.01)	7.45 (2.87)	7.63 (3.49)	0.951[a]
	Range	3.0-12.0	3.0-12.0	3.0-12.0	

[a] P-value from a one-way analysis of variance with factor of treatment group.
[b] P-value from a likelihood ratio test. For the variable race, the p-value was calculated after combining the following categories: Black/African American, Hispanic, American Indian/Alaska Native, and Other.

Baseline disease severity

The sponsor tabulated the mean AK lesion count at baseline and Week 6 for the sponsor's ITT and PP populations in Table II. The mean number of AK lesions at baseline was similar in all treatment groups for the sponsor's ITT population.

Table II: Summary of Lesions at baseline in the ITT and PP populations (per sponsor)

	ITT			**PP**		
Number of patients	**Spear N=138**	**RLD N=142**	**Vehicle N=33**	**Spear N=130**	**RLD N=135**	**Vehicle N=32**
Number of lesions (Std)	**7.4 (3.0)**	**7.5 (2.9)**	**7.8 (3.5)**	**7.5 (3.0)**	**7.4 (2.9)**	**7.7 (3.4)**
Range	**3.0-12.0**	**3.0-12.0**	**3.0-12.0**	**3.0-12.0**	**3.0-12.0**	**3.0-12.0**

Reviewer's Comment: *The lesion counts at baseline in the sponsor's ITT population were similar in all treatment groups.*

Results

Of 318 patients randomized, 21 patients were excluded from the sponsor's PP population due to non-compliance. A total of 313 patients were included in the sponsor's ITT population.

The distribution of patients per treatment arm for each analysis population is shown in Table III. Table IV shows the sponsor's efficacy outcome analysis for the per protocol (PP) population.

Table III: Patient Disposition (per sponsor)

	SPEAR	RLD	VEHICLE	ALL
Safety Population All randomized patients	**141**	**142**	**35**	**318**
Exclusions:				
Did not return for any post-baseline visit/Did not apply study medication	3	0	2	5
Intent-to-Treat Population (all eligible randomized patients)	138	142	33	313
Exclusions:				
Day 42 off schedule	4	4	0	8
Non-dosing compliant	3	2	1	6
Missing day 42	1	1	0	2
Per Protocol Population	**130**	**135**	**32**	**297**

Table IV: Primary Efficacy Analysis: Proportion of patients with complete clearing of Actinic Keratosis at Week 6 (per sponsor)

Parameter	SPEAR	RLD	90% C.I. for Bioequivalence of Spear's product to Efudex® Cream 5%		
Per-Protocol Patients					
Number of Patients	130	135			
Clinical Response at Week 6					
Success (100% Clear)	113 (87%)	119 (88%)	(-0.087, 0.062)		
Failure (<100% Clear)	17 (13%)	16 (12%)			
Intent-to-Treat Patients					
	SPEAR	RLD	Vehicle	P-Value from a Fisher's Exact test	
Number of Patients	138	142	33	T vs. Vehicle	Ref vs. Vehicle
Clinical Response at Week 6					
Success (100% Clear)	117 (85%)	120 (85%)	2 (6%)	<0.001	<0.001
Failure (<100% Clear)	21 (15%)	22 (15%)	31 (94%)		

Reviewer's comments: *Patients with no post baseline AK lesion count were excluded from the FDA analyses.*

D. Bioequivalence Conclusion

Based on the FDA's statistical analyses, the study demonstrates that the 90% CI of the difference in success rate between the test and the reference products at the Week 6 (4 weeks post treatment) is (-0.087, 0.062), which is within the bioequivalence limits of (-.20, +.20). A patient was considered a success by the sponsor if the baseline AK lesions were completely cleared (100%) at Week 6.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed no significant difference between the generic and reference products with regard to the adverse events reported.

B. Description of Adverse Events

No death occurred in the study. Skin irritation, evidenced by erythema and dermatitis, was reported in 131 (93%), 136 (96%), and 6 (17%) patients in the test, reference, and vehicle groups, respectively. At the end of one week of therapy, three patients (#59, 89, 280) in the test group and none in the reference or placebo group had skin irritation that was severe. At the end of two weeks of therapy, five patients (#156, 169, 203, 249, 280) in the test group and two patients (#130, 206) in the reference group had skin irritation that was severe. By day 42, all patients reported mild or no skin irritation.

Other adverse events (15 in the test, 16 in the reference, and 2 in the vehicle group) not related to skin irritation occurred in 33 patients. Most of these events in the two active treatment groups were mild (53% and 81% for the test and reference group) while the 2 events reported in the vehicle group were moderate in severity. Five (33%) events in the test group and 2 (13%) events in the reference group were reported as severe but, none of these events were considered study treatment related.

Two patients (#89: Test and #99: Reference) discontinued the study medication due to adverse event not related to the study treatment. Patient #70 (Test) reported an application site reaction (bleeding on face) and discontinued the study within the first week. Patient #241 (Reference) reported increasing erythema in the treated area and was discontinued by the investigator due to treatment non-compliance.

The sponsor's summary of skin irritation events are shown below.

Skin irritation evaluation scale: 0=none, 1=mild, 2=moderate, 3=severe
(Safety Patients)

	5-Fluorouracil Cream 5%	Efudex® Cream	Vehicle Cream
Week 1			
N	136	142	32
Mean	1.3	1.2	0.2
STD	0.7	0.6	0.4
Range	0.0-3.0	0.0-2.0	0.0-1.0
Week 2			
N	137	141	33
Mean	1.7	1.6	0.1
STD	0.6	0.6	0.3
Range	0.0-3.0	0.0-3.0	0.0-1.0
Week 6			
N	137	140	33
Mean	0.0	0.0	0.0
STD	0.2	0.2	0.0
Range	0.0-1.0	0.0-1.0	0.0-0.0
Maximum Intensity [a]			
N	139	142	33
Mean	1.7	1.7	0.2
STD	0.6	0.6	0.4
Range	0.0-3.0	0.0-3.0	0.0-1.0

		Pairwise Comparisons [b]		
	Overall Treatment Effect	5-Fluorouracil versus Efudex®	5-Fluorouracil versus Vehicle	Efudex® versus Vehicle
Week 2	<0.001	0.236	<0.001	<0.001

[a] Maximum intensity represents the greatest severity reported by a patient during participation in the study regardless of time period reported.
[b] P-Value from an analysis of covariance with factor of treatment and baseline lesion count as a covariate.

The sponsor's summary of frequency of other adverse events, not including skin irritation, is listed below.

Safety Population		**5-Fluorouracil Cream 5%**	**Efudex® Cream**	**Vehicle Cream**
Number of Patients		141	142	35
Number of Events Reported		15	16	2
Number of Patients Reporting One or More Events		11 (8%)	12 (8%)	2 (6%)
Serious	No	10 (67%)	16 (100%)	2 (100%)
	Yes^	5 (33%)	0 (0%)	0 (0%)
Severity	Mild	8 (53%)	13 (81%)	0 (0%)
	Moderate	2 (13%)	1 (6%)	2 (100%)
	Severe	5 (33%)	2 (13%)	0 (0%)
Relationship To Study Drug				
	Not Related	9 (60%)	6 (38%)	2 (100%)
	Unlikely	2 (13%)	2 (13%)	0 (0%)
	Possible	0 (0%)	4 (25%)	0 (0%)
	Probable	3 (20%)	4 (25%)	0 (0%)
	Definite	1 (7%)	0 (0%)	0 (0%)

Body Systems [a]			
Body as a Whole	5 (4%)	4 (3%)	2 (6%)
Abdominal pain	1 (1%)	0 (0%)	0 (0%)
Accidental injury	0 (0%)	0 (0%)	1 (3%)
Allergic Reaction	0 (0%)	0 (0%)	1 (3%)
Asthenia [b]	1 (1%)	0 (0%)	0 (0%)
Chest pain [b]	1 (1%)	0 (0%)	0 (0%)
Face edema	1 (1%)	3 (2%)	0 (0%)
Flu syndrome	0 (0%)	1 (1%)	0 (0%)
Headache	1 (1%)	0 (0%)	0 (0%)
Digestive System	2 (1%)	1 (1%)	0 (0%)
Constipation	1 (1%)	0 (0%)	0 (0%)
Diarrhea	1 (1%)	1 (1%)	0 (0%)

[a] Counts reflect numbers of patients in each treatment group reporting one or more adverse events that map to the COSTART body system. At each level of summarization (body system or event) patients are only counted once. Percentages of patients in each treatment group are also given.
[b] Serious adverse event
^unrelated to the study drug: dyspnea, asthenia, chest pain, epistaxis

Reviewer's Comment: *The reported frequency of skin related adverse events in this study is comparable between the test and reference groups. Several patients experienced severe application site skin irritation (5 test, 2 reference) at the end of the study treatment but by the end of week 6, the severity of skin irritation was none to mild as expected.*

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of the Division of Scientific Investigation (DSI) Report

A DSI inspection was not requested for this study due to a previously acceptable inspection history of other study (ANDA 76-498, Spear's Tretinoin Emollient Cream, 0.05%) at the same clinical site with the same principal investigator. No FDA Form 483 was issued at the previous inspection of this site.

B. Review of the FDA Statistical Report (November 7, 2006)

The conclusion of the FDA statistical analysis confirms the bioequivalence of the test and the reference products. The 90% CI of the difference in success rate between the test and the reference products at Week 6 (4 weeks post treatment) is (-0.087, 0.062), which is within the bioequivalence limits of (-.20, +.20). Both the test and the reference products showed superiority over the placebo group at Week 6.

