

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**ANDA 090164**

**Name:** Triamcinolone Acetonide Injectable  
Suspension USP  
40 mg/mL

**Sponsor:** Sandoz, Inc.

**Approval Date:** June 1, 2009

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 090164**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 090164**

**APPROVAL LETTER**



ANDA 90-164

Sandoz Inc.  
U.S. Agent for: Sandoz Canada Inc.  
Attention: Alison Sherwood  
                    Manager, Regulatory Affairs  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 30, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL, packaged in 1 mL vials.

Reference is also made to your amendments dated May 8, June 10, July 15, July 17, August 1, August 26, and September 26, 2008; and February 19, May 12, and May 28, 2009.

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, effective on the date of this letter. The Division of Bioequivalence has determined your Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Kenalog®-40 Injectable Suspension, of ApotHEcon Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

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 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.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "**Miscellaneous Correspondence - SPL for Approved ANDA 90-164**".

Sincerely yours,

*{See appended electronic signature page}*

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

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

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Robert L. West  
6/1/2009 01:58:01 PM  
Deputy Director, for Gary Buehler

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**ANDA 090164**

**LABELING**



# Triamcinolone Acetonide Injectable Suspension, USP

**R<sub>x</sub> only**

**NOT FOR USE IN NEONATES  
CONTAINS BENZYL ALCOHOL**

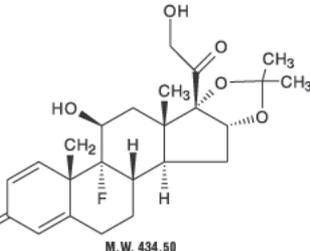
For Intramuscular or Intra-articular Use  
NOT FOR INTRAVENOUS, INTRADERMAL, OR INTRAOCULAR USE

## DESCRIPTION:

Triamcinolone acetonide injectable suspension is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. THIS FORMULATION IS SUITABLE FOR INTRAMUSCULAR AND INTRA-ARTICULAR USE ONLY. THIS FORMULATION IS NOT FOR INTRA-DERMAL INJECTION.

Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with sodium chloride for isotonicity, 0.94% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80. Sodium hydroxide or hydrochloric acid may be added to adjust pH between 5.0 and 7.5. At the time of manufacture, the air in the container is replaced by nitrogen.

The chemical name of triamcinolone acetonide is 9-Fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxy-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. Its structural formula is:



M. W. 434.50

Triamcinolone acetonide occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and very soluble in alcohol.

## CLINICAL PHARMACOLOGY:

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Synthetic analogs such as triamcinolone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Triamcinolone acetonide injectable suspension has an extended duration of effect which may be sustained over a period of several weeks. Studies indicate that following a single intramuscular dose of 60 to 100 mg of triamcinolone acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days. This finding correlates closely with the extended duration of therapeutic action achieved with the drug.

## INDICATIONS AND USAGE:

### Intramuscular:

Where oral therapy is not feasible, injectable corticosteroid therapy, including triamcinolone acetonide injectable suspension is indicated for intramuscular use as follows:

#### Allergic States:

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

#### Dermatologic Diseases:

Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

#### Dermatologic Disorders:

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable); in infancy, mineralocorticoid supplementation is of particular importance; congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

#### Gastrointestinal Diseases:

To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

#### Hematologic Disorders:

Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

#### Miscellaneous:

Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

#### Neoplastic Diseases:

For the palliative management of leukemias and lymphomas.

#### Nervous System:

Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, craniotomy, or head injury.

#### Ophthalmic Diseases:

Sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

#### Renal Diseases:

To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

#### Respiratory Diseases:

Berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonitis, symptomatic sarcoidosis.

#### Rheumatic Disorders:

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic diseases; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

#### Intra-Articular:

The intra-articular or soft tissue administration of triamcinolone acetonide injectable suspension is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

#### CONTRAINDICATIONS:

Triamcinolone acetonide injectable suspension is contraindicated in patients who are hypersensitive to any components of this product.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

#### WARNINGS:

##### General:

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of hemikerics, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see PRECAUTIONS: Pediatric Use).

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see ADVERSE REACTIONS).

Because triamcinolone acetonide injectable suspension is a suspension, it should not be administered intravenously.

Unless a deep intramuscular injection is given, local atrophy is likely to occur. (For recommendations on injection techniques, see DOSAGE AND ADMINISTRATION.) Due to the significantly higher incidence of local atrophy when the material is injected into the deltoid area, this injection site should be avoided in favor of the gluteal area. Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation. Triamcinolone acetonide injectable suspension is a long-acting preparation, and is not suitable for use in acute stress situations. To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery or severe illness) both during treatment with triamcinolone acetonide injectable suspension and for a year afterwards.

## Cardio-Renal:

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when they are used in large doses. Dietary salt restriction and potassium supplementation may be necessary (see PRECAUTIONS). All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

## Endocrine:

Corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticoid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

## Infections:

### General:

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

### Fungal Infections:

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see PRECAUTIONS: Drug Interactions: Amphotericin B Injection and potassium-depleting agents).

### Special Pathogens:

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

## Tuberculosis:

The use of corticosteroids in patients with active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

## Vaccination:

Administration of live or, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.

Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

## Viral Infections:

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

## Neurologic:

Reports of severe medical events have been associated with the intrathecal route of administration (see ADVERSE REACTIONS: Gastrointestinal and Neurologic/Psychiatric).

## Ophthalmic:

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

Adequate studies to demonstrate the safety of triamcinolone acetonide injection use by intrabulbar, subconjunctival, sub-Tenon, retrobulbar and intraocular (intravitreal) injections have not been performed. Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration. Several instances of blindness have been reported following injection of corticosteroid suspensions into the nasal turbinates and intralacrimal injection about the head. Administration of triamcinolone acetonide injectable suspension by any of these routes is not recommended.

## PRECAUTIONS:

### General:

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Most of the sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

## Cardio-Renal:

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

## Endocrine:

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

## Gastrointestinal:

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be mild or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

## Intra-Articular and Soft Tissue Administration:

Intra-articularly injected corticosteroids may be systemically absorbed. Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously injected joint is not usually recommended.

Corticosteroid injection into unstable joints is generally not recommended.

Intra-articular injection may result in damage to joint tissues (see ADVERSE REACTIONS: Musculoskeletal).

## Musculoskeletal:

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

## Neuro-Psychiatric:

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatinine kinase may occur. Gradual improvement or recovery after stopping corticosteroids may require weeks to years.

## (Continued)

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

### **Ophthalmic:**

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

### **Information for Patients:**

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

### **Dose Reduction:**

#### **Aminoglutethimide:**

Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

#### **Amphotericin B injection and potassium-depleting agents:**

When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

### **Antibiotics:**

Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

### **Anticholinesterases:**

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

### **Anticoagulants, oral:**

Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

### **Antidiabetics:**

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

### **Antitubercular drugs:**

Plasma concentrations of isoniazid may be decreased.

### **Cholestyramine:**

Cholestyramine may increase the clearance of corticosteroids.

### **Cyclosporine:**

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

### **Digitalis glycosides:**

Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

### **Erogens, including oral contraceptives:**

Erogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

### **Hepatic enzyme inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin):**

Drugs which induce hepatic microsomal drug-metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

### **Ketconazole:**

Ketconazole has been reported to decrease the metabolism of certain corticosteroids by 60% leading to an increased risk of corticosteroid side effects.

### **Nonsteroidal anti-inflammatory agents (NSAIDs):**

Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

### **Skin tests:**

Corticosteroids may suppress reactions to skin tests.

### **Vaccines:**

Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see WARNINGS: Infections: Vaccination).

### **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

### **Pregnancy:**

#### **Teratogenic Effects:**

#### **Pregnancy Category C:**

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

### **Nursing Mothers:**

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

### **Skin Test Use:**

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gassing syndrome", (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >80 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gassing syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (<1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see ADVERSE REACTIONS). Like adults, pediatric patients should be carefully followed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroid treatment should be weighed against clinical benefits obtained and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

### **Geriatric Use:**

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### **ADVERSE REACTIONS:**

(Listed alphabetically under each subsection)

The following adverse reactions may be associated with corticosteroid therapy:

#### **Allergic reactions:**

Anaphylactoid reaction, anaphylaxis, angioedema.

#### **Cardiovascular:**

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see WARNINGS), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

### **Dermatologic:**

Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, lupus erythematosus-like lesions, purpura, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

### **Endocrine:**

Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetics, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

### **Fluid and electrolyte disturbances:**

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

### **Gastrointestinal:**

Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

### **Metabolic:**

Decrease in nitrogen balance due to protein catabolism.

### **Musculoskeletal:**

Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intrathecal use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, post injection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

### **Neurologic/Psychiatric:**

Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilloedema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychotic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see WARNINGS: Neurologic).

### **Ophthalmic:**

Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with perocular injections.

### **Other:**

Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

### **OVERDOSAGE:**

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuing steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

### **DOSEAGE AND ADMINISTRATION:**

#### **General:**

**NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS).**

The initial dose of triamcinolone acetone injectable suspension may vary from 2.5 mg to 100 mg per day depending on the specific disease entity being treated (see Dosage section below). However, in certain overwhelming, acute, life threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

**IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.**

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

### **Dosage:**

#### **Systemic:**

The suggested initial dose is 60 mg, **injected deeply into the gluteal muscle.** Atrophy of subcutaneous fat may occur if the injection is not properly given. Dosage is usually adjusted within the range of 40 to 80 mg, depending upon patient response and duration of relief. However, some patients may be well controlled on doses as low as 20 mg or less.

Hay fever or pollen asthma: Patients with hay fever or pollen asthma who are not responding to pollen administration and other conventional therapy may obtain a remission of symptoms lasting throughout the pollen season after a single injection of 40 to 100 mg.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of triamcinolone for a week followed by 64 mg every other day for one month are recommended (see PRECAUTIONS: Neuro-Psychiatric).

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in three or four divided doses (3 to 48 mg/m<sup>2</sup>/day).

*For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:*

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

*These dose relationships apply only to oral or intravenous administration of these substances. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.*

### **Local:**

#### **Intra-Articular Administration:**

A single local injection of triamcinolone acetone is frequently sufficient, but several injections may be needed for adequate relief of symptoms.

#### **Initial Dose:**

2.5 to 5 mg for smaller joints and from 5 to 15 mg for larger joints, depending on the specific disease entity being treated. For adults, doses up to 10 mg for smaller areas and up to 40 mg for larger areas have usually been sufficient. Single injections into several joints, up to a total of 80 mg, have been given.

### **Administration:**

#### **General:**

**STRICT ASEPTIC TECHNIQUE IS MANDATORY.** The vial should be shaken before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used. After withdrawal, triamcinolone acetone injectable suspension should be injected without delay to prevent settling in the syringe. Careful technique should be employed to avoid the possibility of entering a blood vessel or introducing infection.

### **Systemic:**

For systemic therapy, injection should be made **deeply into the gluteal muscle** (see WARNINGS). For adults, a minimum needle length of 1-1/2 inches is recommended. In obese patients, a longer needle may be required. Use alternative sites for subsequent injections.

### **Local:**

For treatment of joints, the usual intra-articular injection technique should be followed. If an excessive amount of synovial fluid is present in the joint, some, but not all, should be aspirated to aid in the relief of pain and to prevent undue dilution of the steroid.

With intra-articular administration, prior use of a local anesthetic may often be desirable. Care should be taken with this kind of injection, particularly in the deltoid region, to avoid injecting the suspension into the tissues surrounding the site, since this may lead to tissue atrophy.

In treating acute nonspecific tenosynovitis, care should be taken to ensure that the injection of the corticosteroid is made into the tendon sheath rather than the tendon substance. Epicondylitis may be treated by infiltrating the preparation into the area of greatest tenderness.

### **HOW SUPPLIED:**

Triamcinolone acetone injectable suspension, USP in vials providing 40 mg triamcinolone acetone per mL, are supplied as follows:  
NDC 0781-3245-72 40 mg/mL, 1 mL vial

### **Storage:**

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature). Avoid freezing and protect from light.

U1003019

05-2009M

Manufactured in Canada by

Sandoz Canada Inc. for

Sandoz Inc.

Princeton, NJ 08540

(b) (4)

## DIE FORMAT

	← WIDTH →	↑ HEIGHT	CORNER RADIUS	SPECIAL SHAPE
INCH	1.5000	0.6875	0.09375	NO
MM	38.10	17.4625		

RSS: 1030781324572 5

MAXIMUM SPACE FOR TEXT AND GRAPHICS



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(b) (4)



**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 090164**

**LABELING REVIEWS**

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

---

<b>ANDA Number</b>	90-164
<b>Date of Submission</b>	November 30, 2007 (original)
<b>Applicant</b>	Sandoz Canada Inc.
<b>Drug Name</b>	Triamcinolone Acetonide Injectable Suspension, USP
<b>Strength(s)</b>	40 mg/mL (1 mL (b) (4) vials)

---

**Labeling Deficiencies:**

1. CONTAINER LABELS (1 mL (b) (4) vials)
  - a. Assure that the text is at least 4 point type.
  - b. Please add "Contains Benzyl Alcohol as a Preservative"
  - c. 1 mL vial: revise "For Intramuscular Use Only" to read "For Intramuscular Use"
  - d.  (b) (4)
  - e.
  - f.
  
2. CARTON (1 vial)
  - a. Please add "Contains Benzyl Alcohol as a Preservative"
  - b. Top lid: add the net quantity statement.
  - c. "...sodium hydroxide or hydrochloric..."
  - d.  (b) (4)
  - e.
  
3. PHYSICIAN INSERT
  - a. TITLE:
    - i. Assure that "NOT FOR INTRAVENOUS..." starts on a new line.
    - ii. Add the phrase "Rx only" to a location just under the TITLE of the package insert.
  - b. INDICATIONS AND USAGE: "Nervous system" [spelling]
  - c. PRECAUTIONS, Drug Interactions: "Hepatic enzyme inducers" [spelling]

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling 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://service.govdelivery.com/service/subscribe.html?code=USFDA> 17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

**FOR THE RECORD: \*\*Expedited Review\*\***

- The labeling review was based on the labeling for the reference listed drug Kenalog-40® (Apothecon; NDA 14-901/S-034 approved November 20, 2006). There is currently a SLR pending.

Related ANDA: 90-166 for triamcinolone acetonide injectable suspension usp, 10 mg/ml from sandoz canada inc. pn 12/3/07 (RLD Kenalog-10)

- USP:  
Triamcinolone Acetonide Injectable Suspension monograph (checked 3/10/08)

Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

pH: between 5.0 and 7.5.

**3. PATENT AND EXCLUSIVITY**

Patent Data For NDA 14-901

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	<i>None</i>	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data For NDA 14-901

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

- Drug Product Manufacturer:  
Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL is manufactured, packaged, labeled and tested by Sandoz Canada Inc.  
145 Jules-Léger Street in Boucherville QC J4B 7K8.

- Container/Closure:  
The final product is aseptically filled in (b) (4) sterile clear glass (b) (4) vials using rubber stoppers and Flip-Off aluminium seals under nitrogen.

- Finished Product: White suspension. pH: 5.0 – 7.5

- Product Line:  
RLD:  
40 mg/mL, 1 mL vial NDC 0003-0293-05  
40 mg/mL, 5 mL vial NDC 0003-0293-20  
40 mg/mL, 10 mL vial NDC 0003-0293-28

ANDA:  
NDC 0781-3245-72 40 mg/mL, 1 mL vial  
(b) (4)

**8. Components/Composition**

Components	Quantity per unit	Percentage	Standards	Function
Triamcinolone Acetonide	40.0 mg	4.00000%	USP	Active ingredient (API)
Carboxymethylcellulose Sodium	7.5 mg	0.75000%	USP	(b) (4)
Polysorbate 80	0.4 mg	0.0400%	NF	
Sodium Chloride	(b) (4)	(b) (4)	USP	Tonicity agent
Benzyl Alcohol	0.9405% w/v*	0.9405%	NF	Antimicrobial preservative
Nitrogen	Head space	+	NF	Air displacement agent

Hydrochloric Acid** (initial concentration (b) (4))	+	+	NF	pH adjustment agent
Sodium Hydroxide**	+	+	NF	pH adjustment agent
(b) (4)				
Water for Injection	q.s. 1 mL	94.45095%	USP	Solvent
<b>Total</b>	1 mL	100%		

\* : Density of Benzyl Alcohol = (b) (4)

\*\* : For pH adjustment: (b) (4)

+ = Present

There are no differences between the Sandoz Canada formulation and the RLD with respect to excipients quantitatively or qualitatively except the benzyl alcohol content. The benzyl alcohol is reduced to 0.9405% w/v compared to 0.99% w/v in the RLD. This reduction has no significant impact on the preservative effectiveness and falls under differences permitted for inactive ingredients under 21 CFR 314.94 (9)(iii). The reasons for this reduction was to harmonize the benzyl alcohol content in our different Triamcinolone Acetonide Injectable Suspension formulations (10 and 40 mg/mL).

#### 9. Storage/Dispensing

NDA: Store at controlled room temperature, 20°–25°C (68°–77°F), avoid freezing and protect from light.

ANDA: Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Avoid freezing and protect from light. Cartons has the statement "Store vial in carton".

---

Date of Review: March 10, 2008

Date of Submission: November 30, 2007

Primary Reviewer: Ruby Wu

Team Leader: John Grace

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ANDA: 90-164

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Review

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/s/

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Ruby Wu  
3/10/2008 11:09:08 AM  
LABELING REVIEWER

John Grace  
3/11/2008 07:42:20 PM  
LABELING REVIEWER

# APPROVAL SUMMARY

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

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<b>ANDA Number</b>	90-164
<b>Date of Submission</b>	July 17, 2008 (amendment)
<b>Applicant</b>	Sandoz Canada Inc.
<b>Drug Name</b>	Triamcinolone Acetonide Injectable Suspension, USP
<b>Strength(s)</b>	40 mg/mL (1 mL (b)(4) vials)

---

### APPROVAL SUMMARY:

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER LABELS (1 mL (b)(4) vials)  
Satisfactory in final print as submitted in the July 17, 2008 amendment.
2. CARTON (1 vial)  
Satisfactory in final print as submitted in the July 17, 2008 amendment.
3. PHYSICIAN INSERT  
Satisfactory in final print as submitted in the July 17, 2008 amendment.

Revisions needed post-approval: No.

### BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Kenalog-40®

NDA Number: 14-901

NDA Drug Name: Triamcinolone Acetonide Injectable Suspension, USP

NDA Firm: Apothecon

Date of Approval of NDA Insert and supplement: NDA 14-901/S-034 approved November 20, 2006

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

### PATENTS/EXCLUSIVITIES

Patent Data For NDA 14-901

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	<i>None</i>	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data For NDA 14-901

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

**FOR THE RECORD: \*\*Expedited Review\*\***

- The labeling review was based on the labeling for the reference listed drug Kenalog-40® (Apothecon; NDA 14-901/S-034 approved November 20, 2006). There is currently a SLR pending.

Related ANDA: 90-166 for triamcinolone acetonide injectable suspension usp, 10 mg/ml from sandoz canada inc. pn 12/3/07 (RLD Kenalog-10)

- USP:  
Triamcinolone Acetonide Injectable Suspension monograph (checked 7/23/08)

Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

pH: between 5.0 and 7.5.

**3. PATENT AND EXCLUSIVITY**

Patent Data For NDA 14-901

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	<i>None</i>	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data For NDA 14-901

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

- Drug Product Manufacturer:  
Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL is manufactured, packaged, labeled and tested by Sandoz Canada Inc.  
145 Jules-Léger Street in Boucherville QC J4B 7K8.

- Container/Closure:  
The final product is aseptically filled in (b) (4) sterile clear glass (b) (4) vials using rubber stoppers and Flip-Off aluminium seals under nitrogen.