Four patients (test: 70, 89, reference: 99, 316) were excluded from the FDA ITT (FITT) population analysis by the FDA statistician. These patients did not have any post baseline efficacy data due to missing Day 42 visit (visit 4). No patient adjustment was needed from the sponsor's PP population.

The FDA statistician provided the summary of the equivalence test for the per protocol population and efficacy analyses for the FDA ITT (FITT) population as follows:

Primary Endpoint: Complete Clearing of AK at visit 4 (Day 42)

Equivalence Analyses for the Proportion of Patients with Complete Clearing of AK at Visit 4 (week 6)

Population	Test[a] % successes (No. of successes /total)	Reference[a] % successes (No. of successes /total)	Placebo[a] % successes (No. of successes /total)	p-value[b] for Test vs. Placebo	p-value[b] for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
PP	86.923 (113/130)	88.148 (119/135)	6.250 (2/32)			-8.659, 6.208	Yes
FITT*	86.029 (117/136)	85.714 (120/140)	6.061 (2/33)	< 0.001	< 0.001	-7.308, 7.938	Yes

[a]The rate of success equals the number of successes divided by the total number, then multiplied by 100.
[b]The p-values are from Fisher's exact test (2 sided).
*FDA Intent-to-Treat population (FITT) – Includes all randomized subjects who were diagnosed with AK , received at least one dose of study medication and returned for an assessment at visit 4 (week 6).

The FDA statistician also tabulated the skin irritation scores reported at the application site at Visit 2 (week 1), Visit 3 (week 2), and Visit 4 (week 6) for the FITT population. The frequency of the irritation scores reported by the sponsor is summarized as follows:

Frequency of the Irritation Scores by Treatment for the FITT population

	Fluorouracil	Efudex®	Placebo
Irritation Score			
Visit 2 (week 1)			
0	12	18	27
1	70	77	5
2	50	45	0
3	2[a]	0	0
Visit 3 (week 2)			
0	8	6	29
1	30	43	4
2	93	89	0
3	5[b]	2[c]	0
Visit 4 (week6)			
0	130	134	33
1	6	6	0

Skin irritation evaluation scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe
[a] patients 59, and 280
[b] patients 156, 169, 203, 249 and 280
[c] patients 130 and 206

Reviewer's Comment: *The FDA statistical analysis confirms the bioequivalence of the test and the reference products. The skin irritation scores were similar in the test and reference groups at each visit (p>0.05) per FDA statistical review. Five patients experienced severe application site skin irritation at the end of the test study treatment (visit 3) compared to three patients in the*

reference group. By the end of week 6, the severity of skin irritation was none to mild in both treatment groups as expected.

VII. Formulation

Formulation Comparison

Component	Spear formulation /Quantity (%w/w)	RLD formulation*/Per gram
Fluorouracil, USP	5.00	(b) (4)
Purified Water, USP	(b) (4)	
Propylene Glycol, USP		
White Petrolatum, USP		
Polysorbate 60, NF		
Stearyl Alcohol, NF		
Cetyl Alcohol, NF		
Methylparaben, NF		
Propylparaben, NF		
Total weight	**	1000.0

*Per medical officer's Summary Basis of Approval of the NDA 16-831 (Medical officer's review dated 3/18/69), Efudex® Cream, 5%.

** The sponsor states that inactive ingredient concentration differences of ± % from the target weights are considered reasonable for this formula.

On December 7, 2006, Spear provided additional information characterizing the different inactive ingredients in the formulation and explained why the differences are not expected to cause more irritation or different adverse events compared to the reference product.

Spear's formulation includes one ingredient, Cetyl Alcohol, that is not included in the RLD formulation. In addition, the amounts of purified water and polysorbate 60 are more than (b) (4) (b) (4) than in the RLD, and the amounts of white petrolatum, stearyl alcohol, methylparaben, and propylparaben are more than (b) (4) than in the RLD.

Spear has explained that they made every effort to make the formulation Q/Q same as that of the RLD. However, they made over (b) (4) batches at a respected lab with experienced cream formulators, and they became pourable within 3 days. The cetyl alcohol was (b) (4) (b) (4). Spear explained that the combination of stearyl alcohol with cetyl alcohol is used in many cream formulations (b) (4) The (b) (4) % cetyl alcohol content of the product is below the highest level (12%) found in approved drug products for the topical route of administration.

Cetyl Alcohol

Spear provided a reference from Fisher's Contact Dermatitis, fourth Edition, p. 292. This reference includes a table of two studies, including a total of 1939 subjects that were patch tested with both stearyl alcohol and cetyl alcohol among other test articles, and none had an irritation or sensitization reaction to either stearyl or cetyl alcohol.

According to the *Handbook of Pharmaceutical Excipients, 5th edition*, p.151:

Cetostearyl Alcohol is used in the preparation of nonaqueous creams and sticks. It has been used to slow the dissolution of water-soluble drugs. It is generally regarded as non-toxic. It is essentially nonirritating, but rare sensitization reactions have been reported.

According to the *Handbook of Pharmaceutical Excipients, 5th edition,* p.155:
Cetyl Alcohol is used to raise the melting point of the base, and in modified-release dosage forms it may be used to form a permeable barrier coating. In lotions, creams, and ointments cetyl alcohol is used because of its emollient, water-absorptive, and emulsifying properties. It enhances stability, improves texture, and increases consistency. Cetyl alcohol has been associated with allergic delayed-type hypersensitivity reactions in patients with stasis dermatitis. Cross-sensitization with cetostearyl alcohol, lanolin, and stearyl alcohol has also been reported. Highly refined cetyl alcohol has not been associated with hypersensitivity reactions.

Polysorbate 60
According to the *Handbook of Pharmaceutical Excipients, 5th edition,* pp. 580-584:
Polysorbates are used as emulsifying agents, nonionic surfactants, solubilizing agents, and wetting, dispersing/suspending agents. They are widely used in cosmetics, food products, and oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. There have, however, been occasional reports of hypersensitivity to polysorbates following their topical and intramuscular use. They have also been associated with serious adverse effects, including some deaths, in low-birthweight infants intravenously administered a vitamin E preparation containing a mixture of polysorbates 20 and 80.

White petrolatum
According to the *Handbook of Pharmaceutical Excipients, 5th edition,* p.509:
Petrolatum is mainly used in topical pharmaceutical formulations as an emollient-ointment base. It is poorly absorbed by the skin. It is also used in creams and transdermal formulations and as an ingredient in lubricant formulations for medicated confectionery together with mineral oil. It is generally considered to be a nonirritant and nontoxic material. Rare instances of allergic hypersensitivity reactions have been reported.

Stearyl alcohol
According to the *Handbook of Pharmaceutical Excipients, 5th edition*, p.740:
Stearyl alcohol is used in cosmetics and topical pharmaceutical creams and ointments as a stiffening agent. By increasing the viscosity of an emulsion, it increases its stability. Stearyl alcohol also has some emollient and weak emulsifying properties and is used to increase the water-holding capacity of ointments, e.g., petrolatum. In addition, stearyl alcohol has been used in controlled-release tablets, suppositories, and microspheres. It has also been investigated for use as a transdermal penetration enhancer. It is generally considered to be an innocuous, nontoxic material. However, adverse reactions including contact urticaria and hypersensitivity reactions, have been reported.

Methylparaben
According to the *Handbook of Pharmaceutical Excipients, 5th edition*, p.466:

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations (Oral and topical). It is effective over a wide pH range and has a broad spectrum of antimicrobial activity, although it is most effective against yeasts and molds. It is generally regarded as being unsuitable for injections and ophthalmic preparations due to its irritant potential.

Propylparaben
According to the *Handbook of Pharmaceutical Excipients, 5th edition*, p.631:
Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. Its characteristics are similar to those of methylparaben.

Reviewer's Comments: *Given the above information regarding the known characteristics and function of each of the inactive ingredients that are present in different amounts than in the RLD, along with a similar safety and efficacy profile in the clinical endpoint study, the differences in inactive ingredients are acceptable.*

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA 77-524 demonstrate that Spear Pharmaceuticals Inc.'s Fluorouracil Cream, USP 5%, is bioequivalent to the reference listed drug, Efudex® Topical Cream, 5%. The FDA statistical review concludes that the 90% CI of the difference in success (complete clearance of AK lesions) rates between the test and reference products at the 4-week follow-up visit (Visit 4, Week 6) is (-0.087, 0.062) which is within the bioequivalence limits of (-.20,+.20). The test and reference products also demonstrate superiority over Placebo at Week 6.

B. Recommendations to be conveyed to Sponsor

The data submitted to ANDA 77-524, using the primary endpoint of success rate at Week 6 (4 weeks post treatment), are adequate to demonstrate bioequivalence of Spear Pharmaceuticals, Inc.'s Fluorouracil Cream, USP, 5%, with the reference listed drug, ICN Pharmaceuticals, Inc.'s (currently known as Valeant Pharmaceuticals Intl.) Efudex® 5% Cream. Both the test and the reference products showed superiority over placebo at Week 6.

_____ _____

Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date

_____ _____

Dena Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Date

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:77-524 APPLICANT: Spear Pharmaceuticals, Inc.

DRUG PRODUCT: Fluorouracil Cream, USP, 5%

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

The data submitted to ANDA 77-524, using the primary endpoint of success rate at Week 6 (4 weeks post treatment) (Visit 4), are adequate to demonstrate bioequivalence of Spear Pharmaceuticals, Inc.'s Fluorouracil Cream, USP, 5%, with the reference listed drug, ICN Pharmaceuticals, Inc.'s (currently known as Valeant Pharmaceutical Intl.) Efudex® 5% Cream. Both the test and the reference products showed superiority over the placebo at Week 6.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

ANDA 77-524

Applicant Contact Information from 356h Forms:
Name: Robert V. Sarrio-Vice President
Phone number: (321) 543-7039
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BIOEQUIVALENCY - ACCEPTABLE

submission dates:
January 6, 2005
January 16, 2006

1. Bioequivalence Study (STU); January 6, 2005 **Strengths: 5%**
Outcome: AC

2. Study Amendment (STA); **Strengths: 5%**
Outcome: AC

January 16, 2006 (source documents)

Please note: This review should close the BCE and BST assignments.

Outcome Decisions: **AC** - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable

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

/s/

Carol Y. Kim
3/30/2007 11:28:04 AM
BIOEQUIVALENCE CLINICAL END POIN

Dena Hixon
3/30/2007 01:15:24 PM
MEDICAL OFFICER

Dale Conner
3/30/2007 02:05:28 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

STATISTICAL REVIEW

ANDA 77-524
Drug Product: Fluorouracil Cream, USP 5%
Sponsor: Spear Pharmaceuticals, Inc.
Reference Listed Drug: Efudex® 5% Topical Cream, ICN Pharmaceuticals
Submission dates: 1/6/2005
1/16/2006

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Reviewer: Fairouz Makhlouf, Ph.D., DB6/OB/CDER
Requestor: Carol Kim, Pharm.D., OGD/CDER, 03/01/2006

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Spear Pharmaceuticals, Inc., Fluorouracil Cream, USP 5% and the reference product, ICN Pharmaceuticals, Efudex® 5% Topical Cream in the treatment of Actinic Keratosis (AK). The secondary objective was to assess the superiority of the two active treatments to the placebo, a cream Placebo.

Remarks

The sponsor submitted SAS datasets to the Electronic Document Room (EDR), CDER on December 22, 2004 and August 11, 2005. The statistical analyses used information from the **following datasets: 'puredata.xpt', 'comply.xpt', 'cmed.xpt', 'terminat.xpt', 'demo.xpt', 'deviate.xpt'.**

Of the 318 subjects enrolled, 5 were excluded by the **sponsor to result in the sponsor's ITT** population. A further 4 subjects (numbers 70 and 89 in the test treatment group, 99 and 316 in the reference treatment group) were excluded by the FDA medical and statistical reviewers to **result in the FDA's Intent-to-Treat** population (FITT). These 4 subjects missed the Day 42 visit (Visit 4)[1]. **The sponsor's PP population comprised** the ITT population minus seventeen **subjects. The FDA's Per Protocol** population (FPP) was in fact **identical to the sponsor's PP** population for this trial. See details in Table 1, page 5.

Study Design

This was a 3 arm double-blind, randomized, single center, parallel-group study in patients with signs and symptoms of Actinic Keratosis. The three creams were the test product Spear Pharmaceuticals, Inc., Fluorouracil Cream, USP 5%, the reference product, ICN Pharmaceuticals, Efudex® 5% Topical Cream, and the placebo, a cream vehicle.

[1] This study had four visits, visit 1 (enrollment), visit 2 and visit 3 (safety and compliance assessment), and visit 4 (safety and efficacy).

A total of 318 patients with presence of AK were enrolled and randomized in a 4:4:1 ratio to receive the test, reference or placebo product twice daily for 2 weeks.

At the enrollment visit (Visit 1), patients who were at least 45 years of age with clinical signs and symptoms of AK and who met the eligibility criteria were enrolled in the study. Those patients were instructed to apply the cream twice a day for 2 weeks. The number of actinic keratoses on the face was counted.

At visit 2 (day 7 +/- 2 days) and visit 3 (day 14 +/- 2 days) skin irritation[2] (as evidenced by erythema, redness and dermatitis) was evaluated. Adverse events and compliance with the protocol were questioned and documented.

At visit 4 (day 42 +/- 4 days) all actinic keratoses of the face were counted. Study medication and patient's diary were to be returned at this visit. Skin irritation (as evidenced by erythema, redness and dermatitis) was evaluated. Adverse events and compliance with the protocol were questioned and documented.

Outcome Variables

Primary Endpoint

The primary endpoint is the proportion of patients who had 100% clearance of the lesions identified at baseline at the 6 week visit (Visit 4). A cleared actinic lesion was defined as either no evidence of the lesion, or only residual smooth flat redness present without elevation above the skin. Partially cleared lesions were counted as still present in the final count.

Statistical Analysis Methods

Efficacy Analysis

All treatment arms should be similar for signs/symptoms scores at the enrollment visit.

The efficacy analyses for the proportion of patients who had 100% clearance of the lesions identified at baseline were carried out by using Fisher's exact test (two-sided) for each active treatment versus placebo with two-sided significance level of $\alpha = 0.05$.

The active treatment should have been more distinguishable from placebo as the study progressed.

[2] Skin irritation was evaluated using the following scale: 0 = none, 1 = mild, 2=moderate and 3=severe.

Equivalence Analysis

Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -0.20 to 0.20 in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$

or $p_T - p_R > 0.20$

versus

H_A : $-0.20 \leq p_T - p_R \leq 0.20$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment

Let n_T = sample size of test treatment n_R = sample size of reference treatment

and $se = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}$

The 90% confidence interval for the difference in proportions between test and reference was **calculated as follows, using Yates' correction:**

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

Analysis Populations

Two populations are evaluated for efficacy and equivalence:

- **FDA Intent-to-Treat population (FITT) – Includes** all randomized subjects who were diagnosed with AK, received at least one dose of study medication and returned for an assessment at the week 6 visit (Visit 4).

- **Per Protocol population (PP) – Includes all** randomized subjects who were diagnosed with AK , received at least one dose of study medication with the following additional criteria
  - Applied at least 75% to 125% of the expected 28 applications (21 to 35 applications).
  - Discontinued the trial due to lack of efficacy. Those subjects are considered as a treatment failure (In this study no one was discontinued from the trial due to lack of efficacy).
  - Completed the final evaluation visit within the designated window of 6 weeks (± 4 days).
  - Did not have significant protocol violations that could affect the clinical evaluations, such as use of concomitant medication.
  - Were evaluable for the analyses based on the protocol and FDA medical and statistical **reviewers' best judgment.**

The sponsor's PP Population and the FDA PP population were identical in this study.

According to the FDA medical reviewers, the determination of bioequivalence of the Test and the Reference products is to be assessed using the sponsor**'s PP population, while the** superiority comparison of the two active treatments to placebo is to be assessed using the **FDA's Intent-To-Treat population (FITT).**

Statistical Analysis Results

A total of 318 patients were enrolled. The PP population (both sponsor and FDA) included 297 patients and the FITT included 309. Table 1 presents the number of patients in each population per treatment arm.

Table 1 Number of Patients in the PP[a], Sponsor's ITT and FITT Populations

	Total	Fluorouracil	Efudex®	Placebo
Enrollment	**318**	**141**	**142**	**35**
Total sponsor ITT population	313	138	142	33
Total exclusions from the sponsor's ITT population	5	3	0	2
Reason for exclusion from ITT				
Did not apply at least one dose	4	2	0	2
Did not return for any post-baseline visit	1	1	0	0
Total FDA ITT population	309	136	140	33
Total exclusions from FITT population	9	5	2	2
Reason for exclusion from FITT				
Did not apply at least one dose	4	2	0	2
Did not return for any post-baseline visit	1	1	0	0
Did not return for visit 4 (day 42)	4	2	2	0
Total PP population[a]	297	130	135	32
Total Exclusions from PP population	21	11	7	3
Reason for exclusion from PP				
Did not apply at least one dose	4	2	0	2
Did not return for any post-baseline visit	1	1	0	0
Did not return for visit 4 (day 42)[b]	4	2	2	0
Visit 4 (day 42) off-Schedule	8	4	4	0
Non-dosing compliant[b]	6	3	2	1

[a] **Sponsor's PP population is the same as FDA's PP population**

[b]Subjects 70 and 99 were excluded from the PP population for being Non-dosing compliant and also because they did not return for visit 4 (day 42). **For this reason, the counts under "Reason for exclusion from PP" do not add up to the "Total exclusions from PP population" counts.**

Demographics and baseline

Table 2 below tabulates the baseline characteristics for the FITT population. Age, race and gender were comparable among the treatment groups for the FITT population. Table 3, page 6 gives the mean lesion count at baseline for both the FITT and the PP population. There were no statistically significance differences between treatment groups for the lesion counts at baseline in the FITT and the PP populations. Age and lesion count were analyzed using a general linear model with treatment as a factor. Gender was analyzed using a Chi-square test.