- Finished Product: White suspension. pH: 5.0 – 7.5

- Product Line:  
RLD:  
40 mg/mL, 1 mL vial NDC 0003-0293-05  
40 mg/mL, 5 mL vial NDC 0003-0293-20  
40 mg/mL, 10 mL vial NDC 0003-0293-28

ANDA:  
NDC 0781-3245-72 40 mg/mL, 1 mL vial

(b) (4)

**8. Components/Composition**

Components	Quantity per unit	Percentage	Standards	Function
Triamcinolone Acetonide	40.0 mg	4.00000%	USP	Active ingredient (API)
Carboxymethylcellulose Sodium	7.5 mg	0.75000%	USP	(b) (4)
Polysorbate 80	0.4 mg	0.0400%	NF	(b) (4)
Sodium Chloride	(b) (4)	(b) (4)	USP	Tonicity agent
Benzyl Alcohol	0.9405% w/v*	0.9405%	NF	Antimicrobial preservative
Nitrogen	Head space	+	NF	Air displacement agent

Hydrochloric Acid** (initial concentration (b) (4))	+	+	NF	pH adjustment agent
Sodium Hydroxide**	+	+	NF	pH adjustment agent
(b) (4)				
Water for Injection	q.s. 1 mL	94.45095%	USP	Solvent
<b>Total</b>	1 mL	100%		

\* : Density of Benzyl Alcohol = (b) (4)

\*\* : For pH adjustment: (b) (4)

+ = Present

There are no differences between the Sandoz Canada formulation and the RLD with respect to excipients quantitatively or qualitatively except the benzyl alcohol content. The benzyl alcohol is reduced to 0.9405% w/v compared to 0.99% w/v in the RLD. This reduction has no significant impact on the preservative effectiveness and falls under differences permitted for inactive ingredients under 21 CFR 314.94 (9)(iii). The reasons for this reduction was to harmonize the benzyl alcohol content in our different Triamcinolone Acetonide Injectable Suspension formulations (10 and 40 mg/mL).

The 1 mL vial label does not have the statement "Contains Benzyl Alcohol as a Preservative" due to limited space. However, the container labeling has the disclaimer.

#### 9. Storage/Dispensing

NDA: Store at controlled room temperature, 20°–25°C (68°–77°F), avoid freezing and protect from light.

ANDA: Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Avoid freezing and protect from light. Cartons has the statement "Store vial in carton".

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Date of Review: July 23, 2008

Date of Submission: July 17, 2008 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

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ANDA: 90-164  
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Review

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/s/

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Ruby Wu  
7/23/2008 12:08:40 PM  
LABELING REVIEWER

John Grace  
7/23/2008 12:43:24 PM  
LABELING REVIEWER

## APPROVAL SUMMARY

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

**ANDA Number** 90-164

**Date of Submission** May 28, 2009 (amendment)

**Applicant** Sandoz Canada Inc.

**Drug Name** Triamcinolone Acetonide Injectable Suspension, USP

**Strength(s)** 40 mg/mL (1 mL vial)

#### APPROVAL SUMMARY:

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER LABELS (1 mL)  
Satisfactory in final print as submitted in the July 17, 2008 amendment.
2. CARTON (1 vial)  
Satisfactory in final print as submitted in the July 17, 2008 amendment.
3. PHYSICIAN INSERT  
Satisfactory in final print as submitted in the May 28, 2009 amendment.

Revisions needed post-approval: No.

#### FOR THE RECORD: \*\*Expedited Review\*\*

1. The labeling review was based on the labeling for the reference listed drug Kenalog-40® (Apothecon; NDA 14-901/S-034 approved November 20, 2006). There is currently a SLR pending.



Related ANDA: 90-166 for Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL from Sandoz Canada Inc. approved May 27, 2009 (RLD Kenalog-10)

Sandoz's May 28, 2009 amendment:

The physician insert has been revised.

(b) (4)

Sandoz's December 12, 2008 amendment:

**FDA Comment:** As you revised the drug substance

(b) (4)

**Sandoz Response:** Sandoz Canada Inc.

(b) (4)

2. USP:

Triamcinolone Acetonide Injectable Suspension monograph (checked 5/28/09)

Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

pH: between 5.0 and 7.5.

3. PATENT AND EXCLUSIVITY

Patent Data For NDA 14-901

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data For NDA 14-901

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

4. Drug Product Manufacturer:

Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL is manufactured, packaged, labeled and tested by Sandoz Canada Inc.  
145 Jules-Léger Street in Boucherville QC J4B 7K8.

5. Container/Closure:

The final product is aseptically filled in (b) (4) sterile clear glass (b) (4) vials using rubber stoppers and Flip-Off aluminium seals under nitrogen.

From: alison.sherwood@sandoz.com [mailto:alison.sherwood@sandoz.com]

Sent: Thursday, May 28, 2009 4:11 PM

To: Wu, Ruby (Chi-Ann)

Subject: RE: 90-164 Labeling Amendment

Hi Ruby

The stopper used in this drug product is (b) (4) rubber. Enclosed is the statement we included in the original application (note the natural rubber content listed as 0.0% in the middle of page).

Best Regards! Alison Sherwood  
Manager  
Regulatory Affairs  
Sandoz Inc.  
2555 West Midway Boulevard  
Broomfield, CO 80020

USA  
 Phone: +1 303 4384513  
 Fax: +1 303 4384600

-----  
 From: Wu, Ruby (Chi-Ann)  
 Sent: Thursday, May 28, 2009 3:29 PM  
 To: 'alison.sherwood@sandoz.com'  
 Subject: RE: 90-164 Labeling Amendment

Hi Alison,

Please confirm if any component of the container/closure system contains latex/natural rubber or not.

Thanks,

Ruby

6. Finished Product: White suspension. pH: 5.0 – 7.5

7. Product Line:

RLD:

40 mg/mL, 1 mL vial NDC 0003-0293-05

40 mg/mL, 5 mL vial NDC 0003-0293-20

40 mg/mL, 10 mL vial NDC 0003-0293-28

ANDA:

NDC 0781-3245-72 40 mg/mL, 1 mL vial

(b) (4)

8. Components/Composition

Components	Quantity per unit	Percentage	Standards	Function
Triamcinolone Acetonide	40.0 mg	4.00000%	USP	Active ingredient (API)
Carboxymethylcellulose Sodium	7.5 mg	0.75000%	USP	(b) (4)
Polysorbate 80	0.4 mg	0.0400%	NF	(b) (4)
Sodium Chloride	(b) (4)	(b) (4)	USP	Tonicity agent
Benzyl Alcohol	0.9405% w/v*	0.9405%	NF	Antimicrobial preservative
Nitrogen	Head space	+	NF	Air displacement agent
Hydrochloric Acid** (initial concentration (b) (4))	+	+	NF	pH adjustment agent
Sodium Hydroxide**	+	+	NF	pH adjustment agent
(b) (4)				
Water for Injection	q.s. 1 mL	94.45095%	USP	Solvent
<b>Total</b>	1 mL	100%		

\* : Density of Benzyl Alcohol = (b) (4)

\*\* : For pH adjustment: (b) (4)

+ = Present

There are no differences between the Sandoz Canada formulation and the RLD with respect to excipients quantitatively or qualitatively except the benzyl alcohol content. The benzyl alcohol is reduced to 0.9405% w/v compared to 0.99% w/v in the RLD. This reduction has no significant impact on the preservative effectiveness and falls under differences permitted for inactive ingredients under 21 CFR 314.94 (9)(iii). The reasons for this reduction was to harmonize the benzyl alcohol content in our different Triamcinolone Acetonide Injectable Suspension formulations (10 and 40 mg/mL).

The 1 mL vial label does not have the statement "Contains Benzyl Alcohol as a Preservative" due to limited space. However, the carton labeling has the disclaimer.

9. Storage/Dispensing

NDA: Store at controlled room temperature, 20°–25°C (68°–77°F), avoid freezing and protect from light.

ANDA: Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Avoid freezing and protect from light. Cartons has the statement "Store vial in carton".

10. Data elements submitted May 28, 2009: acceptable.

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Date of Review: May 29, 2009

Date of Submission: May 28, 2009 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: Koungh Lee

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ANDA: 90-164

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Review

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/s/

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Ruby Wu  
5/29/2009 01:02:57 PM  
LABELING REVIEWER

Koung Lee  
5/29/2009 02:28:21 PM  
LABELING REVIEWER  
For Wm Peter Rickman

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 090164**

**CHEMISTRY REVIEWS**

**ANDA 90-164**

**Triamcinolone Acetonide Injectable Suspension USP,  
40 mg/mL**

**SANDOZ CANADA INC.**

**Bing Cai, Ph.D.**

# Chemistry Division I

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# Chemistry Review Data Sheet

1. ANDA: 90-164
2. REVIEW #: 1
3. REVIEW DATE: April 25, 2008
4. REVIEWER: Bing Cai, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Previous Documents</u>	<u>Document Date</u>
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original ANDA (Acceptable for Filing: Dec. 3, 2007)	November 30, 2007
Expedited Review Request	February 26, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc.
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Beth Brannon Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, CO 80038-0446
Telephone:	303-438-4237
Fax:	303-438-4600



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A  
b) Non-Proprietary Name (USAN): Triamcinolone Acetonide Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

RLD: Kenalog®-40  
Holder: ApotHecon (NDA 14-901)

10. PHARMACOL. CATEGORY:

Triamcinolone Acetonide Injectable Suspension USP is used intraarticular and intrabursally for the following indications: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute nonspecific tenosynovitis, and post-traumatic osteoarthritis.

Triamcinolone Acetonide Injectable Suspension USP is also indicated for intramuscular use as follows: endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases and edematous state.

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40 mg/mL

13. ROUTE OF ADMINISTRATION: Intraarticular and Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

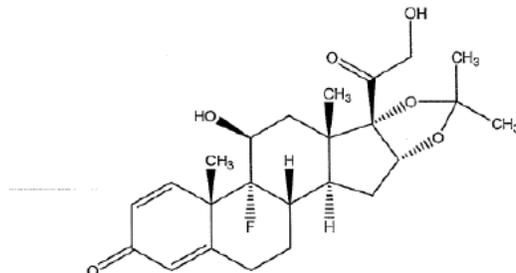
Chemistry Review Data Sheet

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

Chemical Name: 1) Pregna-1,4-diene-3,20-dione,9-Fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis (oxy)]-(11 $\beta$ ,16 $\alpha$ ); 2) 9-fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone; 3) 9-fluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione.

Molecular Formula: C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>

Molecular Weight: 434.50



**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	5/27/08 by Cai	
	III			4			
	III			4			

<sup>1</sup> 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")



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

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

### B. Related NDA/ANDA(s) and Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

### 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending	--	
EES	Pending	--	
Methods Validation	N/A	--	USP DS/DP
Labeling	Deficient	3/11/2008	
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.  Yes  No If no, explain reason(s) below:

# The Chemistry Review for ANDA 90-164

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

ANDA 90-164 is not 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)

Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL is manufactured, packaged, labeled and tested by Sandoz Canada Inc.. The drug product is formulated Q1/Q2 to the RLD (except very minor difference in the content of benzyl alcohol). The finished product is a white suspension, with pH adjusted to 5.0 – 7.5. Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with sodium chloride for isotonicity, 0.94% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethyl-cellulose sodium, and 0.04% polysorbate 80. Sodium hydroxide or hydrochloric acid may be used to adjust pH to 5.0-7.5. At the time of manufacture, the air in the container is replaced by nitrogen. The final product is aseptically filled in (b) (4) sterile clear glass (b) (4) vials using rubber stoppers and Flip-Off aluminium seals under nitrogen.

The drug substance is Triamcinolone Acetonide USP, manufactured by (b) (4) according to DMF (b) (4). Triamcinolone acetonide occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and very soluble in alcohol.

The maximum daily dose of Triamcinolone Acetonide in the drug product is 160 mg/day. The drug substance IT is 0.10% and the QT is 0.15% and the drug product IT is 0.2% and the QT is 0.2%

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

Triamcinolone Acetonide Injectable Suspension USP has an extended duration of effect which may be sustained over a period of several weeks. Studies indicate that following a single intramuscular dose of 60 to 100 mg of Triamcinolone Acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in

## Executive Summary Section

30 to 40 days. This finding correlates closely with the extended duration of therapeutic action achieved with the drug. The initial dose of Triamcinolone Acetonide Injectable Suspension USP may vary from 2.5 mg to 160 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Avoid freezing and protect from light. Cartons has the statement "Store vial in carton".

- 40 mg/mL, 1 mL vial

(b) (4)

The proposed expiration dating for the drug product is 24 months.

### C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

- MINOR Chemistry issues
- Bio: pending
- Labeling: Deficient
- Micro: pending

V:\Chemistry Division I\Team 2\TL Folder\Draft\90164cr1.rev.doc

Following this page, 30 pages withheld in full (b)(4)

## **II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**

### **A. Labeling & Package Insert**

The labeling is deficient per Payne on 3/11/08

Items Reviewed by Chemist: *Satisfactory*

#### **Description Section: Satisfactory**

- a. Structures: Satisfactory
- b. Chemical names: Satisfactory
- c. Empirical formulas: Satisfactory
- d. Name of the inactives: Satisfactory
- e. Physical and Chemical properties of DS: Satisfactory

#### **How Supplied Section: Satisfactory**

### **B. Environmental Assessment Or Claim Of Categorical Exclusion**

Categorical exclusion from the requirement to prepare an Environmental Assessment is provided (Module 1.12.14). It is satisfactory.

## **III. List Of Deficiencies To Be Communicated**

See the section below for details.

## CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-164

APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL

A. The deficiencies presented below represent MINOR deficiencies.

1. DMF <sup>(b) (4)</sup> is inadequate. The Holder has been notified. Please ensure that there is a response.

2. Please conduct a literature search to verify if any <sup>(b) (4)</sup>

3. <sup>(b) (4)</sup>

4.

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

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Your Sterility Assurance information is pending review. Deficiencies, if any, will be communicated separately.
3. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
4. Your reply should also address the labeling deficiencies provided to you by facsimile on 03/11/2008.
5. Please provide any additional long term stability data that may be available.
6. USP<467> becomes official on July 1<sup>st</sup>, 2008. Compliance information will need to be provided to the ANDA unless it is approved prior to that date.

Sincerely yours,

*{See appended electronic signature page}*

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

cc:ANDA 90-164  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/Bing Cai/

HFD-625/M. Smela/

HFD-617/E. Chuh

V:\Chemistry Division I\Team 2\TL Folder\Draft\90164cr1.rev.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

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Bing Cai  
6/4/2008 09:18:22 AM  
CHEMIST

Esther Chuh  
6/5/2008 02:02:45 PM  
CSO

Michael Smela  
6/6/2008 08:54:00 AM  
CHEMIST

**ANDA 90-164**

**Triamcinolone Acetonide Injectable Suspension USP,  
40 mg/mL**

**SANDOZ CANADA INC.**

Bing Cai, Ph. D.

Division of Chemistry I  
Office of Generic Drugs

# Chemistry Division I

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# Chemistry Review Data Sheet

1. ANDA: 90-164
2. REVIEW #: 2
3. REVIEW DATE: September 30, 2008
4. REVIEWER: Bing Cai, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Previous Documents</u>	<u>Document Date</u>
Sandoz Original ANDA Expedited Review Request	November 30, 2007 February 27, 2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment/Minor	September 22, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc.
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Beth Brannon Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, CO 80038-0446
Telephone:	303-438-4237
Fax:	303-438-4600



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Triamcinolone Acetonide Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

RLD: Kenalog®-40

Holder: ApotHECON (NDA 14-901)

10. PHARMACOL. CATEGORY:

Triamcinolone Acetonide Injectable Suspension USP is used intraarticular and intrabursally for the following indications: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute nonspecific tenosynovitis, and post-traumatic osteoarthritis.

Triamcinolone Acetonide Injectable Suspension USP is also indicated for intramuscular use as follows: endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases and edematous state.

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40 mg/mL

13. ROUTE OF ADMINISTRATION: Intraarticular and Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

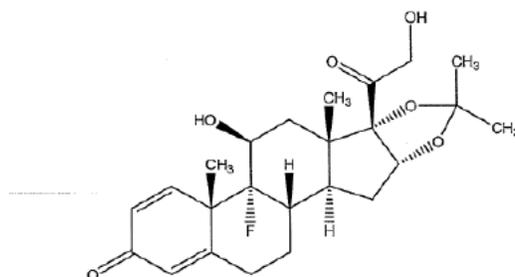
## Chemistry Review Data Sheet

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

Chemical Name: 1) Pregna-1,4-diene-3,20-dione,9-Fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis (oxy)]-(11 $\beta$ ,16 $\alpha$ ); 2) 9-fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone; 3) 9-fluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione.

Molecular Formula: C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>

Molecular Weight: 434.50


**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE 1	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	U. Atwal, 10/08/08	
	III			4			
	III			4			

<sup>1</sup> 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")



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

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

#### B. Related NDA/ANDA(s) and Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

#### 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending	--	
EES	Pending	--	
Methods Validation	N/A	--	USP DS/DP
Labeling	Acceptable	7/23/08	R. Wu
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. \_\_\_ Yes \_\_\_X\_\_\_ No If no, explain reason(s) below: Expedited Review

# The Chemistry Review for ANDA 90-164

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

ANDA 90-164 is not 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)

Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL is manufactured, packaged, labeled and tested by Sandoz Canada Inc.. The drug product is formulated Q1/Q2 to the RLD (except very minor difference in the content of benzyl alcohol). The finished product is a white suspension, with pH adjusted to 5.0 – 7.5. Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with sodium chloride for isotonicity, 0.94% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethyl-cellulose sodium, and 0.04% polysorbate 80. Sodium hydroxide or hydrochloric acid may be used to adjust pH to 5.0-7.5. At the time of manufacture, the air in the container is replaced by nitrogen. The final product is aseptically filled in (b) (4) sterile clear glass (b) (4) vials using rubber stoppers and Flip-Off aluminium seals under nitrogen.

The drug substance is Triamcinolone Acetonide USP, manufactured by (b) (4) according to DMF (b) (4). Triamcinolone acetonide occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and very soluble in alcohol.

The maximum daily dose of Triamcinolone Acetonide in the drug product is 160 mg/day. The drug substance IT is 0.10% and the QT is 0.15% and the drug product IT is 0.2% and the QT is 0.2%

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

Triamcinolone Acetonide Injectable Suspension USP has an extended duration of effect which may be sustained over a period of several weeks. Studies indicate that following a single intramuscular dose of 60 to 100 mg of Triamcinolone Acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in

## Executive Summary Section

30 to 40 days. This finding correlates closely with the extended duration of therapeutic action achieved with the drug. The initial dose of Triamcinolone Acetonide Injectable Suspension USP may vary from 2.5 mg to 160 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Avoid freezing and protect from light. Cartons has the statement "Store vial in carton".

- 40 mg/mL, 1 mL vial

(b) (4)

The proposed expiration dating for the drug product is 24 months.

### C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

- MINOR Chemistry issues
- Consult: Issued by DC III per DMF 14693
- Bio: Pending
- Labeling: Acceptable
- Micro: Pending

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Following this page, 17 pages withheld in full (b)(4)

**Stability Study Summary of Results:** Sandoz has provided 24 months long term stability data (1 ml fill (b)(4)) and 9 months long term stability data on (b)(4). All results meet the current specification. No trends were reported. Based on the data presented, Sandoz requested an expiry of 24 months for Triamcinolone Acetonide Injectable Suspension, 40 mg/mL.

**Post-approval stability protocol:** Satisfactory (See Responses # 16 and #17).

## **II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**

### **A. Labeling & Package Insert**

Items Reviewed by Chemist: *Satisfactory per #1*

**B. Environmental Assessment Or Claim Of Categorical Exclusion: See CR#1**

## CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-164

APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL

A. The deficiencies presented below represent MINOR deficiencies.

1. DMF <sup>(b) (4)</sup> is inadequate. The Holder has been notified. Please ensure that there is a response. <sup>(b) (4)</sup>

2.

3.

4.

5.

6.

7.

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

1. An acceptable compliance evaluation is necessary for approval and the evaluation is pending.

2. Your microbiology and bioequivalence information are pending review. Deficiencies, if any, will be provided under separate cover.