Table 2 Demographic Characteristics in the FITT Population

	Fluorouracil	Efudex®	Placebo	Total
Gender				
Female	46	46	12	104
Male	90	94	21	205
Race				
Caucasian	135	139	33	307
Hispanic	1	0	0	1
American Indian / Alaska Native	0	1	0	1
Age				
Mean (Std)	66.26 (10.75)	67.24 (9.73)	63.94 (68.50)	66.45 (10.25)
Range	45.0-85.0	46.0-84.0	46.0-82.0	45.0-85.0
Lesion Count				
Mean (Std)	7.42 (2.98)	7.48 (2.88)	7.85 (3.47)	7.49 (2.98)
Range	3.0-12.0	3.0-12.0	3.0-12.0	3.0-12.0

Table 3 Summary of Lesion count at baseline in the FITT and the PP[a] Population

	Fluorouracil	Efudex®	Placebo	Total
Lesion Count FITT				
N	136	140	33	309
Mean (Std)	7.42 (2.98)	7.48 (2.88)	7.85 (3.47)	7.49 (2.98)
Range	3.0-12.0	3.0-12.0	3.0-12.0	3.0-12.0
Lesion Count PP				
N	129	134	32	297
Mean (Std)	7.46 (2.97)	7.42 (2.87)	7.72 (3.44)	7.47 (2.97)
Range	3.0-12.0	3.0-12.0	3.0-12.0	3.0-12.0

[a] **Sponsor's PP population is the same as FDA's PP population**

Efficacy and Equivalence Analyses

Primary endpoint: The proportion of patients with complete clearing of AK at week 6 (Visit 4). A cleared actinic keratosis lesion was defined as either no evidence of the lesion, or only residual smooth flat redness present without elevation above the skin. Partially cleared lesions were counted as still present in the final count.

Table 4 Efficacy and Equivalence Analyses for the Proportion of Patients with Complete Clearing of AK at Visit 4 (week 6)

Population	Test[a] % successes (No. of successes /total)	Reference[a] % successes (No. of successes /total)	Placebo[a] % successes (No. of successes /total)	p-value[b] for Test vs. Placebo	p-value[b] for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
PP	86.923 (113/130)	88.148 (119/135)	6.250 (2/32)			-8.659, 6.208	Yes
FITT	86.029 (117/136)	85.714 (120/140)	6.061 (2/33)	< 0.001	< 0.001		

[a]The rate of success equals the number of successes divided by the total number, then multiplied by 100.
[b]The p-values are from Fisher's exact test (2 sided).

The equivalence test passed for the PP for the proportion of patients with complete clearing of AK at week 6 (Visit 4). Also, using Fisher's exact test (two-sided) we conclude that the two active treatments are significantly better than the Placebo in the FITT population (p-values were <0.001 for each of the two comparisons: Fluorouracil versus Placebo and Efudex® versus Placebo.)

Comments on the Sponsor's Analysis

The sponsor's analysis results using their ITT and PP populations for the proportion of patients with complete clearing of AK at week 6 (Visit 4) were summarized in the FDA medical reviewer's report (page 16). The equivalence test was passed for the PP population for the proportion of patients with complete clearing of AK at week 6 (Visit 4), and each of the active products was statistically significantly superior to placebo.

Any differences between our results and the sponsor's were due to the adjustments of the ITT population to the FITT population in accordance with recommendations of the medical and statistical reviewers.

Safety

Per the OGD medical reviewer, the irritation scores at Visit 2 (week 1), Visit 3 (week 2) and visit 4 (week 6) for the FITT are tabulated in Table 5 page 8 and also illustrated in Figures 1 to 3 on pages 9 and 10. The skin irritation evaluation scale is as follows:

0 = none
1 = mild
2 = moderate
3 = severe

Using the Cochran-Mantel-Haenszel test, there were no statistically significance differences in the irritation scores for Visit 2 (week 1), Visit 3 (week 2) and Visit 4 (week 6) between the test treatment group Fluorouracil Cream, and the reference product, Efudex® 5% Cream.
P-values are 0.1253, 0.2977 and 0.9591 for Visit 2 (week 1), Visit 3 (week 2) and Visit 4 (week 6) respectively.

For more safety information please see the **details in the OGD medical reviewer's report.**

Table 5 Frequency of the Irritation Scores by Treatment for the FITT population

	Fluorouracil	Efudex®	Placebo
Irritation Score			
Visit 2 (week 1)			
0	12	18	27
1	70	77	5
2	50	45	0
3	2[a]	0	0
Visit 3 (week 2)			
0	8	6	29
1	30	43	4
2	93	89	0
3	5[b]	2[c]	0
Visit 4 (week 6)			
0	130	134	33
1	6	6	0

[a] Patients 59 and 280.
[b] Patients 156, 169, 203, 249 and 280.
[c] Patients 130 and 206.

Figure 1 Visit 2 (Week 1): Proportion of Subjects with Irritation Scores 0, 1, 2, 3 by Treatment

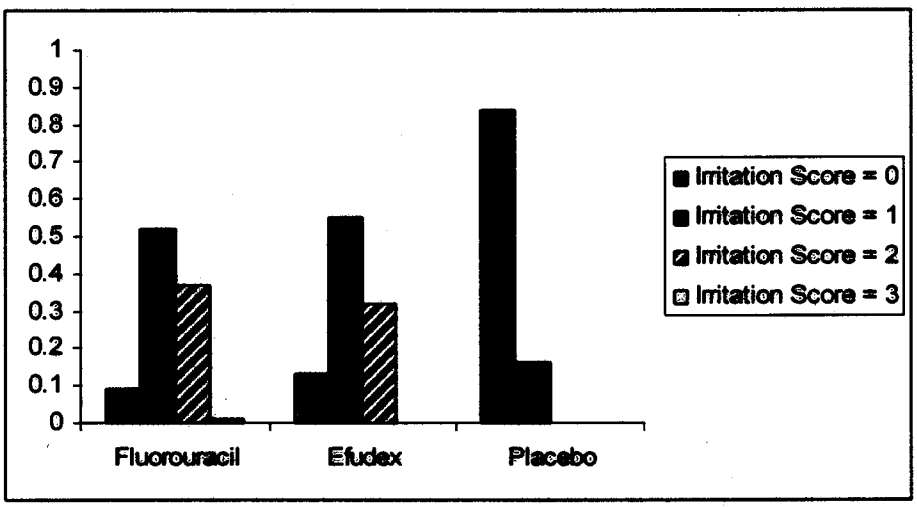


Figure 2 Visit 3 (Week 2): Proportion of Subjects with Irritation Scores 0, 1, 2, 3 by Treatment

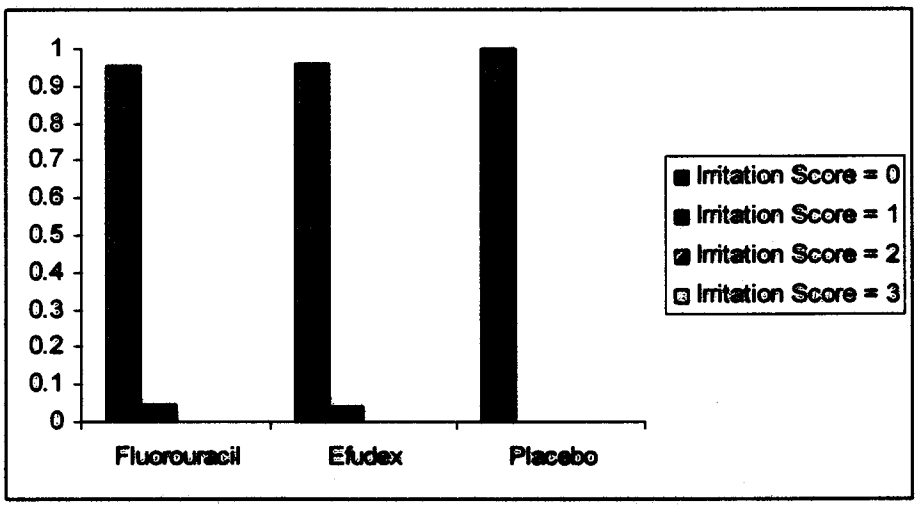
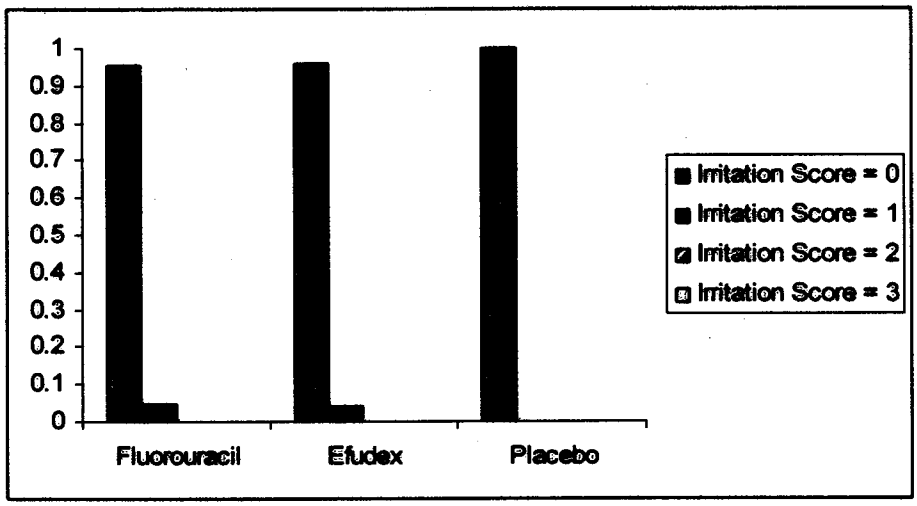


Figure 3 Visit 4 (Week 6): Proportion of Subjects with Irritation Scores 0, 1, 2, 3 by Treatment



Conclusion

The two active treatments Fluorouracil and Efudex® were significantly better than the Placebo for the FITT population. Also, the equivalence test passed for the PP population for the proportion of patients with complete clearing of AK at week 6 (Visit 4).