Sincerely yours,

*{See appended electronic signature page}*

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

cc:ANDA 90-164  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/Bing Cai/

HFD-625/M. Smela/

HFD-617/E. Chuh

V:\Chemistry Division I\Team 2\TL Folder\Draft\90164cr2.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

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Bing Cai  
10/29/2008 08:04:37 AM  
CHEMIST

Esther Chuh  
11/3/2008 04:47:40 PM  
CSO

Michael Smela  
11/4/2008 09:00:36 AM  
CHEMIST

**ANDA 90-164**

**Triamcinolone Acetonide Injectable Suspension USP,  
40 mg/mL**

**SANDOZ CANADA INC.**

Bing Cai, Ph. D.

Division of Chemistry I  
Office of Generic Drugs

# Chemistry Division I

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# Chemistry Review Data Sheet

1. ANDA: 90-164
2. REVIEW #: 3
3. REVIEW DATE: January 21, 2009
4. REVIEWER: Bing Cai, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Previous Documents</u>	<u>Document Date</u>
Sandoz Original ANDA Expedited Review Request Amendment/Minor	November 30, 2007 February 27, 2008 September 22, 2008

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment/Minor	December 12, 2008
Gratuitous Amendment	January 14, 2009

## 7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc.
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Alison Sherwood Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, CO 80038-0446
Telephone:	303-438-4513
Fax:	303-438-4600



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A  
b) Non-Proprietary Name (USAN): Triamcinolone Acetonide Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

RLD: Kenalog®-40  
Holder: Apotthecon (NDA 14-901)

10. PHARMACOL. CATEGORY:

Triamcinolone Acetonide Injectable Suspension USP is used intraarticular and intrabursally for the following indications: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute nonspecific tenosynovitis, and post-traumatic osteoarthritis.

Triamcinolone Acetonide Injectable Suspension USP is also indicated for intramuscular use as follows: endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases and edematous state.

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40 mg/mL

13. ROUTE OF ADMINISTRATION: Intraarticular and Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

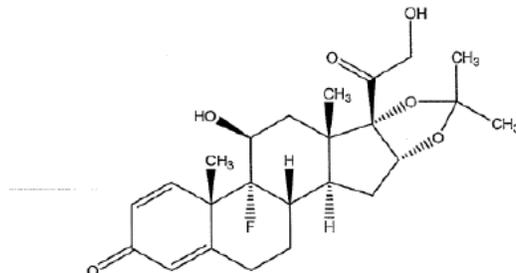
## Chemistry Review Data Sheet

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

Chemical Name: 1) Pregna-1,4-diene-3,20-dione,9-Fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis (oxy)]-(11 $\beta$ ,16 $\alpha$ ); 2) 9-fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone; 3) 9-fluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione.

Molecular Formula: C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>

Molecular Weight: 434.50



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	Bing Cai 01/25/09	Pending Pharm-Tox consult
	III			4			
	III			4			

<sup>1</sup> 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")



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

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

#### B. Related NDA/ANDA(s) and Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

#### 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	10/21/08	J. Wells
EES	Acceptable	02/05/09	S. Adams
Methods Validation	N/A	--	USP DS/DP
Labeling	Acceptable	07/23/08	R. Wu
Bioequivalence	Acceptable	12/23/08	D. Mitchell
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. \_\_\_ Yes \_\_\_X\_\_\_ No If no, explain reason(s) below: Expedited Review

# The Chemistry Review for ANDA 90-164

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

ANDA 90-164 is not 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)

Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL is manufactured, packaged, labeled and tested by Sandoz Canada Inc.. The drug product is formulated Q1/Q2 to the RLD (except very minor difference in the content of benzyl alcohol). The finished product is a white suspension, with pH adjusted to 5.0 – 7.5. Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with sodium chloride for isotonicity, 0.94% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethyl-cellulose sodium, and 0.04% polysorbate 80. Sodium hydroxide or hydrochloric acid may be used to adjust pH to 5.0-7.5. At the time of manufacture, the air in the container is replaced by nitrogen. The final product is aseptically filled in (b) (4) sterile clear glass (b) (4) vials using rubber stoppers and Flip-Off aluminium seals under nitrogen.

The drug substance is Triamcinolone Acetonide USP, manufactured by (b) (4) according to DMF (b) (4). Triamcinolone acetonide occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and very soluble in alcohol.

The maximum daily dose of Triamcinolone Acetonide in the drug product is 160 mg/day. The drug substance IT is 0.10% and the QT is 0.15% and the drug product IT is 0.2% and the QT is 0.2%

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

Triamcinolone Acetonide Injectable Suspension USP has an extended duration of effect which may be sustained over a period of several weeks. Studies indicate that following a single intramuscular dose of 60 to 100 mg of Triamcinolone Acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days. This finding correlates closely with the extended duration of therapeutic

action achieved with the drug. The initial dose of Triamcinolone Acetonide Injectable Suspension USP may vary from 2.5 mg to 160 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Avoid freezing and protect from light. Cartons has the statement "Store vial in carton".

- 40 mg/mL, 1 mL vial

(b) (4)

The proposed expiration dating for the drug product is 24 months.

### **C. Basis for Approvability or Not-Approval Recommendation**

The ANDA is not approvable at this time for the following reasons:

- MINOR Chemistry issues
- Consult: Issued by DC III per DMF (b) (4)
- Bio: Acceptable
- Labeling: Acceptable
- Micro: Acceptable
- EES: acceptable

Following this page, 10 pages withheld in full (b)(4)

**Stability Study Summary of Results (See CR#2):** Sandoz has provided 24 months long term stability data. All results meet the current specification. No trends were reported. Based on the data presented, Sandoz requested an expiry of 24 months for Triamcinolone Acetonide Injectable Suspension, 40 mg/mL.

**Post-approval stability protocol:** Satisfactory.

## **II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**

### **A. Labeling & Package Insert**

Items Reviewed by Chemist: *Satisfactory per #1*

**B. Environmental Assessment Or Claim Of Categorical Exclusion: See CR#1**

## CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-164      APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT:    Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL

The deficiency presented below represents Minor deficiency.

A. Deficiency:

Please provide updated drug product specifications for 40 mg/mL (1 ml fill size).

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

DMF <sup>(b) (4)</sup> is inadequate. <sup>(b) (4)</sup>  
<sup>(b) (4)</sup>. This comment also pertains to your related application (ANDA #90166).

Sincerely yours,

*{See appended electronic signature page}*

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

cc:ANDA 90-164  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/Bing Cai/

HFD-625/Mike Darj (ACT)/

HFD-617/E. Chuh

V:\Chemistry Division I\Team 2\TL Folder\ANDA\90164cr3.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

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Bing Cai  
2/9/2009 09:57:28 AM  
CHEMIST

Esther Chuh  
2/9/2009 11:33:10 AM  
CHEMIST

Mike Darj  
2/9/2009 12:56:10 PM  
CHEMIST  
(Acting TL)

**ANDA 90-164**

**Triamcinolone Acetonide Injectable Suspension USP  
40 mg/mL  
Packaged in 1 mL vials**

**SANDOZ CANADA INC.**

Bing Cai, Ph. D.

Division of Chemistry I  
Office of Generic Drugs

# Chemistry Division I

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# Chemistry Review Data Sheet

1. ANDA: 90-164
2. REVIEW #: 4
3. REVIEW DATE: March 21, 2009
4. REVIEWER: Bing Cai, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Previous Documents</u>	<u>Document Date</u>
Sandoz	
Original ANDA	November 30, 2007
Expedited Review Request	February 27, 2008
Amendment/Minor	September 22, 2008
Amendment/Minor	December 12, 2008
Gratuitous Amendment	January 14, 2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment/Minor	February 19, 2009
Amendment/Telephone	May 12, 2009
Labeling Amendment	May 28, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc.
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Alison Sherwood Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, CO 80038-0446



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Telephone/Fax:	303-438-4513/303-438-4600
----------------	---------------------------

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Triamcinolone Acetonide Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

RLD: Kenalog®-40  
Holder: Apotthecon (NDA 14-901)

10. PHARMACOL. CATEGORY:

Triamcinolone Acetonide Injectable Suspension USP is used intraarticular and intrabursally for the following indications: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute nonspecific tenosynovitis, and post-traumatic osteoarthritis.

Triamcinolone Acetonide Injectable Suspension USP is also indicated for intramuscular use as follows: endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases and edematous state.

11. DOSAGE FORM: Injectable Suspension packaged in 1mL vials

12. STRENGTH/POTENCY: 40 mg/mL

13. ROUTE OF ADMINISTRATION: Intraarticular and Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

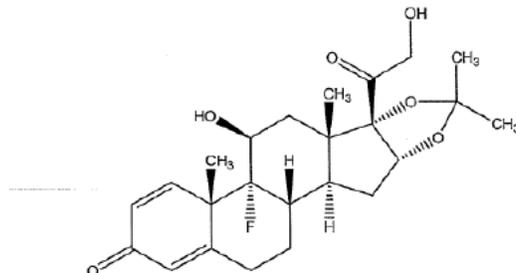
## Chemistry Review Data Sheet

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

Chemical Name: 1) Pregna-1,4-diene-3,20-dione,9-Fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis (oxy)]-(11 $\beta$ ,16 $\alpha$ ); 2) 9-fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone; 3) 9-fluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione.

Molecular Formula: C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>

Molecular Weight: 434.50


**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE 1	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	Bing Cai 03/23/09	
	III			4			
	III			4			

<sup>1</sup> 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")



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

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

### B. Related NDA/ANDA(s) and Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	90-166	Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL
Toxicity Consult	Consult# 2008-0276	(b) (4)

### 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	10/21/08	J. Wells
EES	Acceptable	02/05/09	S. Adams
Methods Validation	N/A	--	USP DS/DP
Labeling	Acceptable	07/23/08	R. Wu
Bioequivalence	Acceptable	12/23/08	D. Mitchell
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. \_\_\_ Yes \_\_\_X\_\_\_ No If no, explain reason(s) below: Expedited Review

# The Chemistry Review for ANDA 90-164

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

ANDA 90-164 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)

Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL is manufactured, packaged, labeled and tested by Sandoz Canada Inc.. The drug product is formulated Q1/Q2 to the RLD (except very minor difference in the content of benzyl alcohol). The finished product is a white suspension, with pH adjusted to 5.0 – 7.5. Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with sodium chloride for isotonicity, 0.94% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethyl-cellulose sodium, and 0.04% polysorbate 80. Sodium hydroxide or hydrochloric acid may be used to adjust pH to 5.0-7.5. At the time of manufacture, the air in the container is replaced by nitrogen. The final product is aseptically filled in (b) (4) sterile clear glass (b) (4) vials using rubber stoppers and Flip-Off aluminium seals under nitrogen.

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action achieved with the drug. The initial dose of Triamcinolone Acetonide Injectable Suspension USP may vary from 2.5 mg to 160 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Avoid freezing and protect from light. Cartons has the statement "Store vial in carton".

- 40 mg/mL, 1 mL vial

(b) (4)

The proposed expiration dating for the drug product is 24 months.

### **C. Basis for Approvability or Not-Approval Recommendation**

The ANDA is approvable:

- CMC: Acceptable
- Bio: Acceptable
- Labeling: Acceptable
- Micro: Acceptable
- EES: acceptable

Following this page, 10 pages withheld in full (b)(4)

**Stability Study Summary of Results (See CR#2):** Sandoz has provided 24 months long term stability data. All results meet the current specification. No trends were reported. Based on the data presented, Sandoz requested an expiry of 24 months for Triamcinolone Acetonide Injectable Suspension, 40 mg/mL.

**Post-approval stability protocol:** Satisfactory.

## **II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**

### **A. Labeling & Package Insert**

Items Reviewed by Chemist: *Satisfactory per #1*

**B. Environmental Assessment Or Claim Of Categorical Exclusion: See CR#1**

cc:ANDA 90-164  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/Bing Cai/

HFD-625/R. Randad (ACT)/ 3/25/09; 3/27/09

HFD-617/E. Chuh

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TYPE OF LETTER: APPROVABLE

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

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Bing Cai  
6/1/2009 02:23:45 PM  
CHEMIST

Simon Eng  
6/1/2009 03:07:38 PM  
CSO

Ramnarayan Randad  
6/2/2009 09:18:38 AM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 090164**

**BIOEQUIVALENCE REVIEWS**

ANDA 90164 and 90166  
Single-Dose Fasting Bioequivalence Study Review

**DIVISION OF BIOEQUIVALENCE REVIEW**

<b>ANDA No.</b>	90164 (40 mg/mL) and 90166 (10 mg/mL)		
<b>Drug Product Name</b>	Triamcinolone Acetonide Injectable Suspension USP		
<b>Strength(s)</b>	10 and 40 mg/mL		
<b>Applicant Name</b>	Sandoz Canada Inc.		
<b>Address</b>	145, rue Jules-Leger Boucherville, Quebec J4B 7K8 Canada  2555 W. Midway Blvd., P.O. Box 446 (US Agent) Broomfield, Colorado 80038		
<b>Applicant's Point of Contact</b>	Ms. Beth Brannan, c/o Sandoz Inc.		
<b>Contact's Telephone Number</b>	Tel: 303-438-4237		
<b>Contact's Fax Number</b>	Fax: 303-438-4600		
<b>Original Submission Date(s)</b>	November 30, 2007		
<b>Submission Date(s) of Amendment(s) Under Review</b>	None		
<b>Reviewer</b>	Minglei Cui, Ph.D.		
<b>Study Number (s)</b>	3270		
<b>Study Type (s)</b>	Fasting		
<b>Strength (s)</b>	40 mg/mL		
<b>Clinical Site</b>	Biovail Contract Research (a Division of Biovail Corporation)		
<b>Clinical Site Address</b>	460 Comstock Road / 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4S4 / M1L 4R6		
<b>Analytical Site</b>	Biovail Contract Research (a Division of Biovail Corporation)		
<b>Analytical Site Address</b>	460 Comstock Road Toronto, Ontario, Canada M1L 4S4		
<b>OUTCOME DECISION</b>	<b>Incomplete</b>		

## 1 EXECUTIVE SUMMARY

This application contains the results of the fasting bioequivalence (BE) study comparing the test product, Sandoz Inc.'s Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL, to the corresponding reference product, Apothecan's Kenalog-40® (triamcinolone acetonide) Injection, Suspension. This is a potential first generic product. The fasting BE study was designed as a two arm parallel, open label, single-dose study in healthy male and female subjects. The firm's fasting study is incomplete due to bioanalytical method deficiency. The results are summarized in the tables below.

Triamcinolone Acetonide Injectable Suspension USP 1.5 x 40 mg/mL Fasting Bioequivalence Study No. 3270, N=125 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (ng·hr/mL)	1376.92	1344.23	1.02	94.12	111.48
AUC <sub>∞</sub> (ng·hr/mL)	1616.13	1702.45	0.95	86.62	104.03
C <sub>max</sub> (ng/mL)	2.90	2.88	1.01	81.44	124.39

There is no USP dissolution method for this product. Also, the product is not listed in the current OGD internal and external dissolution databases. The firm has developed its own method (720 mL of 0.35% SDS in water using USP apparatus IV (Flow-through cell) at 8 mL/min). The firm should conduct additional dissolution testing using the following DBE-recommended method: 900 mL of water using USP apparatus II (paddle) at 75 rpm, and in different pH media, such as pH 1.2, pH 4.5 and pH 6.8 buffers. It is acceptable to add a small amount of surfactant if necessary.

The waiver request for 10 mg/mL strength of the test product is incomplete pending acceptable in vitro dissolution testing.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is **incomplete**.

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### 3 SUBMISSION SUMMARY

#### 3.1 Drug Product Information

<b>Test Product</b>	Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL
<b>Reference Product</b>	Kenalog-40®
<b>RLD Manufacturer</b>	Apothecon
<b>NDA No.</b>	014901 (Kenalog®-40) and 012041 (Kenalog®-10)
<b>RLD Approval Date</b>	January 4, 1960 for Kenalog®-10 and September 30, 1964 for Kenalog®-40.
<b>Indication</b>	Indicated for treating severe allergic conditions including seasonal or perennial allergic rhinitis, asthma, atopic or contact dermatitis, drug hypersensitivity reactions, and serum sickness.

#### 3.2 PK/PD Information<sup>1</sup>

<b>Bioavailability</b>	Not available for this route of administration.
<b>Food Effect</b>	NA
<b>T<sub>max</sub></b>	3 hours – 68 hours
<b>Metabolism</b>	Metabolized extensively in the liver. The major active metabolites are 6(beta)-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6(beta)-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination.
<b>Excretion</b>	Extensively excreted via the kidney. The majority of a dose is excreted as metabolites; only 15% is excreted unchanged.
<b>Half-life</b>	72 hours – 156 hours*
<b>Drug Specific Issues (if any)</b>	Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see <a href="#">PRECAUTIONS: Pediatric Use</a> ).

<sup>1</sup> <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6521#nlm34067-9>

ANDA 90164 and 90166  
Single-Dose Fasting Bioequivalence Study Review

	This formulation is suitable for IM and IA use only, and not for intradermal injection.
--	---

### 3.3 OGD Recommendations for Drug Product

<b>Number of studies recommended:</b>	1, fasting
---------------------------------------	------------

<b>1.</b>	<b>Type of study:</b>	Fasting
	<b>Design:</b>	Open label, single-dose in vivo BE study
	<b>Strength:</b>	40 mg/mL
	<b>Subjects:</b>	Normal healthy males and females, general population
	<b>Additional Comments:</b>	None

<b>Analytes to measure (in plasma/serum/blood):</b>	Triamcinolone Acetonide
<b>Bioequivalence based on:</b>	90% CI of Triamcinolone Acetonide
<b>Waiver request of in-vivo testing:</b>	10 mg/mL
<b>Source of most recent recommendations:</b>	OGD CD# 02-037 (b)(4), submission date: 1/11/2002-Full control review) OGD CD# 06-0452 (b)(4), submission date: 3/27/2006)
<b>Summary of OGD or DBE History</b>	<p>ANDA: none</p> <p>CDs: 02-037 (b)(4) submission date: 1/11/02), 03-0173 (b)(4) submission date: 3/13/2003) 06-0919 (b)(4) submission date: 7/20/2006)</p> <p>Protocols: 02-066 (b)(4) submission date: 12/20/2002) 04-041 (b)(4) submission date: 1/10/2005) 07010 (b)(4) submission date: 2/01/2007) 06028 (b)(4) submission date: 3/24/2006) 03037 (b)(4) submission date: 6/12/2003) 06018 (b)(4) submission date: 2/22/2006)</p>

### 3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	0
Clinical Endpoints	No	0

ANDA 90164 and 90166  
Single-Dose Fasting Bioequivalence Study Review

<b>Failed Studies</b>	No	0
<b>Amendments</b>	No	0

### 3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Vol. XVII, pg. 198-254
Analyte	Triamcinolone Acetonide
Internal Standard (IS)	(b) (4)
Method description	This method involves the extraction of Triamcinolone Acetonide and the internal standard, (b) (4) from human plasma by solid phase extraction. The analytes are separated by HPLC using reversed phase chromatographic conditions and detected by using tandem mass spectrometry. The results are quantified by peak area ratio method.
Limit of quantitation (ng/mL)	0.050
Average recovery of drug (%)	90.8
Average recovery of IS (%)	88.1
Standard curve concentrations (ng/mL)	0.050 to 6.403
QC concentrations (ng/mL)	LLOQ (0.050) QC LOW (0.150) QC MED (1.201) QC HIGH (4.802)
QC intraday precision range (%)	1.5 to 9.2
QC intraday accuracy range (%)	0.4 to 10.0
QC interday precision range (%)	4.1 to 15.8
QC interday accuracy range (%)	-0.2 to 2.1
Bench-top stability (hrs)	24 Hours @ room temperature
Stock stability (days)	19 Days @ -25°C ± 10°C
Processed stability (hrs)	95 Hours @ 4°C ± 4°C
Freeze-thaw stability (cycles)	3 cycles @ -25°C ± 10°C
Long-term storage stability (days)	To be determined
Dissolution integrity	Concentration diluted 2-fold, 4-fold, and 8-fold
Selectivity	None of the 14 sources showed significant interference at the retention time of Triamcinolone Acetonide and the internal standard.
Anticoagulant	Potassium K <sub>2</sub> EDTA

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

#### Comments on the Pre-Study Method Validation:

The %CV of the average recovery of the drug and IS is 10.8% and 5.7%, respectively.