Fairouz Makhlouf, Ph.D.
Mathematical Statistician, DB6/OB

Donald J. Schuirmann
Expert Mathematical Statistician, DB6/OB

Stella G. Machado, Ph.D.
Director, DB6/OB
cc:
HFD-600 Dena R Hixon, Carol Kim, Debra M Catterson
HFD-705 Stella G. Machado, Donald J. Schuirmann, Fairouz Makhlouf, DB6 Chron

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

/s/

Fairouz Makhlouf
11/7/2006 02:43:47 PM
BIOEQUIVALENCE STATISTICIAN

Please Sign: ANDA 77-524 Stat Review

Donald Schuirmann
11/7/2006 02:49:24 PM
BIOMETRICS

Stella Machado
11/17/2006 11:06:53 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-524

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

SPEAR
PHARMACEUTICALS

13100 Ponderosa Way • Fort Myers, FL 33907 • Phone/Fax: (239) 433-7546 • Spear@SpearPharma.com

505(j)(5)(A)(i)
4 March 2005
77-524

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

RE: Original ANDA for Fluorouracil Cream, USP 5%

Dear Mr. Buehler:

Pursuant to the provisions of Section 505 (j)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 CFR Part 314, Subpart C-Abbreviated Applications, Spear Pharmaceuticals herein submits an Abbreviated New Drug Application for a generic drug product, Fluorouracil Cream, USP 5%.

The purpose of this submission is to obtain FDA approval for Spear Pharmaceuticals, Inc., to manufacture the topical product Fluorouracil Cream, USP 5% that will be marketed in the USA. This product is the generic equivalent of Efudex® (Fluorouracil Topical Cream 5%) the reference listed drug which is marketed by Valeant Pharmaceuticals, International Inc., (Formerly ICN Pharmaceuticals, Inc.) under NDA 16-831. The ANDA holder is Valeant Pharmaceuticals, International, Inc., Costa Mesa, California. ICN announced its new name, Valeant, on November 12, 2003.

This application also contains data from a bioequivalence study in humans showing statistically validated bioequivalence between Spear Pharmaceuticals' Fluorouracil Cream, USP 5% and the reference listed drug Efudex® (Fluorouracil Topical Cream 5%) . This study was conducted under bioequivalence IND 69-813 and amendments 0001, 0002, and 0003.

Our contractor who manufactures the drug product is CCI Pharmaceuticals, Inc., of Rockledge, Florida.

In accordance with the Orange Book, the reference listed drug has no unexpired patents and enjoys no exclusivity, *to wit:*

Active Ingredient:	FLUOROURACIL
Dosage Form;Route:	CREAM; TOPICAL
Proprietary Name:	EFUDEX
Applicant:	VALEANT PHARM INTL
Strength:	5%
Application Number:	016831
Product Number:	003
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Spear Pharmaceuticals' generic drug, Fluorouracil Cream, USP 5% is essentially the same as Valeant's Efudex® (Fluorouracil Topical Cream 5%) concerning the active ingredient and inactive ingredients. We have added an additional inactive ingredient which is cetyl alcohol, NF, at (b) (4) in the formula to (b) (4). The proposed level (b) (4) is below that found in a previously approved drug application for the topical route of administration (12% according to the FDA CDER Inactive Ingredient Database). The generic product labeling is the same as the labeling currently approved for the marketing of Efudex® (Fluorouracil Topical Cream 5%) except for the NDC numbers, trade name, distributor (*Dist. by Spear Dermatology Products, 1247 Sussex Turnpike, Ste 120, Randolph, NJ 07869*) and other labeling information specific to the pioneer drug which is detailed in Section V of this application in a side-by-side analysis.

Spear is also committed to ensuring that we will resolve any issues identified in the methods validation process after approval.

This ANDA consists of three (3) volumes, each containing the required Table of Contents. Besides the Archival copy and the Review Copy (Two Parts: (1) Review-Pharmacokinetic copy, and (2) Review-Chemistry copy), an additional copy is provided as the "field copy" that contains the technical sections of this ANDA. The field copy has been sent to the Orlando District Office. All required copies contain four (4) sets of draft labeling. The Archival copy bears original signatures on specific required statements, certifications, and Form FDA 356h.

Portions of the labeling section and bioequivalence study information of this application are submitted in electronic format as per regulations (68 FR 69009) and the current thinking outlined in agency guidances. Enclosed are two (2) compact discs #1 and #2. CD #1 contains the packaging insert for the labeling section in pdf and word formats while CD #2 contains the BE study statistical data sets in SAS Transport format.

Portions of this submission are considered confidential. Specifically, these are analytical methods validation, processing instructions, BE study protocols, and facilities description.

The applicant's information is as follows:

Spear Pharmaceuticals, Inc.
13100 Ponderosa Way
Fort Myers, FL 33907
Tel./Fax: (239) 433-7546
Cell (239) 560-2411

Please address communications related to this ANDA by contacting:

12-22-2004

David Christ VP
6 Longacre Court
Port Jefferson, NY 11777
Tel./Fax (631) 476-5860

Date

or

12-22-2004

Robert V. Sarrio VP
6329 Whispering Lane
Titusville, FL 32780
Tel. (321) 543-7039
Fax: (321) 267-7968

Date

SPEAR
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13100 Ponderosa Way • Fort Myers, FL 33907 • Phone/Fax: (239) 433-7546 • Spear@SpearPharma.com

February 28, 2005

Project Manager, Office of Generic Drugs
ATTN: Ms. Emily Thakur
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Tel (301) 827-5713
Fax (301) 594-1174

N/MC

[VIA FAX and FEDEX]

RE: Requested Documents for Original ANDA 77-524 for Fluorouracil Cream, USP 5%.

Dear Ms. Thakur:

I received your communication this afternoon and am submitting the following requested documents as per your request:

(1) Our Type II DMF Authorization from our API supplier (b) (4) for (b) (4).
(2) GMP Statement from (b) (4)
(3) Revised Environmental Assessment (request for Categorical Exclusion under 21 CFR 25.31(a) and (g).
(4) A copy of our withdrawal letter for our Bio-IND #69-813.

Hardcopies of the above documents in triplicate are being sent via FEDEX.

Please update our files accordingly.

Please do not hesitate to call if you have any questions.

Sincerely,

2-28-2005

Bob Sarrio
VP Spear Pharmaceuticals, Inc.
6329 Whispering Lane
Titusville, FL 32780
Tel (321) 543-7039
Fax (321) 267-7968

ANDA 77-524

MAR 14 2005

Spear Pharmaceuticals, Inc.
Attention: Robert V. Sarrio
6329 Whispering Lane
Titusville, FL 32780

Dear Sir:

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

Reference is made to the telephone conversation dated February 28, 2005 and the correspondence dated March 1, and March 2, 2005.

NAME OF DRUG: Fluorouracil Cream USP, 5%

DATE OF APPLICATION: December 22, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 6, 2005

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:

Ann Vu
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-524
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610
HFD-92
Endorsement:
HFD-615/MShimer, Chief, RSB _____ date 4 March 05
HFD-615/EThakur, CSO _____ date
Word File V:\Firmsnz\spear\ltrs&rev\77524.ack
F/T ETT03/03/05
ANDA Acknowledgment Letter!

14882 Bellezza Lane • Naples, FL 34110 • Phone: (239) 560-2411 • Spear@SpearPharma.com

ORIG AMENDMENT

July 11, 2005

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

MINOR AMENDMENT TO ANDA 77-524
RESPONSE TO FDA CHEMISTRY LETTER DATED JUNE 23, 2005
Fluorouracil Cream USP, 5%

Dear Mr. Buehler:

Reference is made to the above referenced ANDA and to the Agency's Minor deficiency letter dated June 23, 2005, regarding our original ANDA dated December 22, 2004. Reference is also made to the related Bio-IND # 69-813, and the agency's letter dated September 1, 2004 to that Bio-IND. We have evaluated the issues raised in the letter and provide the following information in response to those deficiencies. Spear Pharmaceuticals believes that this amendment will satisfactorily address those deficiencies and permit approval of this ANDA.

For ease of review, the Agency's comments have been restated in bold print followed by our responses:

A. Deficiencies

1. (b) (4)

Following this page, 4 pages withheld in full- (b)(4) Chemistry review #1

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(b) (4)

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

1. **Please provide all available drug product room temperature stability data.**

   We have included in Attachment 7 currently available drug product room temperature stability data through 12 months storage.

2. **Bioequivalence and labeling information you have provided is pending review. After the reviews are completed, any deficiencies found will be communicated to you separately.**

   We acknowledge your comment.

3. **All facilities referenced in your ANDA should be in compliance with cGMP at the time of approval. We have requested an evaluation from the Office of Compliance.**

   We acknowledge your comment.

4. **The USP methods for the drug substance and the drug product are the regulatory methods and they will prevail in the event of any dispute.**

   We acknowledge your comment.

MINOR AMENDMENT

Fluorouracil Cream, USP 5%
Amendment to Original ANDA 77-524
July 11, 2005

We trust that we have addressed the agency's concerns and that our proposed ANDA may be approved. This submission contains a total of 46 pages and is being submitted in triplicate with an additional copy being sent to the Orlando District Office as a "Field Copy."

Please address communications related to this ANDA by contacting one of the following:

David J. Christ
V.P. Regulatory Affairs
6 Longacre Court
Port Jefferson, NY 11777
Tel/Fax: 631-476-5860

Robert V. Sarrio
Chemistry
6329 Whispering Lane
Titusville, FL 32780
Tel. Mobile: 321-543-7039
Tel. Titusville: 321-267-2820 or 321-268-2300

SPEAR
PHARMACEUTICALS

14882 Bellezza Lane • Naples, FL 34110 • Phone: (239) 560-2411 • Spear@SpearPharma.com

August 2, 2005

ORIG AMENDMENT
N/AF

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

AMENDMENT TO ANDA 77-524 - LABELING
Response to Labeling Deficiency Letter dated 7/20/05
Fluorouracil Cream USP, 5%

Dear Mr. Buehler:

Reference is made to the above referenced ANDA dated December 22, 2004, and to the Agency's deficiency letter dated July 20, 2005 regarding the labeling of the proposed drug product. Spear Pharmaceuticals has evaluated the 7/20/05 letter and our response follows. For ease of review, we have restated the Agency's comments in bold type followed by our responses.

1. **GENERAL COMMENT (ALL LABELING)**
Inactive Ingredients - Include "Purified Water" in your inactive ingredients, to be consistent with your "components and composition" statement.

We have added "purified water" to the inactive ingredient listing for the container, carton, and insert, to be consistent with the components and composition statement.

2. **CONTAINER (25 gram tube):**
   - **See GENERAL COMMENT**
   - **Please assure that your container labels are of actual size, color, and clarity when submitting in final print. In addition, assure all text is clear and readable.**

   As noted above, Spear Pharmaceuticals acknowledges and has addressed the Agency's general comment as it relates to the container, carton, and insert (deficiency comments 2, 3, and 4). We are including in this amendment final "printers proof" labeling of actual size, color and clarity. We have carefully

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reviewed the labeling provided in this amendment, and have concluded that all text is clear and readable.

3. **CARTON (25 gram)**
   - **See GENERAL COMMENT**
   - **The white text on the blue background is difficult to read. Increase readability by changing background and/or printing color.**

   We have increased the readability of the white text on the blue background by increasing the font size for the smallest portions of the text (i.e., name and place of business) that may have been difficult to read in our original ANDA dated 12/22/04. We believe that the labeling provided in this amendment, which is in its final "printers proof" form, is indisputably readable.

4. **INSERT**
   - **See GENERAL COMMENT**
   - **Revise to "USP" with the established name only in the TITLE, DESCRIPTION, and HOW SUPPLIED sections.**

Please revise your labeling, as instructed above, and submit each labeling piece in final print. The electronic labeling rule published December 11, 2003 (68 FR 69009)...guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Each labeling piece (container, carton, and insert) is being submitted in final print (printers proof, with the package insert in pdf format and MS Word format per the guidance and Agency request). Twelve copies of the container and carton and one hard copy of the package insert are included per OGD's request (See Attachment 1).

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug.

Spear Pharmaceuticals acknowledges the Agency's comment.

To facilitate review of your next submiss ion, 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.

We have included side-by-side comparisons of our proposed labeling with our last submission (original ANDA dated 12/22/04) – See Attachment 2.

This amendment consists of one volume and includes labeling information in paper and electronic format (package insert). In summary, the following is enclosed in support of this amendment:

- Form FDA 356h
- 12 copies of Final Printed Labeling (Printers Proof) for Proposed Container and Carton
- CD Containing Package Insert in PDF and MsWord Formats, as well as one hard copy of Final Printed (Printers Proof) Insert
- Side-by-Side Labeling Comparisons for Revised Tube, Carton and Package Inserts.

We trust that we have addressed the agency's concerns.

Please address communications related to this ANDA by contacting one of the following:

David J Christ 8/2/05
David J. Christ
V.P. Regulatory Affairs
37 Jefferson Landing Circle
Port Jefferson, NY 11777
Tel/Fax: 631-476-5860

David J Christ for
Robert V. Sarrio
V.P. Quality and Technical Affairs
6329 Whispering Lane
Titusville, FL 32780
Tel. Mobile: 321-543-7039
Tel. Titusville: 321-267-2820

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TELEPHONE AMENDMENT
ANDA 77-524

August 18, 2005

ORIG AMENDMENT
NAM

Mr. Gary J. Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Tel.: (301) 827-5860
Fax: (301) 594-0180

[VIA FEDEX]

Reference: ANDA 77-524
Fluorouracil Cream, USP 5%

RE: Telephone Amendment to ANDA 77-524 Fluorouracil Cream, USP 5%
Response to 8/17/2005 Telecommunication with OGD

Dear Mr. Buehler:

Reference is made to the subject ANDA dated December 22, 2004, and to our Minor Amendment dated July 11, 2005. Reference is also made to the telephone conversation between Ms. Susan Pittinger, Review Chemist, Office of Generic Drugs (OGD), FDA, and (b) (4) consultant to Spear Pharmaceuticals, on August 17, 2005, regarding the aforementioned application.

In that 8/17/05 telecommunication, OGD requested the following information:

(1) A clarification of our specification for Combined Total Related Substances (CTRS) at release and on stability.

(2) A request to tighten our specification for Combined Total Related Substances such that it is "more in-line with your stability test data."

(3) A request for any additional stability test data we may have.

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C:\Documents and Settings\Robert Sarrio\Desktop\DESKTOP\Fluorouracil\5FU Amendment-08-18-05-Telephone-FINAL DRAFT.doc

TELEPHONE AMENDMENT
ANDA 77-524

Spear Pharmaceuticals, Inc.
August 18, 2005
RE: ANDA 77-524

In response to the above requests:

(1) As discussed, the CTRS specification is simply the sum of the total related substances results obtained from our two (2) different test methods.

(b) (4)

[redacted]

(2) In response to OGD's request to tighten our CTRS specification such that it is more in-line with our current test data we propose the following:

(b) (4)

[redacted]

TELEPHONE AMENDMENT
ANDA 77-524

Spear Pharmaceuticals, Inc.
August 18, 2005
RE: ANDA 77-524

Our proposed change is tabulated below for reviewer convenience:

Specification*	Current Release and Shelf-Life	Proposed Release and Shelf-Life
Total Combined RS (b) (4)	NMT (b) (4)%	NMT (b) (4),

*Release and stability specifications are the same.

Consistent with OGD's telephone request, we believe the proposed specification submitted above is more in-line with our current stability data (please refer to the Minor Amendment dated 7/11/05, Attachment 7, pages 41-45).

(3) In response to your request for any additional long term stability data we may have; our next test station at 18 months is not due until October of this year so we have no further data to submit at this time. 12 months of long term data has already been submitted as discussed. (please refer to the Minor Amendment dated 7/11/05, Attachment 7, pages 41-45)

This submission contains a total of 6 pages which consists of the Cover letter/response, Form 356h and a Field Copy Certification. Submitted via facsimile transmission and FedEx (in triplicate).

Please accept this latest information to our file. We trust that this latest information will satisfactorily answer OGD's questions.

Please address communications related to this ANDA by contacting one of the following:

David J. Christ
V.P. Regulatory Affairs
37 Jefferson Landing Circle
Port Jefferson, NY 11777
Tel/Fax: 631-476-5860

or

Robert V. Sarrio
Chemistry Consultant
6329 Whispering Lane
Titusville, FL 32780
Tel. Mobile: 321-543-7039
Tel. Titusville: 321-267-2820 or 321-268-2300

MEMORANDUM

To: **ANDA 77-524**

Drug: **Fluorouracil Cream USP, 5%**

Sponsor: **Spear Pharmaceuticals, Inc.**
Robert V. Sarrio Vice President
PH: (321) 543-7039; FAX: (321) 267-7968

From: **Carol Y. Kim, Pharm.D.**
Clinical Reviewer
Office of Generic Drugs
FAX: (301) 827-6363

Carol Y. Kim 1/6/06

Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs

Dena R. Hixon 1/6/06

Date: **January 6, 2006**
Re: **Request for Information**

In order to complete the review of a bioequivalence study with clinical endpoints for ANDA 77-524 (SPR00-5FU-01), please provide the following information:

1. Provide a frequency table showing the number of patients with skin irritation by severity (none, mild, moderate, and severe) for each treatment group and per visit.

2. Please submit source documents and transcribed CRF that collected all essential study data for the following patients:

   #70 and 89 (only source document needed)
   #130, 156, 159, 203, 206, 236, 249, 280, 297 (both source document and CRF)

3. Did the same investigator evaluate AK lesions at both visits (baseline and final visit) for each patient?

4. Based on the study report, the sponsor's representatives had an access to informed consent documentation, source documents, and all other trial documentation at all times during the study. Did they have an access to randomization scheme and treatment records during the study?

5. When was the original data from source document entered into an electronic case report form? Is it during the study or after completion of the study? When was the identity of the study drug transcribed into the electronic CRF? Who had access to the electronic data system? Who were two individuals that had edit privileges? Did the sponsor's representatives have an access to the electronic data system during the study?