The firm performed dilution integrity validation at 2x, 4x, and 8x. The %accuracy and %CV are 93.37% and 2.3%, 91.458% and 2.3%, and 93.762% and 1.6%, for the 2x, 4x, and 8x dilutions, respectively.

The firm did not submit long-term storage stability data. The firm should provide long term storage stability data that exceeds 128 days.

### 3.6 In Vivo Studies

**Table 1. Summary of all in vivo Bioequivalence Studies**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr) <sup>*</sup>	AUC <sub>0-t</sub> (ng·hr/mL)	AUC <sub>∞</sub> (ng·hr/mL)	T <sub>1/2</sub> (hr)	K <sub>el</sub> (hr <sup>-1</sup> )	
Study # 3270	The objective of this study was to determine and compare the rate and extent of absorption of triamcinolone acetonide from a test formulation of Triamcinolone Acetonide 40 mg/mL Injectable Solution versus the reference Kenalog <sup>®</sup> -40, 40 mg/mL Injectable Solution under fasting conditions.	Two-arm parallel, randomized	Triamcinolone Acetonide 40 mg/mL Injectable Solution i.m. Lot #1370607-1	59 completing (45M/14F) healthy subjects 41 years (19 to 77 years)	3.04 (42.15)	48.00 (1.00 - 360.00)	1362.34 (23.49)	1447.61 <sup>†</sup> (24.03)	431.83 <sup>†</sup> (43.94)	1.61E-03 <sup>†</sup> (4.17E+01)	Vol. I p.1-53
			Kenalog <sup>®</sup> -40, 40 mg/mL Injectable Solution i.m. Lot #6F11295	66 completing (53M/13F) healthy subjects 42 years (19 to 75 years)	3.03 (198.54)	48.00 (1.00 - 456.00)	1323.91 (26.71)	1517.39 <sup>†</sup> (24.22)	483.02 <sup>†</sup> (44.88)	1.44E-03 <sup>†</sup> (4.72E+01)	

\* median (range)

<sup>†</sup> n = 51

**Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer**

Triamcinolone Acetonide Injectable Suspension Dose 60 mg (1.5 mL x 40 mg/mL) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. 3270)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (units)	1376.92	1344.23	1.02	94.12	111.48
AUC <sub>∞</sub> (units)	1616.13	1702.45	0.95	86.62	104.03
C <sub>max</sub> (units)	2.90	2.88	1.01	81.44	124.39

**Table 3. Reanalysis of Study Samples**

Study No. 3270 (Groups 1-3) Additional information in Volumes XIII-XVII								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical Repeat Processing error/Outlier internal standard	9	16	0.3	0.5	9	16	0.3	0.5
Analytical Repeat Above the Limit of Quantitation	3	16	0.1	0.5	3	16	0.1	0.5
Analytical Repeat Processing error/Outlier internal standard	1	1	0.0	0.0	1	1	0.0	0.0
Analytical Repeat Poor Chromatography	2	0	0.1	0.0	2	0	0.1	0.0
Total	15	33	0.5	1.0	15	33	0.5	1.0

Study No. 3270 (Group 4) Additional information in Volumes XIII-XVII								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical Repeat Processing error/Outlier internal standard	0	2	0.0	0.6	0	2	0.0	0.6
Total	0	2	0.0	0.6	0	2	0.0	0.6

**Did use of recalculated plasma concentration data change study outcome?**

NA

**Comments from the Reviewer:**

Acceptable. No recalculation is necessary. All samples were repeated for analytical reasons according to SOP BAL-0028.

### 3.7 Formulation

Location in appendix	Section 4.2, Page 27
If a tablet, is the RLD scored?	NA
If a tablet, is the test product biobatch scored	NA
Is the formulation acceptable?	<b>FORMULATION ACCEPTABLE</b>
If not acceptable, why?	

### 3.8 In Vitro Dissolution

Location of DBE Dissolution Review	No Dissolution Review
Source of Method (USP, FDA or Firm)	Firm's method
Medium	0.35% SDS
Volume (mL)	720 mL
USP Apparatus type	USP Apparatus IV (Flow-through cell), open system & off-line
Rotation (rpm)	Dissolution Flow Rate: 8 mL/min
DBE-recommended specifications	NA
If a modified-release tablet, was testing done on ½ tablets?	NA
F2 metric calculated?	No
If no, reason why F2 not calculated	Pending the submission of dissolution testing data using FDA-recommended method
Is method acceptable?	<b>INCOMPLETE</b>
If not then why?	

Reviewer's Note: The firm's dissolution testing employed apparatus IV (flow through cell). The firm should submit additional dissolution data using apparatus II (paddle) in several media. An acceptable dissolution method and specification will be determined upon review of the additional data.

### 3.9 Waiver Request(s)

Strengths for which waivers are requested	10 mg/mL
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	Incomplete pending on the firm's satisfactory response to deficiencies
If not then why?	

### 3.10 Deficiency Comments

1. There is no USP dissolution method for this product. Also, the product is not listed in the current OGD internal and external dissolution databases. The firm has developed its own method (720 mL of 0.35% SDS in water using USP apparatus IV (Flow-through cell) at 8 mL/min), which is different from the DBE-recommended method. The firm should conduct additional dissolution testing using the following DBE-recommended method: 900 mL of water using USP apparatus II (paddle) at 75 rpm, and in different media, such as pH 1.2, pH 4.5 and pH 6.8 buffers. It is acceptable to add a small amount of surfactant if necessary.
2. The firm did not submit long-term storage stability data. The firm should provide Long Term Storage Stability data that exceeds 128 days.
3. The firm submitted chromatograms from 24 subjects. 20% of the chromatograms should be for 25 subjects (i.e. 20% of chromatograms= 20% x 125 subjects=25). For future studies, the firm should be notified to submit 20% of the total chromatograms.

### 3.11 Recommendations

#### Standard BE Studies

1. The Division of Bioequivalence finds the fasting BE study # 3270 conducted by Sandoz, Inc. on its Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL, lot # 1370607-1 comparing it to Apothecon's Kenalog-40® (triamcinolone acetonide) Injection, Suspension, lot # 6F11295, incomplete due to bioanalytical method deficiency.
2. The dissolution testing conducted is incomplete. There is no USP or DBE-recommended dissolution testing method for the test product. The DBE requests the firm to develop a suitable dissolution testing method. The method that the firm proposed is not acceptable. The firm should conduct additional dissolution testing using the following DBE-recommended dissolution method:  
  
Additional dissolution testing should be conducted in 900 mL of water, pH 1.2, pH 4.5 and pH 6.8 buffers using apparatus 2 (paddle) at 75 rpm. It is acceptable to add a small amount of surfactant if necessary. The sampling should be conducted at 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 minutes and until at least 80% of the drug is dissolved.
3. The 10 mg/mL strength is proportionally formulated to the 40 mg/mL strength. The biowaiver request for the 10 mg/mL strength of the test product is denied pending acceptable fasting study and in vitro dissolution testing.
4. The firm did not submit long-term storage stability data. The firm should provide long-term storage stability data exceeds 128 days.

5. The firm submitted chromatograms from 24 subjects. 20% of the chromatograms should be for 25 subjects (i.e. 20% of chromatograms= 20% x 125 subjects=25). For future studies, the firm should be notified to submit 20% of the total chromatograms.

**3.12 Comments for Other OGD Disciplines**

Discipline	Comment
None	

## 4 APPENDIX

### 4.1 Individual Study Reviews

#### 4.1.1 Single-dose Fasting Bioequivalence Study

##### 4.1.1.1 Study Design

**Table 4 Study Information**

<b>Study Number</b>	3270
<b>Study Title</b>	A Two Arm Parallel, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Triamcinolone Acetonide 40 mg/mL Injectable Solution Versus Kenalog <sup>®</sup> -40, 40 mg/mL Injectable Solution in Normal, Healthy, Non-Smoking Male and Post-Menopausal or Surgically Sterile Female Subjects
<b>Clinical Site (Name, Address, Phone #)</b>	Biovail Contract Research (a Division of Biovail Corporation) 460 Comstock Road / 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4S4 / M1L 4R6 Telephone: (416) 752-3636 / (416) 686-6334 Fax: (416) 752-7610 / (416) 690-1880
<b>Principal Investigator</b>	Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
<b>Dosing Dates</b>	Group 1 (10-14-2006) Group 2 (10-21-2006) Group 3 (11-04-2006) Group 4 (01-06-2007)
<b>Analytical Site (Name, Address, Phone #)</b>	Biovail Contract Research (a Division of Biovail Corporation) 460 Comstock Road Toronto, Ontario, Canada M1L 4S4 Telephone: (416) 752-3636 Fax: (416) 752-7610
<b>Analytical Dates</b>	February 01, 2007 to February 18, 2007 (Groups 1-3) April 04, 2007 to April 11, 2007 (Group 4)
<b>Analytical Director</b>	(b)(6) Ph.D.
<b>Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)</b>	128 (Groups 1-3) 95 (Group 4)

Note:

Group 1= Subjects: 1-10, 12-26, 28, 29, 31, 32, 34-50, 57-62.

Group 2=Subjects: 65-72, 75-98, 100-107.

Group 3=Subjects: 113-119, 121-134.

Group 4=Subjects: 135-142, 145, and 146.

Subjects 11, 27, 30, 33 withdrew from the study; other missing subjects were randomized before dosing but were never dosed.

**Table 5. Product information**

Product	Test	Reference
Treatment ID	Treatment A: Triamcinolone Acetonide Injectable Suspension USP	Treatment B: Kenalog®
Product Name	Triamcinolone Acetonide Injectable Suspension USP	Triamcinolone Acetonide Injectable Suspension USP
Manufacturer	Sandoz Canada Inc.	Bristol-Myers Squibb
Batch/Lot No.	1370607-1	6F11295
Manufacture date	2006-07-05	N/A
Expiration Date	N/A	Dec 2007
Strength	40 mg/mL	40 mg/mL
Dosage Form	Injectable Suspension	Injectable Suspension
Bio-batch size	(b)(4)	N/A
Production Batch Size		N/A
Potency	101.5%	101.0%
Content Uniformity (mean, %CV)	41.36 mg/mL, 1.5%	N/A
Dose Administered	60 mg	60 mg
Route of Administration	Intramuscular	Intramuscular

Note: Firm did not supply the following information in the summary table. Therefore, the reviewer has provided it below:

- 60 mg dose (1.5 mL) reflects the recommended starting dose specified in the Kenalog®-40 labeling
- Route of Administration was IM at the gluteal muscle (as per RLD labeling)

**Table 6. Study Design, Single-Dose Fasting Bioequivalence Study**

Number of Subjects	129 subject dosed (125 subjects completed, 125 analyzed)
No. of Sequences	1
No. of Periods	1
No. of Treatments	1
No. of Groups	4
Washout Period	NA
Randomization Scheme	A: 1, 2, 5, 9, 13, 14, 21, 23, 24, 25, 27, 28, 30, 31,33, 34, 38, 39, 41, 43, 45, 46, 48, 49, 51, 52, 53, 55,59, 60, 62, 64, 65, 66, 67, 71, 74, 76, 79, 82, 83, 84, 91, 92, 93, 95, 96, 97, 99, 102, 103, 104, 108, 109, 111, 112, 113, 116, 117, 119, 121, 123, 126, 127, 130, 131, 134.  B: 3, 4, 6, 7, 8, 10, 11, 12, 15, 16, 17, 18, 19, 20, 22, 26, 29, 32,35, 36, 37, 40, 42, 44, 47, 50, 54, 56, 57, 58, 61, 63, 68, 69, 70, 72, 73, 75, 77, 78, 80, 81, 85, 86, 87, 88, 89, 90, 94, 98, 100, 101, 105, 108, 109, 111, 112, 114, 115, 118, 120, 122, 124, 125, 128, 129, 132, 133.
Blood Sampling Times	0 (pre-dose), 1, 3, 6, 9, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 216, 288, 360, 456, 552, 720, 888, 1056, 1224, 1392, 1488, 1656, 1920, and 2064 hours post-dose.
Blood Volume Collected/Sample	10 ml/sample in tubes containing K2 EDTA

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<b>Blood Sample Processing/Storage</b>	Blood samples were stored in an ice bath after collection and then centrifuged for 7 minutes at 3500 rpm at 4°C. The plasma was then transferred to duplicate polypropylene tubes and stored in the freezer at -25°C until analysis.
<b>IRB Approval</b>	July 15, 2006
<b>Informed Consent</b>	July 15, 2006
<b>Length of Fasting</b>	Overnight fast of at least 10 hours
<b>Length of Confinement</b>	Overnight for at least 10 hours and up until the 36 hour post-dose blood draw (approximately 46 hours)
<b>Safety Monitoring</b>	Clinical examinations including recording of vital signs and oral body temperature were conducted at the time of check-in, check-out and at the end of study. Subjects were monitored by medical staff throughout the study period for adverse event.

**Comments on Study Design:**

The study design is acceptable

#### 4.1.1.2 Clinical Results

**Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study**

		Study No. 3270	
		Treatment Groups	
		Test Product N = 59	Reference Product N = 66
Age (years)	Mean ± SD Range	41 ± 14 (19 – 77)	42 ± 13 (19 – 75)
Age Groups	<18	0 (0.0%)	0 (0.0%)
	18 – 40	31 (52.5%)	36 (54.5%)
	41 – 64	24 (40.7%)	27 (40.9%)
	65 – 75	3 (5.1%)	3 (4.5%)
	> 75	1 (1.7%)	0 (0.0%)
Sex	Male	45 (76.3%)	53 (80.3%)
	Female	14 (23.7%)	13 (19.7%)
Race	Asian	9 (15.3%)	9 (13.6%)
	Black	5 (8.5%)	13 (19.7%)
	Caucasian	38 (64.4%)	36 (54.5%)
	Hispanic	7 (11.9%)	8 (12.1%)
	Other	0 (0.0%)	0 (0.0%)
BMI (kg/m <sup>2</sup> )	Mean ± SD	26.3 ± 3.4	26.7 ± 3.1
	Range	(19.4 – 33.6)	(20.0 – 31.5)
Other Factors			
Height (cm)	Mean ± SD	171 ± 9	173 ± 9
	Range	(150 – 191)	(151 – 192)
Weight (kg)	Mean ± SD	77 ± 12	79 ± 12
	Range	(48 – 102)	(58 – 107)

**Table 8. Dropout Information, Fasting Bioequivalence Study**

Study No. 3270				
Subject No.	Reason for dropout/replacement *	Period	Replaced?	Replaced with
011	Administrative Reasons - Dismissed on ██████████ <sup>(b)(6)</sup> at 08:40 due to non-compliance (4 consecutively missed return blood draws).	I	No	N/AP
027	Personal Reasons	I	No	N/AP
030	Personal Reasons	I	No	N/AP
033	Administrative Reasons - Dismissed on ██████████ <sup>(b)(6)</sup> at 08:40 due to non-compliance (7 missed return blood draws).	I	No	N/AP

**Table 9. Study Adverse Events, Fasting Bioequivalence Study**

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study No. 3270	
	Test	Reference
Ear and labyrinth disorders [ELD]		
Ear Pain	1 (2.4%)	0 (0.0%)
Eye disorders [EYED]		
Eye Redness	1 (2.4%)	0 (0.0%)
Gastrointestinal disorders [GD]		
Toothache	3 (7.3%)	0 (0.0%)
Abdominal Pain Lower	1 (2.4%)	0 (0.0%)
Tongue Discolouration	1 (2.4%)	0 (0.0%)
Stomach Discomfort	0 (0.0%)	1 (2.6%)
Constipation	0 (0.0%)	1 (2.6%)
General disorders and administrative site conditions [GDASC]		
Influenza Like Illness	0 (0.0%)	1 (2.6%)
Asthenia	0 (0.0%)	1 (2.6%)
Investigations [INV]		
Blood Glucose Increased	3 (7.3%)	3 (7.9%)
Blood Calcium Decreased	3 (7.3%)	1 (2.6%)
Glucose Urine Present	2 (4.9%)	0 (0.0%)
Blood Urea Increased	1 (2.4%)	0 (0.0%)
Eosinophil Count Increased	1 (2.4%)	0 (0.0%)
Platelet Count Decreased	1 (2.4%)	0 (0.0%)
Protein Urine Present	1 (2.4%)	0 (0.0%)
Aspartate Aminotransferase Increased	0 (0.0%)	4 (10.5%)
Alanine Aminotransferase Increased	0 (0.0%)	4 (10.5%)
Blood Bilirubin Increased	0 (0.0%)	1 (2.6%)
Blood Lactate Dehydrogenase (LD) Increased	0 (0.0%)	1 (2.6%)
Urine Ketone Body Present	0 (0.0%)	1 (2.6%)
Infections and infestations [IAI]		
Influenza	4 (9.8%)	1 (2.6%)
Nasopharyngitis	0 (0.0%)	1 (2.6%)
Ear Infection	0 (0.0%)	1 (2.6%)
Musculoskeletal and connective tissue disorders [MCTD]		
Back Pain	1 (2.4%)	2 (5.3%)
Pain in Extremity	2 (4.9%)	1 (2.6%)
Nervous system disorders [NSD]		
Headache	4 (9.8%)	6 (15.8%)
Somnolence	1 (2.4%)	0 (0.0%)
Dizziness	0 (0.0%)	1 (2.6%)
Reproductive system and breast disorders [RSBD]		
Prostatitis	0 (0.0%)	1 (2.6%)
Respiratory, thoracic and mediastinal disorders [RTMD]		
Cough	2 (4.9%)	3 (7.9%)
Pharyngolaryngeal Pain	2 (4.9%)	2 (5.3%)
Rhinorrhoea	1 (2.4%)	0 (0.0%)
Skin and subcutaneous tissue disorders [SSTD]		
Swelling Face	2 (4.9%)	0 (0.0%)
Rash	1 (2.4%)	0 (0.0%)
Pruritus	2 (4.9%)	0 (0.0%)
Total	41 (100%)	38 (100%)

**Table 10. Protocol Deviations, Fasting Bioequivalence Study**

Study No. 3270		
Type	Subject #s (Test)	Subject #s (Ref.)
Blood sample collection	014, 028, 030, 033, 034, 039, 046, 048, 049, 060, 083, 091, 092, 093, 096, 097, 102, 103, 126, 130, 131, 137, 144, 145	011, 016, 036, 042, 044, 047, 070, 075, 077, 078, 085, 086, 088, 089, 090, 094, 098, 101, 105, 106, 107, 114, 122, 124, 125, 132, 133, 146
Blood sample processing	N/AP	047
Concomitant medication	059, 076, 092, 096, 126, 135	008, 088, 114, 122, 139
Vital sign measurement	142	017, 090
Number of subjects and females per group	N/AP	N/AP
Posture requirement	N/AP	107
Dietary Restrictions	N/AP	129
Meal Contents	135, 137, 140, 142, 144, 145	136, 138, 139, 141, 143, 146

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

1. All of the subjects who experienced adverse events during the study were able to complete the study, with the exception of Subjects #11 (dismissed for administrative reasons) and #27 (withdrew because of personal reasons).
2. For all blood sampling time adjustments, the difference of each individual blood sampling time from the scheduled time was less than 5%, which is not considered to be significant.