6. The detailed explanation of retention sample procedure was not provided in the study report. Please explain how the study samples were selected for retention in this study.

SPEAR
PHARMACEUTICALS

14882 Bellezza Lane • Naples, FL 34110 • Phone: (239) 560-2411 • Spear@SpearPharma.com

ORIG AMENDMENT

N/AF

January 9, 2006

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

AMENDMENT TO PENDING ANDA 77-524 - LABELING
Update As Per Reference Listed Drug Labeling Supplement Approval (NDA 16-831, S-049)
Fluorouracil Cream USP, 5%

Dear Mr. Buehler:

Reference is made to the above referenced ANDA dated December 22, 2004, and to the Labeling Amendment Dated August 2, 2005, in which Spear Pharmaceuticals responded to the Agency's labeling deficiency letter dated July 20, 2005. In that letter dated July 20, 2005, it is written: "*Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug.*" As noted above, since our last labeling amendment, changes were subsequently approved for the reference-listed drug (see NDA 16-831 S-049 labeling supplement approval dated 10-13-05). Consequently, we are now submitting this amendment to show that the proposed labeling is the same as the labeling approved for the listed drug, Efudex Cream. To that end, it is noted that the FDA CDER provided through its website copies of the revised RLD package insert only and not the primary labeling (carton and tube). Subsequent requests to the OGD Labeling and Program Support Group did not provide any additional information about possible changes to the carton and tube. Therefore, in the absence of available revised primary labeling for the RLD, and, in order to achieve consistency across all three pieces comprising the proposed drug product labeling, we are herewith applying the same changes approved for the RLD package insert to the proposed carton and tube. The specific change provided in this amendment pertains to the "For Topical Use" statement and is detailed in the enclosed side-by-side labeling comparisons.

Each proposed labeling piece is submitted in final print (12 copies of printers proof labeling is provided in Attachment 1). Per the electronic labeling rule published December 11, 2003 (68 FR 69009) and the December 2005 SPL Guidance...the package insert is also submitted in SPL and MS Word format.

To facilitate review of our next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), we are providing a side-by-side comparison of our proposed labeling with our last submission (dated 8-2-05) for the carton and tube, and with the revised RLD insert approved in the 10-13-05 NDA Labeling Supplement, with all differences annotated and explained –See Attachment 2.

This amendment consists of one volume and includes labeling information in paper and electronic format (package insert). In summary, the following is enclosed in support of this amendment:

- Form FDA 356h
- 12 copies of Final Printed Labeling (Printers Proof) for Proposed Container, Carton and Insert
- CD Containing Package Insert in SPL and MsWord Formats
- Side-by-Side Labeling Comparisons for Revised Tube and Carton vs. that submitted in the 8-2-05 Labeling Amendment
- Side-by-Side Labeling Comparison for Revised Package Insert vs. that approved 10-13-05 in the RLD NDA 16-831 Supplement S-049

Please address communications related to this ANDA by contacting one of the following:

David J. Christ
V.P. Regulatory Affairs
37 Jefferson Landing Circle
Port Jefferson, NY 11777
Tel/Fax: 631-476-5860

David J. Christ <for>
Robert V. Sarrio
VP Quality and Technical Affairs
6329 Whispering Lane
Titusville, FL 32780
Telephone: 321-543-7039

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January 16, 2006

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

ORIGINAL
N/A

BIOEQUIVALENCE AMENDMENT TO ANDA 77-524
RESPONSE TO FDA REQUEST FOR INFORMATION DATED JANUARY 6, 2006
Fluorouracil CREAM, USP 5%

Dear Mr. Buehler:

Reference is made to the above referenced ANDA dated December 22, 2004, and to the Agency's Request for Information (Bioequivalence) Memorandum dated January 6, 2006. We have completed our evaluation of the Agency's requests and are providing our response to the memorandum in this amendment.

For ease of review, the Agency's requests have been restated in bold print followed by our responses:

1. **Provide a frequency table showing the number of patients with skin irritation by severity (none, mild, moderate, and severe) for each treatment group and per visit.**

   A frequency table showing the number of patients with skin irritation by severity for each treatment group and per visit is provided in Attachment 1.

2. **Please submit source documents and transcribed CRF that collected all essential study data for the following patients:**

   #70 and 89 (only source document needed)
   #130, 156, 159, 203,206, 236, 249, 280, 297 (both source document and CRF)

   We have enclosed as Attachment 2 the requested source documents and CRFs. Please note that patients 159 and 236 were lost to follow up and therefore do not include CRF Document #5 (subject diary).

3. **Did the same investigator evaluate AK lesions at both visits (baseline and final visit) for each patient?**

   Yes, the same investigator evaluated AK lesions at both visits for each patient. Specifically, Dr. Shari Skinner MD, Dermatologist, evaluated the AK lesions at both the baseline and final visit for each patient.

4. **Based on the study report, the sponsor's representative had an access to informed consent documentation, source documents, and all other trial documentation at all times during the study. Did they have an access to randomization scheme and treatment records during the study?**

   In section 9.6.1 of the trial report (third paragraph) it is stated that the sponsor's representative had access to "informed consent documentation, source documents and all other trial documentation..." The sponsor's representative, (b) (4) (b) (4) Pharm.D., clarifies: "We did not have access to the randomization scheme or treatment records. We did have access to dispensing records which were used to reconcile drug inventory. Dispensing records contained coded lot numbers only. The sponsor's representative remained blinded throughout the study and during the monitoring process."

5. **When was the original data form source document entered into an electronic case report form? Is it during the study or after completion of the study? When was the identity of the study drug transcribed into the electronic CRF? Who had access to the electronic data system? Who were two individuals that had edit privileges? Did the sponsor's representatives have an access to the electronic data system during the study?**

When was the original data from source document entered into an electronic case report form? Is it during the study or after completion of the study?

(b) (6) PhD, of SFBC-FM (the clinical trial site) confirmed that the original data were entered into the electronic case report forms throughout the study, and after the study was completed. These data were transcribed and entered into the case report forms by data entry clerks not involved in seeing or reviewing subjects.

When was the identity of the study drug transcribed into the electronic CRF?

(b) (6) PhD of SFBC-FM confirmed that the identity of the study drug was transcribed into the electronic CRF as the drug was dispensed, by the data entry clerks. These data were transcribed along with the other study data, and were generally entered at the time the other baseline visit data was entered.

Who had access to the electronic data system?

(b) (6) PhD of SFBC-FM confirmed that only people with knowledge of the required password had access to the electronic data system. These people consisted of the designer of the database ((b) (6) , the data entry clerks, and other supervisory staff (not including the principal investigator). Dr. (b) (6) further clarified that the password-controlled access to the system would not allow access to study drug assignment. As noted in the question at the bottom of this page, the sponsor's monitors had access to output from the databases, but did not have access to the study drug assignment. The study databases were provided to the Sponsor's biostatistician on CD-ROM following completion of the study.

Who were the two individuals that had edit privileges?

It is acknowledged that the study report (in 9.6.1.1 Data Management and Entry Procedures) stated that only two users had edit privileges (database designer (b) (6) (b) (6) PhD, and a data entry clerk). It has since been confirmed by Dr. (b) (6) that from time to time during the process four data entry clerks and the data base designer ((b) (6)) had password-controlled edit access to the databases. Please note that a large majority of the edits were made by just one of the four data entry clerks, and none of these clerks were involved in seeing or reviewing patients.

Did the sponsor's representatives have an access to the electronic data system during the study?

The Sponsor's representative, (b) (4) of (b) (4) writes: "We had access only to printouts, never to the "live" system. The printouts were used to verify transcription of source data. The treatment field was not available on the printout at all, and therefore we were blinded throughout."

6. **The detailed explanation of retention sample procedure was not provided in the study report. Please explain how the study samples were selected from retention in the study?**

   In a Note to file dated 10/26/04 SFBC-FM details how study samples were selected for retention. See Attachment 3.

   "Placebo, reference, and study drug were retained on site by (b) (6) Clinic Manager and (b) (6), Director of Clinical Operations. Retains were selected randomly from each treatment group. This included 100 test product, 50 reference product, and 40 placebo. Neither (b) (6) labeled or packaged the drug during the study."

Please note that this amendment consists of one volume, and that a portion of this submission is in electronic format. The electronic data is included in a single CD enclosed as Attachment 2.

We trust that we have addressed the Agency's request for information. Please forward any further questions you may have to:

David J Christ 1-16-06

David J. Christ
V.P. Regulatory Affairs
Tel and Fax 631-476-5860

David J Christ <for> 1-16-06

K. L. Spear, M.D.
President
Tel 239-560-2411
Fax 239-254-9404

SPEAR
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Mr. Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
Document Control Room Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

December 6, 2006

MC

Subject: Request for a Meeting re: ANDA 77-524 (Fluorouracil Cream USP 5%)

Dear Mr. Buehler:

Reference is made to our telephone discussion of December 4 concerning pending ANDA dated December 22, 2004. During the phone conversation, you indicated that OGD is gearing up for a meeting with DDDP "soon" (not next week) regarding the issues raised in the 12/21/04 Citizen petition. You also said Dr. Hixon is working on both fronts (to get citizen's petition resolved and the application approved), and if OGD is not successful it is time to come in with your data.

We appreciate your advice and also understand that OGD and DDDP have multiple priorities, and that the latter parties have been meeting since June 2006 concerning the Valeant citizen petition with uneven progress toward an agreement. **If the next OGD/DDDP meeting is unsuccessful (i.e., no agreement is reached), we are hereby requesting that such an unsuccessful outcome automatically triggers the scheduling of a follow-up meeting** involving Spear Pharmaceuticals, pursuant to the provisions of Title 21 CFR Part 10.65(c). Rather than wait until the conclusion of your next meeting with DDDP, we are trying to avoid more delays to schedule an additional meeting if OGD's opinion does not prevail.

As you are aware, OGD's review of the subject pending ANDA with data demonstrating our product's bioequivalence to Efudex is substantially complete. In follow-up to our July 20, 2006 meeting request, we would like the opportunity, in a face-to-face meeting with Dr. Hixon and her professional counterpart (dermatologist) in DDDP and any other staff that is deemed appropriate, to review our Cadaver skin data which demonstrates similar penetration into the mid dermis. We are requesting that this meeting occur ***before*** a final decision is made by the Agency.

In light of the hypothetical concerns raised by Valeant (we are unaware of any data to support their concerns), the Agenda for our meeting will focus on the following:

- The actinic keratosis study has been found acceptable
- The results of a cadaver skin study demonstrating that penetration of the test and reference product to the mid-dermis is comparable
- The test and reference products are bioequivalent for both approved indications

Spear is prepared to provide a full meeting background package (including the results of the cadaver skin study) immediately if a meeting is deemed necessary.

Thank you in advance for your understanding of our concerns and request for this meeting.

Sincerely,
K.L. Spear, M.D.

SPEAR
PHARMACEUTICALS

14882 Bellezza Lane • Naples, FL 34110 • Phone: (239) 560-2411 • Spear@SpearPharma.com

January 26, 2007

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

ORIG AMENDMENT
N-AB

BIOEQUIVALENCE AMENDMENT TO ANDA 77-524
RESPONSE TO FDA REQUEST FOR INFORMATION DATED 12/6/06
FLUOROURACIL CREAM, USP 5%

Dear Mr. Buehler:

Reference is made to the above referenced ANDA dated December 22, 2004, and to the Agency's request for information from Dena Hixon, M.D., on December 6, 2006. Reference is also made to the 1-26-07 telephone conversation between Ms. Debbie Catterson and K.L. Spear, M.D., requesting that this information be submitted as a bioequivalence amendment.

In fulfillment of the Agency's request, we are providing the following information in this amendment:

Attachment	Description	Page
1	Form FDA 356h	01-03
2	Copy of 12-7-06 Email/Fax Response to 12-6-06 Information Request From Dena Hixon, M.D.	04-07
2 a	Copy of 1st Attachment to 12-7-06 Response: • Article entitled "North American Contact Dermatitis Group patch test results.."; J.A.A.D, June 1998	08-16
2 b	Copy of 2nd Attachment to 12-7-06 Response: • Composition Statement (Page 988 of Original ANDA 77-524 dated 12-22-04) • Excerpt from University of Maryland School of Pharmacy Website comparing RX Ingredient Properties of Cetyl Alcohol and Stearyl Alcohol • "Hazardous Ingredients" Excerpt from Material Safety Data Sheet (MSDS) for Efudex (reference WWW.msds.com) • Excerpt (Page 292) from *Fisher's Contact Dermatitis: Fourth Edition,* comparing cetyl alcohol and stearyl alcohol	17 18 19 20 21-22

RECEIVED
JAN 29 2007
OGD / CDER

This amendment consists of one volume. Please forward any further questions you may have to:

David J Christ 1/26/07
David J. Christ
V.P. Regulatory Affairs
Tel and Fax 631-476-5860

David J Christ <fn> 1/26/07
K. L. Spear, M.D.
President
Tel 239-560-2411
Fax 239-254-9404

7-1

SPEAR
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14882 Bellezza Lane • Naples, FL 34110 • Phone: (239) 560-2411 • Spear@SpearPharma.com

March 14, 2007

ORIGINAL ORIG AMENDMENT

N-000-AB

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

ANDA 77-524, FLUOROURACIL CREAM, USP 5%
New Correspondence

Dear Mr. Buehler:

Reference is made to the above referenced ANDA dated December 22, 2004, and to our 1-26-07 response to the Agency's recent request for bioequivalence information. It is our understanding that despite our provision of this additional information, the Agency continues to have an internal debate regarding whether a proposed generic fluorouracil cream 5% may be considered bioequivalent to Efudex Cream, even though data have been provided demonstrating bioequivalence of the test product in accordance with a study design agreed upon by OGD (i.e., actinic keratosis), and these study results subsequently found acceptable by OGD.

We now offer the expert opinion of Jonathan Wilkin, M.D. As you are aware, Dr. Wilkin directed the Division of Dermatology and Dental Products at the U.S. Food and Drug Administration from 1994 to 2005. He is therefore uniquely qualified to offer pivotal judgment on this longstanding issue. Significantly, **Dr. Wilkin supports OGD's original position that actinic keratoses is an appropriate clinical endpoint sufficient for demonstrating bioequivalence of a generic product to Efudex Cream** (see attached written expert opinion).

In summary, in addition to this cover letter, we are providing the expert opinion of Jonathan Wilkin, M.D. and associated references supporting that opinion (12 pages total).

Sincerely,

K. L. Spear, M.D.
President
Tel 239-560-2411
Fax 239-254-9404

RECEIVED
MAR 16 2007
OGD / CDER

MEMORANDUM

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

DATE: 4/28/08

FROM: Beverly Weitzman
Labeling Reviewer
Office of Generic Drugs
Center for Drug Evaluation and Research

THRU: John Grace
Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

TO: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs
Office for Drug Evaluation and Research

SUBJECT: ANDA 77-524 – Fluorouracil cream 5 % (Approval Summary #2) – Correction to the date of the labeling amendment submitted for final approval. The correct submission date for the labeling amendment was January 9, 2006. However January 9, 2005 was entered incorrectly on the Approval Summary #2. Please note the date for the final version of the approved labeling for ANDA 77-524 is January 9, 2006.

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

/s/

Beverly Weitzman
4/28/2008 01:14:43 PM
LABELING REVIEWER

John Grace
4/29/2008 01:37:57 PM
LABELING REVIEWER

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-524 Applicant Spear Pharmaceuticals, Inc.
Drug Fluorouracil Cream USP, Strength(s) 5%

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 3 April 2007 Initials MHS	Date _____ Initials _____

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked _____
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Nothing Submitted ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Written request issued ☐
Has case been settled: Yes ☐ No ☐
Study Submitted ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments: No patents or exclusivities remain protecting the RLD. This ANDA is eligible for Full Approval.

2. Project Manager, Rosalyn Adigun Team 3 Review Support Branch	Date April 2, 2007 Initials RA	Date _____ Initials _____

Original Rec'd date December 22, 2004
Date Acceptable for Filing January 6, 2005
Patent Certification (type) II
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes ☒ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status December 6, 2005
Date of Office Bio Review March 30, 2007
Date of Labeling Approv. Sum January 26, 2006
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date April 20, 2007	Date April 20, 2007
Name/Initials ra for bw	Name/Initials ra for jfg

Comments:
From: Grace, John F
Sent: Friday, April 20, 2007 1:15 PM
To: Weitzman, Beverly
Cc: Adigun, Rosalyn
Subject: RE: ANDA 77-524 Spear's Fluorouracil Cream USP, 5%

I concur

From: Weitzman, Beverly
Sent: Friday, April 20, 2007 11:09 AM
To: Grace, John F
Cc: Adigun, Rosalyn

Subject: RE: ANDA 77-524 Spear's Fluorouracil Cream USP, 5%

The labeling approval summary signed by B. Weitzman 1/25/06 and John Grace 1/26/06 remains acceptable. There are no new changes to the RLD labeling at this time.
No changes noted in Comis, the OB, or the USP/NF.

From: Adigun, Rosalyn
Sent: Friday, April 20, 2007 11:02 AM
To: Weitzman, Beverly
Cc: Grace, John F
Subject: ANDA 77-524 Spear's Fluorouracil Cream USP, 5%

Please review and endorse the labeling ap summary #2 as well as the approval letter for ANDA 77-524, Spear's Fluorouracil Cream USP, 5%.

<< File: 77-524.lblapsumm2.pdf >>

<< File: 77-524.ap.DOC >>
Thanks,
Rosalyn

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials_____
Comments:

5. Div. Dir./Deputy Dir. Date4/25/07
Chemistry Div. I Initials PS

Comments:CMC is OK

6. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)

7. Vacant Date_____
Deputy Dir., DLPS Initials_____

8. Peter Rickman Date4/11/08
Director, DLPS Initialswpr
Para.IV Patent Cert: Yes☐ No☒;Pending Legal Action: Yes ☐ No ☒; Petition: Yes☒ No☐
Comments:no patents or exclusivity issues; okay for full approval; labeling acceptable 1/26/2006, no changes to the RLD; bio acceptable 3/30/2007; EER acceptable 12/6/2005; CP response completed.

okay for full approval

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Rosalyn Adigun Team 3 Date April 11, 2008

Review Support Branch Initials _____
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10:30 am Time notified of approval by phone
10:38 am Time approval letter faxed

FDA Notification:
April 11, 2008 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
April 11, 2008 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Rosalyn Adigun
4/11/2008 11:46:01 AM