#### 4.1.1.3 Bioanalytical Results

**Table 11. Assay Validation – Within the Fasting Bioequivalence Study**

Bioequivalence Study No. 3270 (Groups 1-3) Triamcinolone Acetonide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	0.050	0.100	0.200	0.400	0.799	1.599	3.198	6.395
Inter day Precision (%CV)	9.2	7.2	6.1	6.3	5.9	5.8	5.5	5.4
Inter day Accuracy (%Actual)	0.6	-0.5	-1.8	0.0	1.0	0.4	0.8	-0.5
Linearity	(Range of R <sup>2</sup> values) 0.9807 to 0.9981							
Linearity Range (ng/mL)	0.050 to 6.395							
Sensitivity/LOQ (ng/mL)	0.050							

Bioequivalence Study No. 3270 (Groups 1-3) Triamcinolone Acetonide			
Parameter	Quality Control Samples		
Concentration (ng/mL)	0.150	1.199	4.797
Inter day Precision (%CV)	8.3	6.8	6.5
Inter day Accuracy (%Actual)	1.2	3.8	3.9

Bioequivalence Study No. 3270 (Group 4) Triamcinolone Acetonide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	0.050	0.100	0.200	0.399	0.799	1.598	3.195	6.390
Inter day Precision (%CV)	8.4	6.4	5.7	4.8	4.0	4.5	7.7	6.4
Inter day Accuracy (%Actual)	0.5	-0.7	-2.6	3.2	1.3	2.3	-2.4	-0.9
Linearity	(Range of R <sup>2</sup> values) 0.9902 to 0.9958							
Linearity Range (ng/mL)	0.050 to 6.390							
Sensitivity/LOQ (ng/mL)	0.050							

Bioequivalence Study No. 3270 (Group 4) Triamcinolone Acetonide			
Parameter	Quality Control Samples		
Concentration (ng/mL)	0.150	1.200	4.800
Inter day Precision (%CV)	7.5	7.5	6.9
Inter day Accuracy (%Actual)	-2.7	3.3	3.8

Reviewer's Note: The firm reports %RE as %actual instead of %nominal.

#### Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	No
Were chromatograms serially or randomly selected?	Serially

#### Comments on Chromatograms:

The firm submitted chromatograms from 24 subjects (Subjects 105, 106, 107, 113, 114, 115, 116, 117, 118, 119, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134). 20% of chromatograms= 20% x 125 subject=25 subjects. For future studies, the firm should provide 20% of subject chromatograms.

**Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples**

SOP No.	Effective Date of SOP	SOP Title
BAL-0028 Rev. 06	07-07-2006	Criteria for Sample Reassay and Determination of Final Reported Values

**Table 13. Additional Comments on Repeat Assays**

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	NA
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	NA

**Summary/Conclusions, Study Assays:**

Acceptable

**4.1.1.4 Pharmacokinetic Results**

**Table 14. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in [Table 18](#) and [Figure 1](#)

Fasting Bioequivalence Study, Study No. 3270					
Parameter (units)	Test		Reference		T/R
	Mean	%CV	Mean	% CV	
AUC <sub>0-t</sub> (hr *ng/ml)	1400.92	23.50	1373.88	26.74	1.02
AUC <sub>∞</sub> (hr *ng/ml)	1632.52	34.01	1686.70	29.65	0.97
C <sub>max</sub> (ng/ml)	3.40	42.15	4.86	198.54	0.70
T <sub>max</sub> * (hr)	48.00	.	48.00	.	1.00
K <sub>el</sub> (hr <sup>-1</sup> )	0.00	64.57	0.00	68.54	1.46
T <sub>1/2</sub> (hr)	718.81	117.44	1157.96	130.19	0.62

\* T<sub>max</sub> values are presented as median, range

**Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated**

Triamcinolone Acetonide 40 mg/mL Injectable Solution Dose (60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (3270)				
Parameter	Test	Reference	Ratio of Means	90% Confidence Interval
AUC <sub>0-t</sub>	1362.34	1323.91	102.90%	95.05% to 111.40%
AUC <sub>∞</sub>	1447.61	1517.39	95.40%	87.90% to 103.54%
C <sub>max</sub>	3.04	3.03	100.25%	82.22% to 122.23%

**Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

Triamcinolone Acetonide 60 mg (1.5 mL x 40 mg/mL) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. 3270					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (hr *ng/ml)	1376.92	1344.23	1.02	94.12	111.48
AUC <sub>∞</sub> (hr *ng/ml)	1616.13	1702.45	0.95	86.62	104.03
C <sub>max</sub> (ng/ml)	2.90	2.88	1.01	81.44	124.39

Comments:

As the study was conducted in 4 groups, an analysis of variance was performed to test for the group by treatment interaction (Group\*Treatment). There was no statistically significant difference for the group\*treatment term for LC<sub>max</sub> ( $P > 0.1$ ), LAUCT ( $P > 0.1$ ), and LAUCI ( $P > 0.0.1$ ]. The group\*treatment, therefore, was dropped from the final statistical analysis (the pooled data from groups 1-4). The analysis model used is the following: Model Y=GRP SEQ GRP\*SEQ SUBJ (GRP\*SEQ) PER (GRP) TRT, where GRP, SEQ, PER and TRT are class variables for group, sequence, period and treatment. The 90% confidence intervals were calculated based on the model without GRP\*TRT factor.

**Table 17. Additional Study Information, Fasting Study No. 3270**

Root mean square error, AUC <sub>0-t</sub>	0.265597	
Root mean square error, AUC <sub>∞</sub>	0.276469	
Root mean square error, C <sub>max</sub>	0.664381	
	<b>Test</b>	<b>Reference</b>
Kel and AUC <sub>∞</sub> determined for how many subjects?	56*	62
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	none	none
first measurable drug concentration as C <sub>max</sub>	0	2
Were the subjects dosed as more than one group?	Yes, 4	Yes, 4

\* Of the 125 subjects whose plasma samples were analyzed, Subjects 45, 104, for the test product and Subjects 17, 22, 90, 141 for the reference product, did not have measurable Kel due to zero concentrations for the last 5 time points. This is acceptable and will likely not affect the study outcome.

Ratio of AUC <sub>0-t</sub> /AUC <sub>∞</sub>				
Treatment	n	Mean	Minimum	Maximum
Test	56	0.90	0.24	0.99
Reference	62	0.85	0.18	0.99

**Comments on Pharmacokinetic and Statistical Analysis:**

Acceptable

**Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:**

The fasting study meets the 90% confidence interval acceptance criteria for log-transformed AUC<sub>0-t</sub>, AUC<sub>∞</sub> and C<sub>max</sub> of triamcinolone acetonide. However, the fasting study is incomplete.

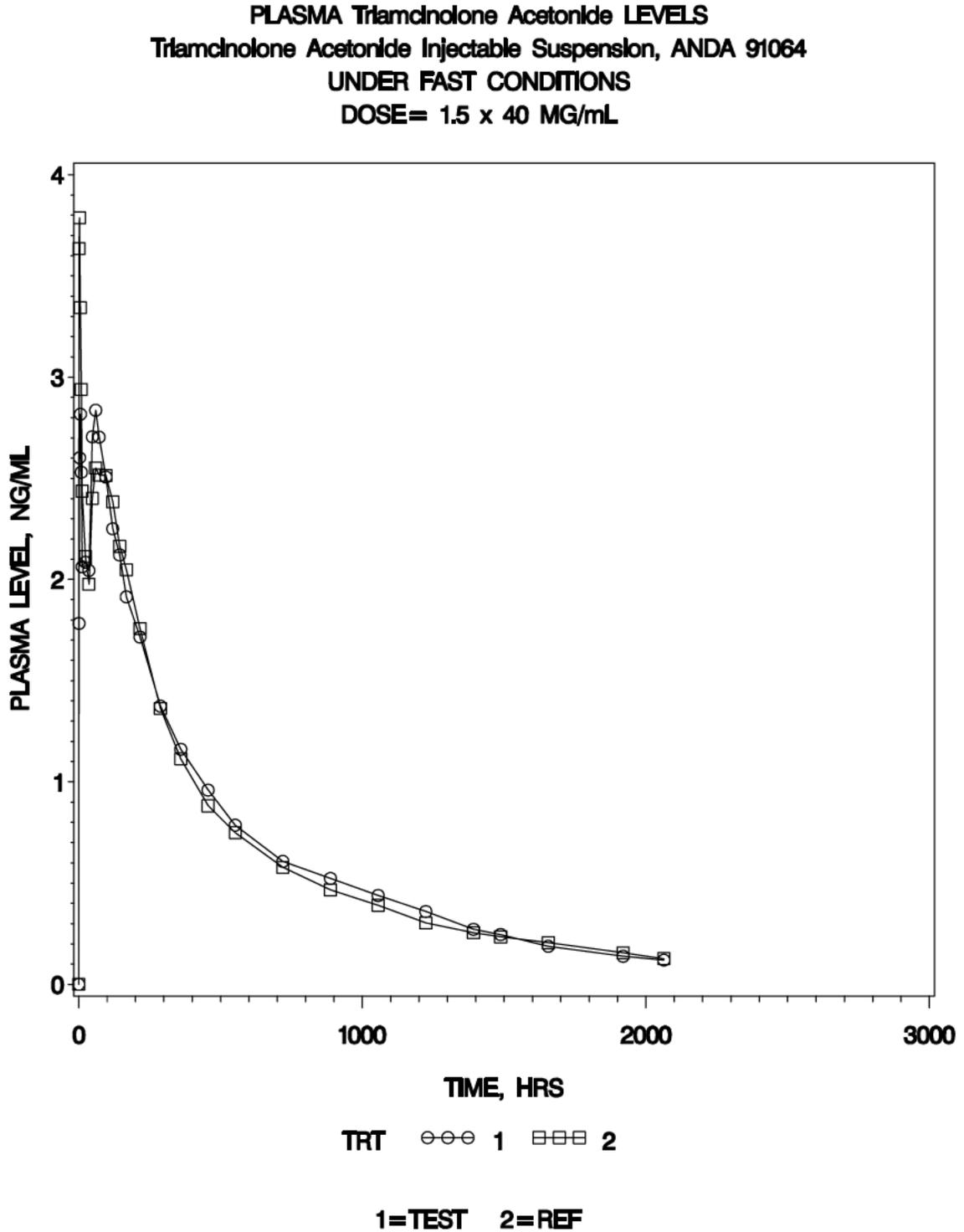
**Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

Triamcinolone Acetonide 60 mg (1.5 mL x 40 mg/mL)					
Time (hr)	Test (n=59)		Reference (n=66)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0.00	.	0.00	.	.
1	1.78	37.65	3.64	269.99	0.49
3	2.60	43.06	3.79	193.50	0.69
6	2.82	46.06	3.34	135.48	0.84
9	2.53	45.03	2.94	117.02	0.86
12	2.06	45.82	2.44	100.26	0.85
24	2.09	37.49	2.11	59.25	0.99
36	2.04	43.87	1.98	52.77	1.03
48	2.71	44.22	2.40	48.29	1.13
60	2.84	53.68	2.55	52.27	1.11
72	2.70	43.77	2.52	47.76	1.07
96	2.51	43.40	2.51	44.35	1.00
120	2.25	39.66	2.38	45.82	0.94
144	2.12	38.16	2.16	41.97	0.98
168	1.91	37.40	2.05	45.77	0.93
216	1.72	30.24	1.76	37.74	0.98
288	1.37	29.84	1.36	40.38	1.01
360	1.16	29.51	1.11	40.91	1.04
456	0.96	28.55	0.88	36.29	1.09
552	0.79	27.42	0.75	35.99	1.05
720	0.61	32.98	0.58	37.35	1.05
888	0.52	34.31	0.47	39.55	1.12
1056	0.44	46.26	0.39	48.01	1.12
1224	0.36	43.89	0.30	52.02	1.19
1392	0.27	55.57	0.25	57.92	1.07
1488	0.25	60.13	0.23	60.16	1.05
1656	0.19	72.30	0.21	67.37	0.91

ANDA 90164 and 90166  
Single-Dose Fasting Bioequivalence Study Review

<b>1920</b>	0.14	88.42	0.16	81.01	0.89
<b>2064</b>	0.12	98.54	0.13	83.04	0.95

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.2 Formulation Data<sup>2,3,4</sup>

% w/v Cores	Test				Reference		Function	% difference (T vs R)	IIG levels
	40 mg/mL		10 mg/mL		40 mg/mL				
	mg/mL	%w/v	mg/mL	%w/v	mg/mL	%w/v			
Triamcinolone Acetonide	40	4.0	10	4.0	40	0.4	Active	0	
Carboxymethylcellulose Sodium	7.5	0.75	7.5	0.75	7.5	0.75	(b) (4)	0	(b) (4)
Polysorbate 80	0.4	0.04	0.4	0.04	0.4	0.04		0	
Sodium Chloride	(b) (4)						Tonicity agent	0	
Benzyl Alcohol	9.4	0.94	9.4	0.94	9.9	0.99	Preservative	5%	
Nitrogen*	Head space	+	Head space	+			Head space blanket	-	-
Hydrochloric Acid (initial concentration) (b) (4) **	+	+	+	+	q.s.p H to 5.0-7.5		pH adjuster	-	-
Sodium Hydroxide**	+	+	+	+	q.s.p H to 5.0-7.5		pH adjuster	-	-
(b) (4)								-	-
Water for Injection	q.s. 1 mL		q.s. 1 mL				Solvent	-	-

<sup>2</sup> COMIS

<sup>3</sup> 90166 ANDA Checklist General in DFS

<sup>4</sup> Control Document # 060919

ANDA 90164 and 90166  
Single-Dose Fasting Bioequivalence Study Review

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	No
Comments on the drug product formulation:	See below

**Comments:**

1. All the inactive ingredients are below the levels published in the IIG data base.
2. There are no differences between the test product and the RLD, same excipients quantitatively and qualitatively except the benzyl alcohol content. For the test product, benzyl alcohol was reduced to 0.94% w/v compared to 0.99% w/v in the RLD. Per FDA guidance under 21 CFR 314.94 (9)(iii), *“an applicant may seek approval of a drug product for parental use that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the difference and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug”*. Since the difference of benzyl alcohol between and the test product is only 5% and no safety issues was observed during the *In-Vivo* Bioequivalence study (study #3270), the difference is permitted for inactive ingredients under 21 CFR 314.94 (9)(iii).
3. The formulation of the test 10 mg/mL is proportionally similar in its active and inactive ingredients to that of the 40 mg/mL strength.

### 4.3 Dissolution Data

<b>Dissolution Review Path</b>	No dissolution review
--------------------------------	-----------------------

**Table 19. Dissolution Data**

Dissolution Conditions		Apparatus:		USP Apparatus IV (Flow-through cell), open system & off-line												Study Report Locat	
		Speed of Rotation:		Dissolution Flow Rate: 8 mL/ min													
		Medium:		0.35% SDS													
		Volume:		720 mL													
		Temperature:		37°C													
Dissolution Testing Site (Name, Address)		Sandoz Canada Inc., 145 Jules Leger Street, Boucherville (QC) Canada J4B 7K8															
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) Reference – Expiration Date)	Dosage Strength & Form	No. of Dosag e Units		Collection Times (minutes)											
						5	10	15	20	30	40	50	60	70	80		90
Study Report #: ADSR- 07-21(01)	07/05/22	Triamcinolone Acetonide Injectable Suspension Lot 1280605	10 mg/mL Injectable	12	Mean	13.5	26.1	35.6	43.1	53.9	61.3	66.8	71.0	74.4	77.1	79.5	(b) (4)
					Range												
					%CV	5.3	3.0	4.0	4.8	6.2	7.3	8.0	8.4	8.8	9.0	9.2	
	07/05/22	Reference, Kenalog <sup>®</sup> Exp: 04 - 2008 Lot 6G15740	10 mg/mL Injectable	12	Mean	14.7	29.6	42.0	50.9	62.1	69.2	73.8	77.2	79.7	81.8	83.5	(b) (4)
					Range												
					%CV	5.1	3.0	2.7	2.7	3.0	3.4	3.6	3.7	3.7	3.7	3.7	
	07/05/22	Triamcinolone Acetonide Injectable Suspension Lot 1370607-1	40 mg/mL Injectable	12	Mean	13.8	27.4	38.5	46.8	57.9	65.0	70.0	73.8	76.8	79.4	81.6	(b) (4)
					Range												
					%CV	2.5	2.4	3.4	4.1	4.5	4.2	4.2	4.2	4.2	4.2	4.2	
	07/05/22	Triamcinolone Acetonide Injectable Suspension Lot 1120702	40 mg/mL Injectable	12	Mean	14.2	28.1	39.0	46.8	57.2	64.5	70.0	74.1	77.2	79.7	81.6	(b) (4)
					Range												
					%CV	4.0	2.6	2.6	2.7	3.3	3.8	4.1	4.4	4.6	4.7	4.7	
	07/05/22	Reference, Kenalog <sup>®</sup> Exp: 04 - 2008 Lot 6F11295	40 mg/mL Injectable	12	Mean	14.6	29.0	40.9	49.9	62.0	69.5	74.8	78.7	81.7	84.2	86.2	(b) (4)
					Range												
					%CV	3.9	2.1	2.1	2.5	3.2	3.3	3.3	3.2	3.2	3.2	3.2	

Modul  
5.3.1.3  
Page 1

Comments:

1. There is no USP dissolution method for this product. Also, the product is not listed in the current OGD internal and external dissolution databases. The firm has developed its own method (720 mL of 0.35% SDS in water using USP apparatus IV (Flow-through cell) at 8 mL/min). The firm should conduct additional dissolution testing using the following DBE-recommended method: 900 mL of water using USP apparatus II (paddle) at 75 rpm, and in different pH media, such as pH 1.2, pH 4.5 and pH 6.8 buffers. It is acceptable to add a small amount of surfactant if necessary. The sampling times are 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 minutes until at least 80% of the drug is dissolved.

2. The firm did try to develop a method in 900 mL of water (with and without SDS) using Apparatus II (paddle) at 50 rpm. The method was rejected because of the poor solubility of Triamcinolone Acetonide Suspension in the water and lack of dissolution profile of the test and reference products in water with SDS.

2. F2 values are not calculated pending on the firm's satisfactory response to the DBE reviewer's comments and submission of dissolution testing data using FDA-recommended method.

Dissolution testing data are **incomplete**.

Following this page, 18 pages withheld in full (b)(4) SAS Output

BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-164 (40 mg/mL) and 90-166 (10 mg/mL)

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Triamcinolone Acetonide Injectable  
Suspension USP, 10 mg/mL and 40 mg/mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. Your proposed dissolution method is not acceptable. Please conduct additional comparative dissolution testing on 12 individual dosage units for the test and reference products using the following DBE-recommended method:

Additional dissolution testing should be conducted in 900 mL of water using USP apparatus II (paddle) at 75 rpm and in different pH media, i.e. pH 1.2, pH 4.5 and pH 6.8 buffers, at 37°C ± 0.5°C. It is acceptable to add a small amount of surfactant if necessary. The sampling times are 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 minutes until at least 80% of the drug is dissolved.

2. Please submit long term storage stability data that exceeds 128 days.

3. You have submitted chromatograms from 24 subjects. 20% of chromatograms= 20% x 125 analyzed subject= 25 subject chromatograms. For future studies, please submit 20% of the total chromatograms.

Sincerely yours,

{See appended electronic signature page}

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

**4.5 Outcome Page**

ANDA: 90164 and 90166

**Reviewer:** Cui, Minglei

**Date Completed:**

**Verifier:** ,

**Date Verified:**

**Division:** Division of Bioequivalence

**Description:** also ANDA 90166

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
5031	11/30/2007	Bioequivalence Study	Fasting Study	1	1
5031	11/30/2007	Other	Dissolution Waiver	1	1
				<b>Bean Total:</b>	<b>2</b>

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

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Minglei Cui  
3/18/2008 02:09:11 PM  
BIOPHARMACEUTICS

Paul Seo  
3/18/2008 02:22:32 PM  
BIOPHARMACEUTICS

Barbara Davit  
3/18/2008 06:33:33 PM  
BIOPHARMACEUTICS

## DIVISION OF BIOEQUIVALENCE REVIEW

<b>ANDA No.</b>	90164 (40 mg/mL) and 90166 (10 mg/mL)
<b>Drug Product Name</b>	Triamcinolone Acetonide Injectable Suspension
<b>Strength(s)</b>	10 mg/mL and 40 mg/mL
<b>Applicant Name</b>	Sandoz Canada Inc.
<b>Address</b>	2555 W. Midway Blvd. P.O. Box 446 (US Agent) Broomfield, Colorado 80038
<b>Applicant's Point of Contact</b>	Ms. Beth Brannan, c/o Sandoz Inc.
<b>Contact's Telephone Number</b>	303-438-237
<b>Contact's Fax Number</b>	303-438-4600
<b>Original Submission Date(s)</b>	November 30, 2007 (ANDA # 90164 and # 90166)
<b>Submission Date(s) of Amendment(s) Under Review</b>	May 08, 2008 (ANDA # 90164 and # 90166) June 10, 2008 (ANDA # 90164 and #90166)
<b>Reviewer</b>	Deanah L. Mitchell, Ph.D.
<b>Study Number (s)</b>	3270
<b>Study Type (s)</b>	Fasting
<b>Strength (s)</b>	40 mg/mL
<b>Clinical Site</b>	Biovail Contract Research (a Division of Biovail Corporation)
<b>Clinical Site Address</b>	460 Comstock Road / 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4S4 / M1L 4R6
<b>Analytical Site</b>	Biovail Contract Research (a Division of Biovail Corporation)
<b>Analytical Site Address</b>	460 Comstock Road Toronto, Ontario, Canada M1L 4S4
<b>OUTCOME DECISION</b>	<b>INCOMPLETE</b>

### Review of an Amendment

#### 1 Executive Summary

On May 08, 2008, the firm, Sandoz, Inc., submitted an amendment to its *first generic* application for Triamcinolone Acetonide Injectable Suspension. The amendment is in response to a deficiency letter sent to the firm dated March 25, 2008 from the Division of Bioequivalence (DBE) concerning bioanalytical deficiencies and incomplete dissolution testing. In the deficiency letter the DBE requested the firm (1) to conduct and submit additional comparative dissolution testing using the DBE-recommended method [900 mL of Water using USP Apparatus II (Paddle) at 75 rpm and in different pH media, i.e. pH 1.2, pH 4.5 and pH 6.8 buffers, at 37°C ± 0.5°C], (2) to submit sufficient long-term storage stability data for triamcinolone in the biological matrix, and (3) to submit 20% of the subjects chromatograms. The firm addressed the bioanalytical deficiencies in its responses to the deficiency letter for its fasting bioequivalence (BE) study No. 3270

(ANDA #90164). The firm's responses to the bioanalytical deficiencies are acceptable. The fasting BE study is now acceptable. In addition, the firm also conducted and submitted the additional comparative dissolution testing results using the FDA-recommended method and in the different pH media (pH 1.2, 4.5 and 6.8 buffer). The DBE recommends the dissolution medium of Water with the firm's addition of 0.35% Sodium Dodecyl Sulfate (SDS) and no pH adjustment because the difference in pH does not affect the drug release. The firm did not propose any specifications for its test product.

Therefore, based on the dissolution testing data, the firm should acknowledge and accept the following FDA-recommended method and specifications:

Medium:	Water with 0.35% SDS
Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Speed:	75 rpm
Volume:	900 mL

Specifications:	15 min: NLT <span style="background-color: #cccccc; padding: 0 5px;">(b) (4)</span>
	60 min: NLT <span style="background-color: #cccccc; padding: 0 5px;"> </span>

The waiver of *in vivo* BE study requirements for its 10 mg/mL strength suspension (ANDA # 90166) is granted as per the criteria set forth in 21 CFR § 320.22 (d) (2).

However, the application is still incomplete pending the firm's acknowledgement of the FDA-recommended dissolution method and specifications.

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### 3 Background

On November 30, 2007, the firm submitted two applications. **ANDA # 90-164** contained a single dose, two arm parallel, open label, *in vivo* bioequivalence (BE) study under fasting conditions comparing its test product, Triamcinolone Acetonide Injectable Suspension, 40 mg/mL to the corresponding reference product, Kenalog-40<sup>®</sup> Injection (triamcinolone acetonide injectable suspension, USP) by Bristol-Myers Squibb Company. **ANDA # 90-166** contained a biowaiver request for 10 mg/mL strength of the test product. The BE study results are provided below (DFS, Review/Bioequivalence Review/Biopharmaceutics/ N 090166 N 000 30-Nov-2007):

<b>Triamcinolone Acetonide Injectable Suspension USP</b>					
<b>1.5 x 40 mg/mL</b>					
<b>Fasting Bioequivalence Study No. 3270, N=125</b>					
<b>Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals</b>					
<b>Parameter (units)</b>	<b>Test</b>	<b>Reference</b>	<b>Ratio</b>	<b>90% C.I.</b>	
<b>AUC<sub>0-t</sub> (ng·hr/mL)</b>	1376.92	1344.23	1.02	94.12	111.48
<b>AUC<sub>∞</sub> (ng·hr/mL)</b>	1616.13	1702.45	0.95	86.62	104.03
<b>C<sub>max</sub> (ng/mL)</b>	2.90	2.88	1.01	81.44	124.39

However, the firm's fasting BE study was incomplete due to bioanalytical deficiencies. The firm did not submit sufficient long-term storage stability data for triamcinolone in the biological matrix nor did the firm submit 20% of the subjects' chromatograms.

There is no USP dissolution method for this product. The product is not listed in the current Office of Generic Drugs (OGD) internal and external dissolution databases. The firm developed its own dissolution method (720 mL of 0.35% SDS in Water using USP Apparatus IV (Flow-through cell) at 8 mL/min) and submitted comparative dissolution testing on all strengths of its test and reference products. The firm's dissolution testing with its proposed method was determined to be not acceptable. Therefore, the firm was asked to conduct additional dissolution testing using the following DBE-recommended method: 900 mL of Water using USP Apparatus II (Paddle) at 75 rpm, and in different pH media, such as pH 1.2, pH 4.5 and pH 6.8 buffers with the addition of surfactant if necessary.

The 10 mg/mL strength is proportionally similar to the 40 mg/mL strength. The biowaiver request for the 10 mg/mL strength of the test product was denied pending an acceptable fasting BE study and comparative *in vitro* dissolution testing.

Therefore, at the time of the initial review, the application was determined to be incomplete with deficiencies.

## 4 Deficiency Comments

### 4.1 Deficiency Comment No. 1

1. *Your proposed dissolution method is not acceptable. Please conduct additional comparative dissolution testing on 12 individual dosage units for the test and reference products using the following DBE-recommended method. Additional dissolution testing should be conducted in 900 mL of water using USP apparatus II (paddle) at 75 rpm and in different pH media, i.e. pH 1.2, pH 4.5 and pH 6.8 buffers, at 37°C ± 0.5°C. It is acceptable to add a small amount of surfactant if necessary. The sampling times are 5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 minutes until at least 80% of the drug is dissolved.*

### **Firm's Response**

Additional comparative dissolution studies have been performed on the Sandoz Canada products and on the reference listed drugs (RLDs), Kenalog. Please note that the study could not be performed on the same RLD lots described in ANDA 90-164 and 90-166. The limited quantity available on the market per lot, the quantity required for the bioequivalence study (including the required retained samples) and the quantity required to perform the proposed study (more than 40 vials), did not allow Sandoz Canada to use the same lots. Both concentrations (10 mg/mL and 40 mg/mL) have been tested according to the parameters summarized in the following table.

Tested products	-Triamcinolone Acetonide Injectable Suspension 10 mg/mL vs Kenalog 10 mg/mL -Triamcinolone Acetonide Injectable Suspension 40 mg/ml vs Kenalog 40 mg/mL
Apparatus	USP apparatus II (paddle)
Medium:	0.35% Sodium Dodecyl Sulfate
Speed	75 rpm
Temperature:	37 ± 0.5°C
pH	1.2 ± 0.5, 4.5 ± 0.05 and 6.8 ± 0.05
Units	12
Volume of solution	900 mL
Sampling times	5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 minutes

The choice and the amount of surfactant used in the present study was based on the dissolution results presented in the ANDA 90-164 and 90-166 submissions which demonstrate that the addition of 0.35% of surfactant is necessary to reach an 80% level of drug dissolution. Dispersion in water produced an apparent steady-state level of 40% drug dissolution over time. The obtained results (please refer to appendix -1-) demonstrate that under the prescribed conditions, the drug dissolved rapidly in the first 5 minutes (47% to 66%). The 80% level of dissolution was reached at 30 to 40 minutes. Thereafter, the dissolution increase slowly to a plateau level between 89% to 98%. The dissolution profiles are similar between the Sandoz Canada products and the RLD. Furthermore, the results presented in the ADSR0725 and ADSR0726 reports using the

original RLD lots have similar profiles which validate the results from the new RLD lots (Data tables extracted from these reports are presented in appendix -2-). The study parameters were equivalent (only the mixing speed is lower; 50 rpm instead of 75 rpm). The data also demonstrate that the pH has no impact on the dissolution profile of these suspensions. Based on the presented results, the USP Apparatus II might not be the best system to evaluate the dissolution of these suspension products when compared to the USP Apparatus IV. The Apparatus IV design reduces the quantity of solvent in contact with the suspension, delaying the dissolution of the powder and giving a more discriminatory dissolution profile.

#### **4.2 Deficiency Comment No. 2**

2. *Please submit long term storage stability data that exceeds 128 days.*

#### **Firm's Response**

Please find enclosed in appendix -3- the requested long term storage stability data that exceeds 128 days for Triamcinolone Acetonide Injectable Suspension. The data is included in page 32 of 51 of the Bioanalytical Method Validation Report.

#### **4.3 Deficiency Comment No. 3**

3. You have submitted chromatograms from 24 subjects. 20% of chromatograms = 20% x 125 analyzed subject = 25 subject chromatograms. For future studies, please submit 20% of the total chromatograms.

#### **Firm's Response**

Sandoz Canada Inc. duly notes that in future studies we will submit 20% of the total chromatograms. Also, find enclosed in appendix -4- the requested 25th chromatogram for Triamcinolone Acetonide Injectable Suspension.

### **5 Reviewer's Comments**

1. The firm conducted and submitted the comparative dissolution testing data for the 12 dosage units of the test and RLD products using the DBE-recommended method [900 mL of Water using USP Apparatus II (Paddle) at 75 rpm and in different pH media, pH 1.2, pH 4.5 and pH 6.8 buffers, at 37°C ± 0.5°C] (see [Additional Attachments](#) section). The firm added 0.35% of the surfactant, Sodium Dodecyl Sulfate (SDS) to each of the media.

Based on the reviewer's assessment and a dissolution consult it was determined that the firm's proposed dissolution method using Apparatus IV appears to be more discriminatory, however, at 90 minutes, the drug release from the dosage form did not reach 80%. Also, USP Apparatus IV is not generally used and the method introduces too many variables (i.e., flow rate, type of cells, glass beads, and size of sampling

tube). Therefore, the firm's dissolution testing with its proposed method is not acceptable.

The dissolution profiles using the DBE-recommended method in the different pH media shows that the dissolution profiles of the test product are pH independent. The dissolution profiles for both strengths are comparable for all pHs. The DBE recommends no pH adjustment for this product.

The firm did not propose any specifications for its test product using the DBE-recommended method.

Based on the dissolution testing data, the DBE proposes the following specifications for the firm's test product:

15 min: NLT (b) (4)  
60 min: NLT [REDACTED]

The firm should acknowledge and accept the DBE-recommended method and specifications

*Note: The amendment submitted by the firm on June 10, 2008 contained the comparative dissolution testing using the DBE-recommended method. The firm added 0.35% SDS to the media.*

2. The long-term storage stability data provided by the firm in human plasma at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  for Triamcinolone Acetonide for 458 days is acceptable.
3. The firm provided the requested chromatograms.
4. At this time, the BE study for ANDA 90164 is considered acceptable. The waiver request for ANDA 90166 is granted. However, the firm's application is **incomplete** pending the firm's acknowledgement of the DBE-recommended method and specifications for its test product.

## 6 Deficiency Comment

The firm should acknowledge the following DBE-recommended method and specifications:

Medium: Water with 0.35% Sodium Dodecyl Sulfate  
Apparatus: USP Apparatus II (Paddle)  
Temperature: 37°C ± 0.5°C  
Speed: 75 rpm  
Volume: 900 mL

Specifications: 15 min: NLT (b) (4)  
60 min: NLT (b) (4)

## 7 Recommendation

1. The Division of Bioequivalence (DBE) accepts the fasting BE study (study No. 3270) conducted by Sandoz Canada Inc. on its Triamcinolone Acetonide Injectable Suspension, 40 mg/mL strength (lot # 1370607) comparing it to Apothecon's Kenalog-40<sup>®</sup> (Triamcinolone Acetonide) Injection, Suspension (lot # 6F11295).
2. The in-vitro dissolution testing conducted by Sandoz Canada Inc., using the DBE-recommended method is acceptable for its Triamcinolone Acetonide Injectable Suspension, 10 mg/mL strength (lot # 1280605) and 40 mg/mL strength (lot # 1370607). The dissolution testing should be conducted in 900 mL of Water with 0.35% Sodium Dodecyl Sulfate (SDS) using USP Apparatus II (Paddle) at 75 rpm at 37°C ± 0.5°C. The DBE recommends the following specifications:

Time	Specification
15 min	NLT (b) (4)
60 min	NLT (b) (4)

The firm should acknowledge the DBE-recommended method and specifications.

3. The biowavier request for the firm's 10 mg strength suspension is granted as per the criteria set forth in 21 CFR § 320.22 (d) (2). However, the application is still incomplete pending the firm's acknowledgement of the FDA-recommended dissolution method and specification.

The firm should be informed of the above deficiency comment and recommendation.

## 8 Dissolution Consult

### Consult Review #1

**From:** Braddy, April  
**Sent:** Thursday, June 12, 2008 1:23 PM  
**To:** Jiang, Xiaojian; Mitchell, Deanah  
**Cc:** Braddy, April  
**Subject:** FW: ANDA 90164 & 90166- Priority A - TL comments

Xiaojian:

Based on our concurrence we will propose the firm conduct dissolution testing using the DBE-recommended method (as per deficiency letter dated March 25, 2008) of

Medium: Water w/ 0.35% SDS (added by firm)  
Apparatus: USP Apparatus II (Paddle)  
Temperature: 37°C ± 0.5°C  
Speed: 75 rpm  
Volume: 900 mL

Specifications: 15 min: (b) (4)  
30 min: (b) (4)  
60 min: NLT (b) (4)

Deanah, please change your review accordingly.

Thanks,

April

---

**From:** Jiang, Xiaojian  
**Sent:** Thursday, June 12, 2008 1:17 PM  
**To:** Braddy, April  
**Cc:** Jiang, Xiaojian; Mitchell, Deanah  
**Subject:** RE: ANDA 90164 & 90166- Priority A - TL comments

Hi, April:

I agree with you that the surfactant but not the pH plays roles in drug dissolution. There is no FDA method for this Injectable. The firm proposed the method of 0.35% SDS in water using apparatus IV.

The dissolution data in 0.35% SDS in water without pH adjustment are comparable with in 0.35% SDS with pH adjustment to pH 6.8. The dissolution in both media are complete and less variable. I prefer 0.35% SDS without pH adjustment because 1) the dissolution is pH independent 2) the water without pH adjustment is easy to prepare, 3) if we recommend 0.35% SDS at pH 6.8, the firm should use phosphate buffer to prepare this pH not only use NaOH to adjust the pH.

The specification for water without pH adjustment will be slightly different from the previous recommendation. It should be:

15 min: (b) (4)  
30 min: (b) (4)  
60 min: NLT (b) (4)

Thanks

Xiaojian Jiang, Ph.D.  
Division of Bioequivalence, OGD, CDER, FDA  
E-mail: [xiaojian.jiang@fda.hhs.gov](mailto:xiaojian.jiang@fda.hhs.gov)  
1356 MPNI, Phone: 240-276-8799

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**From:** Braddy, April  
**Sent:** Thursday, June 12, 2008 10:35 AM  
**To:** Jiang, Xiaojian  
**Cc:** Braddy, April  
**Subject:** ANDA 90164 & 90166- Priority A - TL comments

Xiaojian,

Upon review of the dissolution data, it appears that the surfactant and not the pH plays a role in the release of the drug. Therefore, it is possible that recommending the FDA-method with surfactant may be acceptable.

Please review the data.

Thanks,

April

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**From:** Mitchell, Deanah  
**Sent:** Thursday, June 12, 2008 10:29 AM  
**To:** Jiang, Xiaojian  
**Cc:** Braddy, April; Mitchell, Deanah  
**Subject:** ANDA 90164 & 90166- Priority A

Good Morning Xiaojian,

In the process of finalizing ANDA 90164 (Triamcinolone), April realized that the original deficiency letter requested the firm to conduct additional comparative dissolution testing in 900 mL of water using USP apparatus II (paddle) at 75 rpm **and** in different pH media, i.e. pH 1.2, pH 4.5 and pH 6.8 buffers. The firm submitted the dissolution testing in the three different pH medias, but did not include dissolution testing in water alone (without pH adjustment). Therefore, we contacted the firm and asked them to submit the dissolution testing in water alone. I have included my review for ease of locating the dissolution data tables (they are not uploaded in the EDR yet, but I have a hard copy). Your original recommendation was for **water adjusted to pH 6.8**. Now that we have water (without pH adjustment), can you please take another look at the data and provide us with your recommendation. I have also included the excel file with the dissolution profiles.

<< File: 90164A0508v2.doc >>      << File: 90164-90166 Dissolution Profiles and F2 Calculation.xls >>

Thank you,

Deanah L. Mitchell, Ph.D.

## Consult Review #2

**From:** Braddy, April  
**Sent:** Thursday, June 19, 2008 11:08 AM  
**To:** Mitchell, Deanah  
**Cc:** Braddy, April  
**Subject:** FW: REVIEW [DBE1] 90164 & 90166 Triamcinolone Acetonide Injectable Suspension - 05-08-08 & 06-10-08 - IC - Approvals Matrix - Deanah

Good morning, Deanah:

As per Hoai's e-mail, please make the requested changes.

Thanks,

April

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**From:** Nguyen, Hoainhon T  
**Sent:** Thursday, June 19, 2008 11:07 AM  
**To:** Braddy, April  
**Cc:** Conner, Dale P; Davit, Barbara M; Nguyen, Hoainhon T  
**Subject:** RE: REVIEW [DBE1] 90164 & 90166 Triamcinolone Acetonide Injectable Suspension - 05-08-08 & 06-10-08 - IC - Approvals Matrix - Deanah

April,

Since the %'s dissolved overlap at the three time points selected, i.e., 15, 30 and 60 minutes, I suggest the following specs for the test product: 15 minutes: NLT (b) (4) and 60 minutes: NLT (b) (4). We don't need the 30 minute time point. The product is a slow-releasing dosage form but it is not exactly ER dosage form.

Also, at this time, we can grant the waiver request since no additional data are needed for consideration of the waiver. The application is still considered incomplete pending the firm's acknowledgement of our recommended method and specs. When the amendment comes in with dissolution acknowledgment only the PM can close out the application without sending the amendment to us for granting the waiver.

Please revise accordingly.

Thanks,

Hoai

**9 Additional Attachments**

**9.1 Dissolution Data**

**A. Summary of In-vitro dissolution profiles for Triamcinolone Acetonide Injectable Suspension 10 mg/mL and 40 mg/mL at pH 6.80**

<b>Dissolution Conditions</b>	<b>Apparatus:</b>	USP apparatus II (paddle)
	<b>Speed of Rotation:</b>	75 rpm
	<b>Medium:</b>	pH 6.80 ± 0.05 (adjusted with NaOH 0.1N) 0.35% SDS (Sodium Dodecyl sulfate)
	<b>Volume:</b>	900 mL
	<b>Temperature:</b>	37.0 ± 0.5°C
	<b>Sampling Times</b>	5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 minutes

**Table 1: Dissolution profile for 12 dosage units of Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL (lot: 1370607-1)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
<b>average</b>	54.3	66.7	74.1	78.6	84.3	87.8	89.9	91.5	92.7	93.6	94.2
<b>%RSD</b>	1.9	1.2	1.7	1.5	1.5	1.7	1.7	1.6	1.7	1.5	1.7
<b>min</b>	(b) (4)										
<b>max</b>											

**Table 2: Dissolution profile for 12 dosage units of Kenalog-40 (lot: 6F13029, exp.: 2008-05)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	49.2	61.5	69.6	75.1	82.8	87.4	90.6	92.3	93.6	94.1	94.6
%RSD	1.4	1.4	1.1	1.1	1.3	1.2	1.3	1.4	1.4	1.5	1.4
min	(b) (4)										
max											

**Table 3: Dissolution profile for 12 dosage units of Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL (lot: 1280605)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	54.1	66.3	73.0	77.7	83.2	86.4	88.4	90.1	91.0	91.6	92.3
%RSD	2.1	1.9	1.6	1.6	1.8	1.4	1.6	1.6	1.7	1.9	1.8
min	(b) (4)										
max											

**Table 4: Dissolution profile for 12 dosage units of Kenalog-10 (lot: 7H28592, exp.: 2009-07)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	65.7	76.9	82.7	86.7	91.2	93.9	95.0	95.7	96.1	96.2	96.7
%RSD	1.4	1.5	1.5	1.6	1.9	1.8	1.8	1.8	1.8	1.8	2.0
min	(b) (4)										
max											

**B. Summary of In-vitro dissolution profiles for Triamcinolone Acetonide Injectable Suspension 10 mg/mL and 40 mg/mL at pH 4.50**

<b>Dissolution Conditions</b>	<b>Apparatus:</b>	USP apparatus II (paddle)
	<b>Speed of Rotation:</b>	75 rpm
	<b>Medium:</b>	pH 4.50 ± 0.05 (adjusted with HCl 0.1N) 0.35% SDS (Sodium Dodecyl sulfate)
	<b>Volume:</b>	900 mL
	<b>Temperature:</b>	37.0 ± 0.5°C
	<b>Sampling Times</b>	5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 minutes

**Table 5: Dissolution profile for 12 dosage units of Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL (lot: 1370607-1)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	51.9	64.1	70.9	75.3	80.6	83.8	85.9	87.5	88.6	89.2	90.1
%RSD	4.1	3.6	3.5	3.7	3.5	3.6	3.8	3.8	3.8	3.6	3.6
min	(b) (4)										
max											

**Table 6: Dissolution profile for 12 dosage units of Kenalog-40 (lot: 6F13029, exp.: 2008-05)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	52.3	62.7	70.3	76.6	84.1	88.8	92.0	94.0	95.3	95.9	96.3
%RSD	2.0	2.2	1.4	1.8	1.3	1.2	1.2	1.0	1.6	1.3	1.2
min	(b) (4)										
max											

**Table 7: Dissolution profile for 12 dosage units of  
Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL (lot: 1280605)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	53.4	64.9	71.5	75.6	80.7	83.7	85.7	87.1	88.0	88.8	89.3
%RSD	2.5	3.2	3.3	3.5	3.2	3.7	3.6	3.6	3.8	3.8	3.8
min	(b) (4)										
max											

**Table 8: Dissolution profile for 12 dosage units of Kenalog-10 (lot: 7H28592, exp.: 2009-07)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	65.8	77.8	84.0	87.9	92.9	95.5	96.7	97.6	98.0	98.1	98.2
%RSD	1.8	0.8	0.6	0.4	0.4	0.3	0.2	0.4	0.3	0.4	0.3
min	(b) (4)										
max											

**C. Summary of In-vitro dissolution profiles for Triamcinolone Acetonide Injectable Suspension 10 mg/mL and 40 mg/mL at pH 1.20**

<b>Dissolution Conditions</b>	<b>Apparatus:</b>	USP apparatus II (paddle)
	<b>Speed of Rotation:</b>	75 rpm
	<b>Medium:</b>	pH 1.20 ± 0.05 (adjusted with HCl) 0.35% SDS (Sodium Dodecyl sulfate)
	<b>Volume:</b>	900 mL
	<b>Temperature:</b>	37.0 ± 0.5°C
	<b>Sampling Times</b>	5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 minutes

**Table 9: Dissolution profile for 12 dosage units of Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL (lot: 1370607-1)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	52.9	64.9	71.7	76.5	81.5	84.5	86.4	87.7	88.6	89.2	89.5
%RSD	1.3	2.4	3.0	3.6	3.5	3.6	3.7	3.7	3.8	3.7	3.5
min	(b) (4)										
max											

**Table 10: Dissolution profile for 12 dosage units of Kenalog-40 (lot: 6F13029, exp.: 2008-05)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	47.2	60.0	68.0	73.7	81.4	86.2	89.2	91.3	92.6	93.3	93.7
%RSD	2.7	2.3	2.3	1.9	2.1	2.2	2.1	2.1	2.3	2.3	2.2
min	(b) (4)										
max											

**Table 11: Dissolution profile for 12 dosage units of  
Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL (lot: 1280605)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	53.0	65.2	72.0	76.4	81.9	85.2	87.2	88.7	89.7	90.2	90.8
%RSD	2.0	2.0	2.3	2.3	2.6	2.5	2.8	2.9	2.8	2.9	2.9
min	(b) (4)										
max											

**Table 12: Dissolution profile for 12 dosage units of Kenalog-10 (lot: 7H28592, exp.: 2009-07)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
average	62.0	74.3	80.2	84.2	88.9	91.7	93.0	94.0	94.3	94.6	94.5
%RSD	3.6	2.6	2.3	2.0	2.1	1.5	1.3	1.4	1.2	1.3	1.3
min	(b) (4)										
max											

**Summary of In-vitro dissolution profiles for Triamcinolone Acetonide Injectable Suspension 10 mg/mL and 40 mg/mL**

<b>Dissolution Conditions</b>	<b>Apparatus:</b>	USP apparatus II (paddle)
	<b>Speed of Rotation:</b>	75 rpm
	<b>Medium:</b>	<b>Water, without pH adjustment</b> 0.35% SDS (Sodium Dodecyl sulfate)
	<b>Volume:</b>	900 mL
	<b>Temperature:</b>	37.0 ± 0.5°C
	<b>Sampling Times</b>	5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 minutes

**Table 13: Dissolution profile for 12 dosage units of Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL (lot: 1370607-1)**

Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
<b>average</b>	53.5	66.7	73.5	78.1	83.6	86.6	88.6	90.0	90.9	91.5	92.0
<b>%RSD</b>	1.2	1.0	1.0	1.4	1.4	1.7	1.9	2.0	2.0	2.1	2.2
<b>min</b>	(b) (4)										
<b>max</b>											

**Table 14: Dissolution profile for 12 dosage units of Kenalog-40 (lot: 6F13029, exp.: 2008-05)**

Dosage unit	Cumulative dissolution of each time point (%)												
	5	10	15	20	30	40	50	60	70	80	90	(b) (4)	
1													(b) (4)
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
<b>average</b>	51.9	65.4	73.6	79.4	87.5	92.5	95.7	97.8	98.9	99.7	100.2	(b) (4)	
<b>%RSD</b>	2.9	2.0	1.7	1.6	1.7	1.6	1.6	1.6	1.7	1.7	1.7	(b) (4)	
<b>min</b>													(b) (4)
<b>max</b>													

**Table 15: Dissolution profile for 12 dosage units of  
Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL (lot: 1280605)**

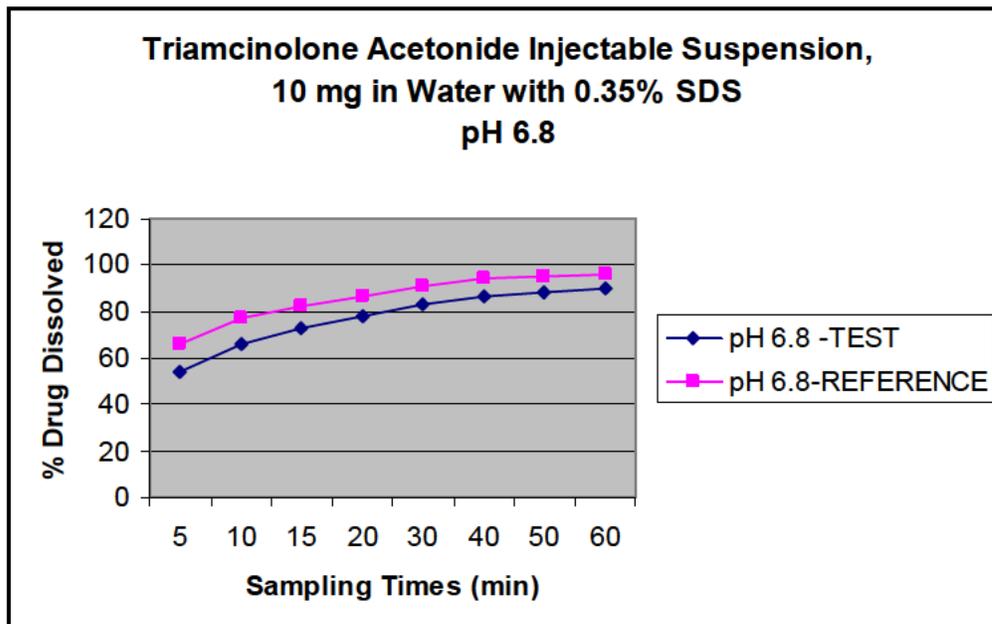
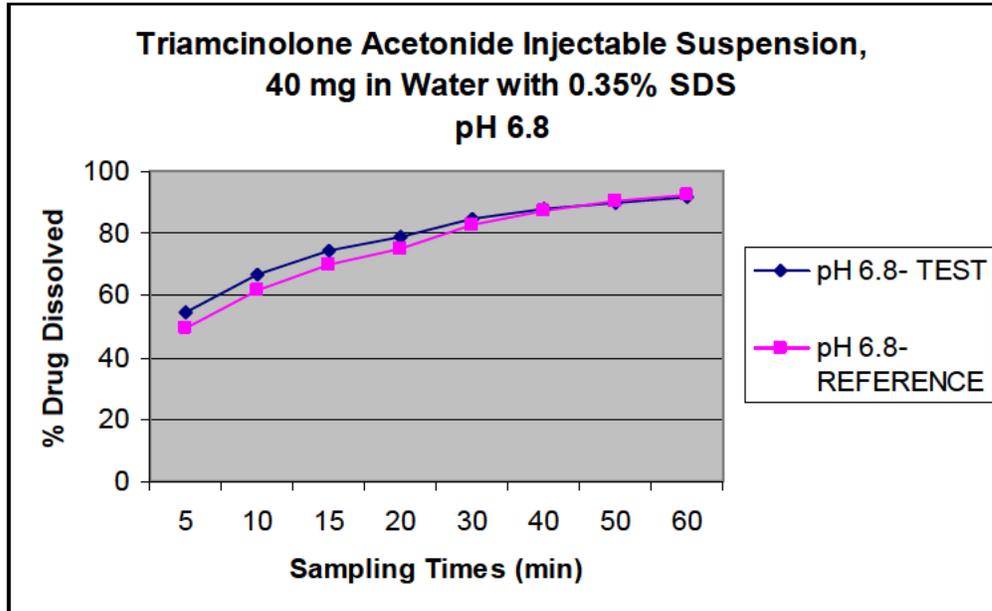
Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
<b>average</b>	54.3	67.1	74.0	78.5	84.2	87.6	89.8	91.2	92.2	93.0	93.7
<b>%RSD</b>	0.8	0.7	0.6	0.8	0.8	0.8	1.0	1.0	1.0	1.0	1.0
<b>min</b>	(b) (4)										
<b>max</b>											

**Table 16: Dissolution profile for 12 dosage units of Kenalog-10 (lot: 7H28592, exp.: 2009-07)**

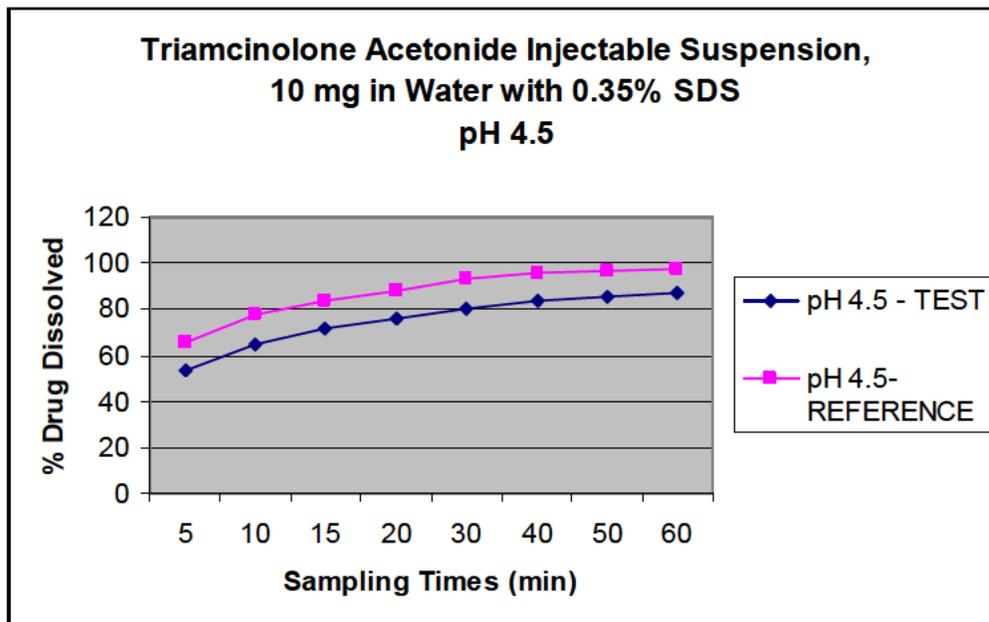
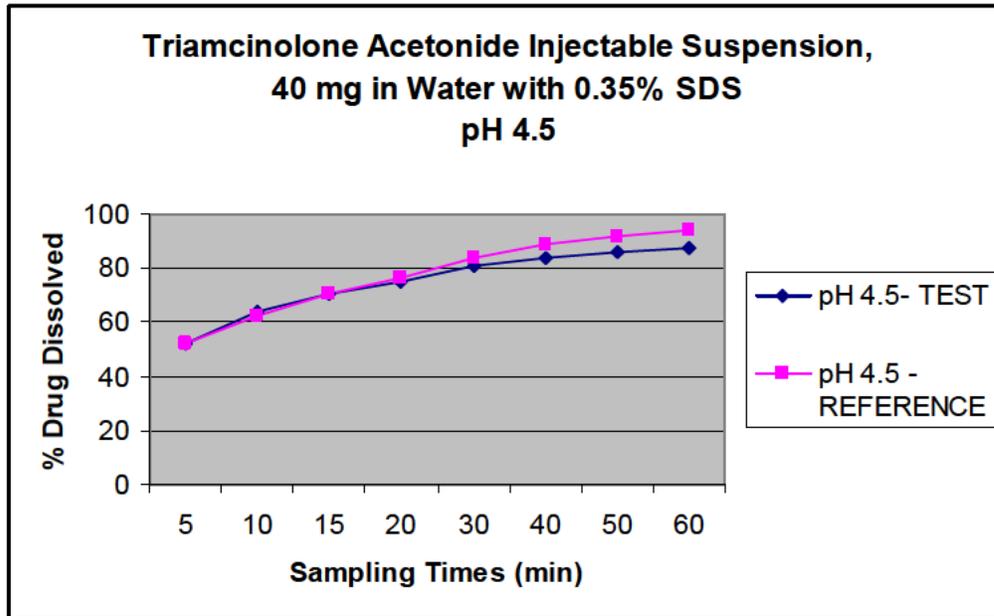
Dosage unit	Cumulative dissolution of each time point (%)										
	5	10	15	20	30	40	50	60	70	80	90
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
<b>average</b>	66.3	77.4	83.3	87.3	91.8	94.2	95.7	96.1	96.7	97.1	97.0
<b>%RSD</b>	1.3	0.8	0.6	0.5	0.7	0.8	0.8	0.9	0.8	0.9	0.9
<b>min</b>	(b) (4)										
<b>max</b>											

## 9.2 Dissolution Profiles

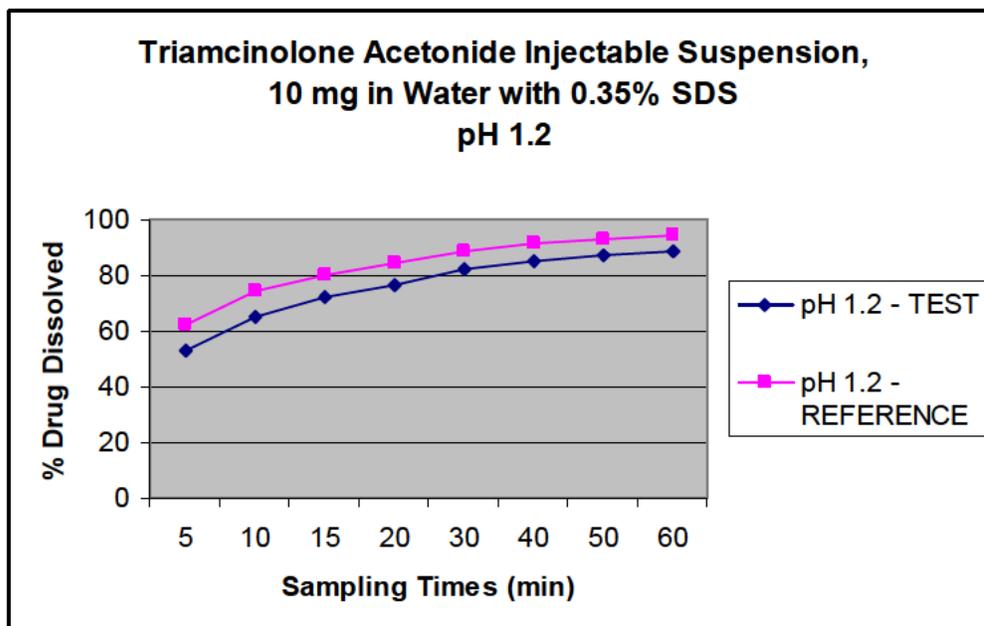
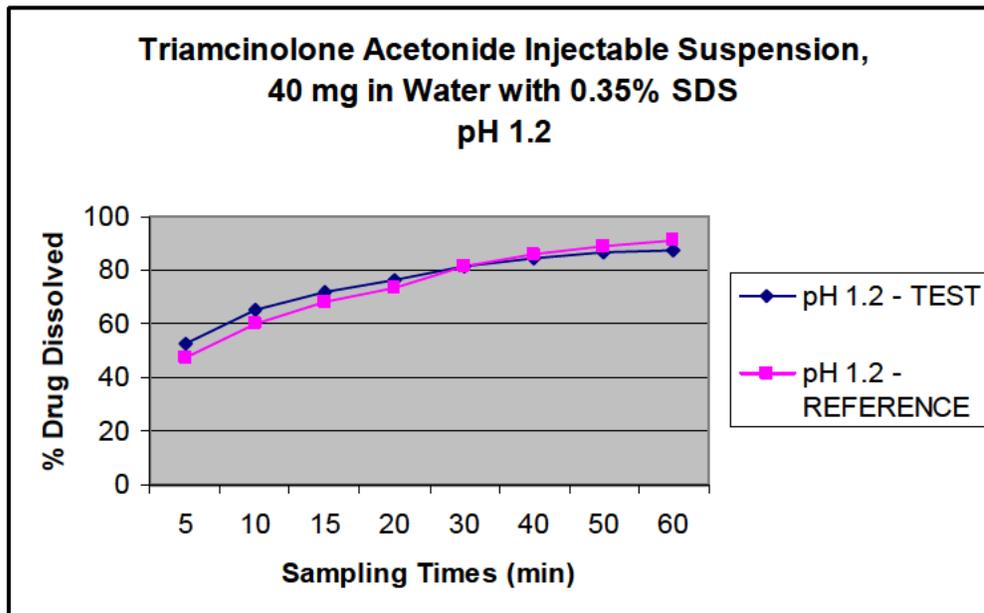
### A. 0.35% at pH 6.8



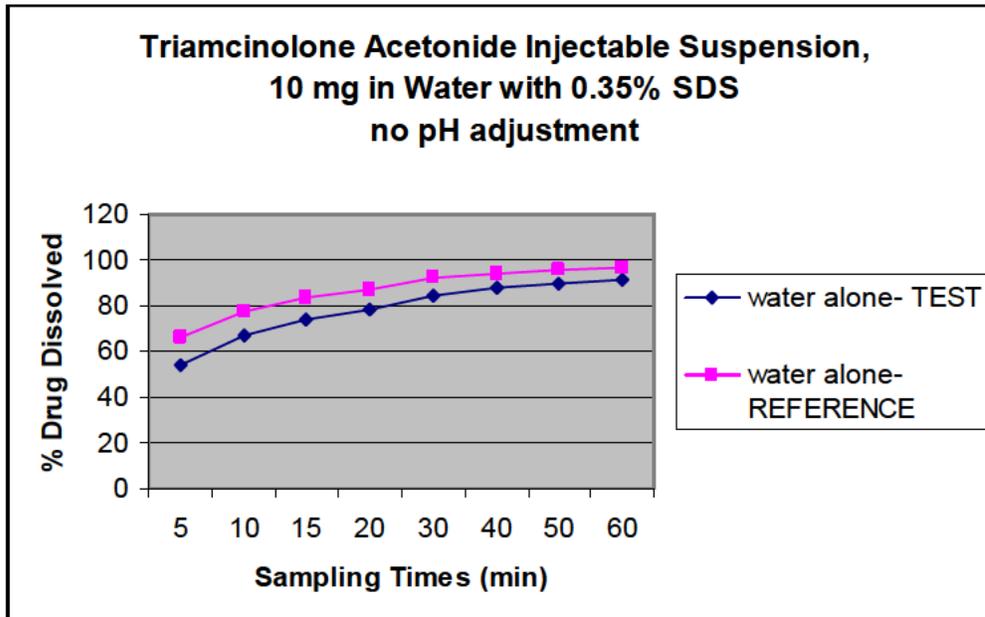
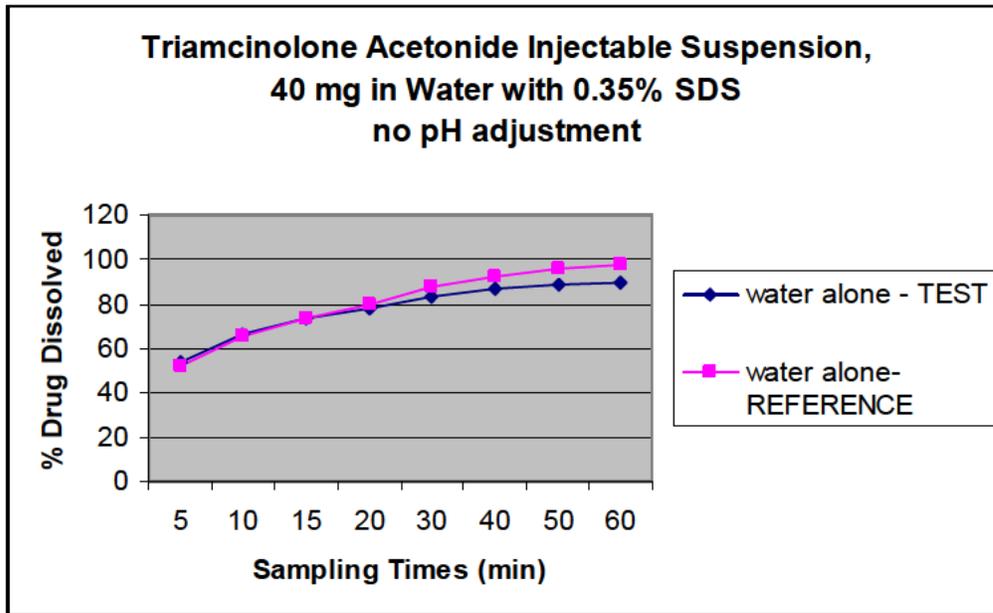
**B. 0.35% SDS at pH 4.5**



C. 0.35% at pH 1.2



**D. 0.35% no pH adjustment**



BIOEQUIVALENCE DEFICIENCY

ANDA: 90-164 and 90-166  
APPLICANT: Sandoz Canada Inc.  
DRUG PRODUCT: Triamcinolone Acetonide Injectable  
Suspension, 10 mg/mL and 40 mg/mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiency has been identified:

The dissolution testing using the FDA-recommended method is acceptable. Based on the submitted dissolution data, the DBE recommends the below specifications for the test product. Please acknowledge the following FDA-recommended method and specifications for your Triamcinolone Acetonide Injectable Suspension, 10 mg/mL and 40 mg/mL:

Medium:	Water with 0.35% Sodium Dodecyl Sulfate (SDS)
Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Speed:	75 rpm
Volume:	900 mL
Specifications:	15 min: NLT  (b) (4)
	60 min: NLT 

Sincerely yours,

{See appended electronic signature page}

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

**10 Outcome Page**

**ANDA: 90-164**

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
5715	5/8/2008	Other	Study Amendment	1	1
5715	6/10/2008	Other	Study Amendment Without Credit (WC)	0	0
				<b>Bean Total:</b>	<b>1</b>

**ANDA 90-166**

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
5716	5/8/2008	Other	Study Amendment	1	1
5716	6/10/2008	Other	Study Amendment Without Credit (WC)	0	0
				<b>Bean Total:</b>	<b>1</b>

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this page is the manifestation of the electronic signature.**  
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/s/

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Deanah L Mitchell  
6/20/2008 04:14:45 PM  
BIOPHARMACEUTICS

April Braddy  
6/23/2008 09:59:48 AM  
BIOPHARMACEUTICS

Hoainhon T. Nguyen  
6/23/2008 11:33:57 AM  
BIOPHARMACEUTICS  
For Dale P. Conner, Pharm. D., Director, Division of  
Bioequivalence I

## DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90164 (40 mg/mL) and 90166 (10 mg/mL)
Drug Product Name	Triamcinolone Acetonide Injectable Suspension USP
Strength(s)	10 mg/mL and 40 mg/mL
Applicant Name	Sandoz Canada Inc.
Address	2555 W. Midway Blvd. P.O. Box 446 (US Agent) Broomfield, Colorado 80038
Applicant's Point of Contact	Ms. Beth Brannan, c/o Sandoz Inc.
Contact's Telephone Number	303-438-4237
Contact's Fax Number	303-438-4600
Original Submission Date(s)	November 30, 2007 (ANDA # 90164 and # 90166 amendment)
Submission Date(s) of Amendment(s) Under Review	August 01, 2008 (ANDA # 90164 and # 90166 amendment)
Reviewer	Deanah L. Mitchell, Ph.D.
<b>OUTCOME DECISION</b>	<b>INCOMPLETE</b>

### Review of an Amendment

#### 1 Executive Summary

On August 01, 2008, the firm, Sandoz, Inc., submitted an amendment to its *first generic* application for Triamcinolone Acetonide Injectable Suspension. The amendment is in response to a deficiency letter sent to the firm dated June 24, 2008 from the Division of Bioequivalence (DBE) concerning incomplete dissolution testing<sup>1</sup>. In the deficiency letter the DBE requested the firm to acknowledge the FDA-recommended dissolution method [900 mL of Water with 0.35% SDS using USP Apparatus II (Paddle) at 75 rpm] and specifications [15 min: NLT (b)(4) and 60 min: NLT (b)(4)]. The firm responded to the deficiency letter and has accepted the FDA-recommended method. However, the firm is proposing the dissolution specification at the 15 minute time point be changed from (b)(4) (as recommended by the FDA) to (b)(4) for both strengths of its test product. The firm based the proposal change on a change in the particle size of the Active Pharmaceutical Ingredient (API) and the drug manufacturer's process capability.

The proposed specification change at the 15 minute time point from (b)(4) (as previously recommended by the FDA) to (b)(4) based on the particle size range of the API, is not acceptable. The firm is asked to submit additional evidence to support its specification adjustment request and demonstrate that the difference in the particle size of the API has no effect on in vivo bioequivalence or performance of the test product.

<sup>1</sup>DFS, Review/Bioequivalence Review/Biopharmaceutics/N 090164 N 000 AB 08-May-2008.

As per the current Division of Bioequivalence policy, the firm should submit additional dissolution data for three fresh finished production lots of its test product (both strengths), and not exhibit lots, as currently submitted. The data of full dissolution profile should be submitted for 12 individual dosage units of each of these production lots which should be manufactured in the same conditions as the bio-lot, using the API of the same particle size (with any difference to be within the approved particle size specification range), in order to justify its proposed specification. Alternatively, the firm should acknowledge and accept the original FDA recommended dissolution method and specifications for its test product:

Medium:	Water with 0.35% SDS
Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Speed:	75 rpm
Volume:	900 mL

Specifications:	15 min: NLT [REDACTED] (b) (4)
	60 min: NLT [REDACTED]

Also, the firm is asked to verify that the bio-lot API lot #0130524 mentioned in the current amendment is the same as the bio-lot API lot # 129830 given in the original submission.

The waiver of *in vivo* BE study requirements for its 10 mg/mL strength suspension (ANDA # 90166) is granted as per the criteria set forth in 21 CFR § 320.22 (d) (2).

However, the application is still incomplete pending the firm's submission of additional information and further clarification on the particle size range of the API used for manufacturing the test product.

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### 3 Background

On November 30, 2007, the firm submitted two applications: (1) **ANDA # 90-164** which contained a single dose, two-arm parallel, open label, *in vivo* bioequivalence (BE) study under fasting conditions comparing its test product, Triamcinolone Acetonide Injectable Suspension, 40 mg/mL to the corresponding reference product, Kenalog-40<sup>®</sup> Injection (triamcinolone acetonide injectable suspension, USP) by Bristol-Myers Squibb Company; (2) **ANDA # 90-166** which contained a biowaiver request for 10 mg/mL strength of the test product. The BE study results are provided below (DFS, Review/Bioequivalence Review/Biopharmaceutics/ N 090166 N 000 30-Nov-2007):

<b>Triamcinolone Acetonide Injectable Suspension USP</b>					
<b>1.5 x 40 mg/mL</b>					
<b>Fasting Bioequivalence Study No. 3270, N=125</b>					
<b>Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals</b>					
<b>Parameter (units)</b>	<b>Test</b>	<b>Reference</b>	<b>Ratio</b>	<b>90% C.I.</b>	
<b>AUC<sub>0-t</sub> (ng·hr/mL)</b>	1376.92	1344.23	1.02	94.12	111.48
<b>AUC<sub>∞</sub> (ng·hr/mL)</b>	1616.13	1702.45	0.95	86.62	104.03
<b>C<sub>max</sub> (ng/mL)</b>	2.90	2.88	1.01	81.44	124.39

However, the firm's fasting BE study was incomplete due to bioanalytical deficiencies. The firm did not submit sufficient long-term storage stability data for triamcinolone in the biological matrix nor did the firm submit 20% of the subjects' chromatograms.

There is no USP dissolution method for this product. The product is not listed in the current FDA internal and external dissolution databases. The firm developed its own dissolution method [720 mL of 0.35% SDS in Water using USP Apparatus IV (Flow-through cell) at 8 mL/min] and submitted comparative dissolution testing on all strengths of its test and reference products. The firm's dissolution testing with its proposed method was determined to be not acceptable. Therefore, the firm was asked to conduct additional dissolution testing using the following DBE-recommended method: 900 mL of Water using USP Apparatus II (Paddle) at 75 rpm, and in different pH media, such as pH 1.2, pH 4.5 and pH 6.8 buffers with the addition of surfactant if necessary.

The 10 mg/mL strength is proportionally similar to the 40 mg/mL strength. The biowaiver request for the 10 mg/mL strength of the test product was denied pending an acceptable fasting BE study and comparative *in vitro* dissolution testing.

Therefore, at the time of the initial review, the application was determined to be incomplete with deficiencies.

In an amendment dated May 08, 2008, the firm provided acceptable responses to the deficiencies in the initial review. The fasting BE study (ANDA 90164) was found to be acceptable and the biowaiver was granted for its 10 mg/mL strength suspension (ANDA # 90166) as per the criteria set forth in 21 CFR § 320.22 (d) (2). Although the firm

conducted dissolution testing as requested, the firm did not propose any specifications for its test product. Therefore, the application was still incomplete pending the firm's acknowledgement of the FDA-recommended dissolution method and specifications for its test product.<sup>1</sup>

The current amendment contains the firm's response to the dissolution method and specification acknowledgement request by the DBE.

## 4 Deficiency Comments

### 4.1 Deficiency Comment No. 1

1. *The dissolution testing using the FDA-recommended method is acceptable. Based on the submitted dissolution data, the DBE recommends the below specifications for the test product. Please acknowledge the following FDA-recommended method and specifications for your Triamcinolone Acetonide Injectable Suspension, 10 mg/mL and 40 mg/mL:*

<i>Medium:</i>	<i>Water with 0.35% Sodium Dodecyl Sulfate (SDS)</i>
<i>Apparatus:</i>	<i>USP Apparatus II (Paddle)</i>
<i>Temperature:</i>	<i>37 °C ± 0.5 °C</i>
<i>Speed:</i>	<i>75 rpm</i>
<i>Volume:</i>	<i>900 mL</i>
<i>Specifications:</i>	<i>15 min: NLT (b) (4)</i>
	<i>60 min: NLT (b) (4)</i>

### **Firm's Response**

We accept the DBE-recommended method for dissolution testing of Triamcinolone Acetonide Injectable Suspension USP 10 and 40 mg/mL using USP Apparatus II. However, we would like to propose a modification of the 15 minute specification from (b) (4) to (b) (4)

Sandoz Canada received a request in our chemistry deficiency letter dated June 6, 2008 with respect to the control of particle size of the API. In response to this request Sandoz Canada is proposing the following drug substance particle size specifications:

D<sub>50</sub>: (b) (4)  
D<sub>90</sub>: (b) (4)

The limits for the particle size distribution have been proposed based on four drug substance lots manufactured by (b) (4). These limits allow for the manufacturer's process capability and this particle size distribution has also been observed in the RLD. Sandoz Canada Inc. performed a series of dissolution tests with the Paddle II apparatus using FDF samples manufactured with these different lots of API with particle sizes spanning the specification limit range. The results of this study are presented in Table 1.

Table 1: Dissolution results obtained with lots spanning the limit range for API particle size

(b) (4)	d50 (µM)	d90	Disso % 15 min	Disso % 60 min
Lot 0080724	(b) (4)			
Lot 0070724	(b) (4)			
Lot 0130524*	(b) (4)			
Lot 0060624	(b) (4)			

\* (b) (4) lot 0130524 is the lot used in the manufacture of Sandoz Canada's 40 mg/mL bio batch and 10 mg/mL ANDA batch, results in this table reflect an optimized particle size method which will be filed in the CMC deficiency response.

On the basis of these results, Sandoz Canada Inc. would like to propose the following: A limit of (b) (4) at 15 minutes.

The information provided in this amendment is identical to the information being submitted at this time to ANDA 90-166 for our 10 mg/mL ANDA.

## 5 Reviewer's Comments

1. Based on the dissolution data provided by the firm, there is a direct relationship between the particle size and the dissolution rate: the smaller the particle size, the faster the dissolution rate. However, the firm has not provided any evidence to demonstrate that difference in the particle size of the API lots will not affect the in vivo performance/bioequivalence of the test product. In addition, there are currently insufficient data provided by the firm to justify for an appropriate particle size range which can be considered as acceptable upper and lower limits of the bio lot particle size.
2. The firm stated that the particle size distribution observed in different API lots for the test product "*has also been observed in the RLD*". It is not clear on which data the firm based this statement since the particle size range of the API of the RLD product is not public information. Only the particle size of the RLD finished product can be measured by the firm. The firm is asked to provide data to support its statement concerning the API particle size range of the RLD product.

With respect to the particle size data of the finished RLD product: ***The firm did not submit particle size data for any lots of the finished RLD product of the 40 mg/mL strength.*** However, the firm has submitted for the Chemistry review of the ANDA 90166 (in the submission dated November 30, 2007) the particle size data for several finished product lots of the 10 mg/mL of the RLD product, for comparison with a test lot No. 1280605 of the same strength, as follow:

Parameter	Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL	Kenalog® Lot 6K21219:Exp.09-08 Lot 5MO6227:Exp.12-07	Kenalog® Lot 6G15740:Exp.04-08	Kenalog® Lot 5M01726:Exp.11-07
Batch No.	1280605	Lots *6K21219 and **5MO6227	6G15740	5M01726
Size	(b) (4)			
Density [g/mL]				
pH***				
Osmolality [mOsm/kg]				
Particle Size [µm]				
Viscosity [cSt]				
Surface tension [dynes/cm]				
* Lot 6K21219 was used for the following tests: Density, Osmolality, Viscosity and Surface Tension was used for the pH test. ** Lot 5MO6227 was used for the pH and Particle size tests. ***Labeling: pH =5.0-7.5. N/P = Not performed				

Based on the particle size data presented above, although the 10 mg/mL strength of the RLD product showed variations in the particle size distribution profile, it appeared that the particle size profile for this strength of the RLD product was much different and (b) (4) than that of the 10 mg/mL strength of the test product.

Comparing the above particle size data with those provided for the 40 mg/mL strength of the test product below, it appeared that the particle size distribution profile for the 40 mg/mL of the test product was much more variable (than the 10 mg/mL strength of the RLD product as seen above). The range of the particle size of the finished test product at the 40 mg/mL was (b) (4) and (b) (4) the range of the particle size of the finished RLD product at the 10 mg/mL, whereas the range of particle size of the bio batch No. 1370607-1 (40 mg/mL) and the exhibit batch No. 1280605 (10 mg/mL) of the test product was more comparable.

Test	Procedure	Specifications (Drug Substance)	Test results Lots# (Drug Substance)		
			129830	137291	138079
Particle size	PS-0008	d50: (b) (4) d90: (b) (4)	(b) (4)		
Test	Procedure	Specifications (Product)	Test results Lots# (Drug Product)		
			1370607-1 (1mL bio batch)	1450710 (b) (4)	1120702 (b) (4)
Particle size	PS-0007	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)

Based on the particle size data provided by the firm for the finished test product (10 mg/mL and 40 mg/mL) and the finished RLD product (10 mg/mL strength only) above, it is not possible to compare the particle size profiles of the bio lots of the test and RLD products which have been found bioequivalent in the fasting BE study.

3. The firm did not provide the following necessary information for the currently submitted dissolution data: (1) how many units of the finished lots were tested, and (2) whether the dissolution values as submitted were single or mean values.
4. For the 15 minute dissolution time point, three out of four of the dissolution values, (b)(4) (lot# 0070724, 0130524, 0060624, respectively) met the FDA-recommended specification [15 min: (b)(4)]. The fourth dissolution value of (b)(4) (lot # 0080724) did not meet the FDA-recommended specification and also does not even meet the firm's new proposed specification [15 min: (b)(4)].
5. The firm states that “(b)(4) lot 0130524 is the lot used in the manufacture of Sandoz Canada's 40 mg/mL bio batch and 10 mg/mL ANDA batch...” However, based on the chemistry review of the original ANDA submission (DFS, Review/Chemist/N 090164 N 000 30-Nov-2007), a different drug substance lot number (i.e., #129830) was used to manufacture the test bio lot # 1370607-1. The firm should verify the API lot #0130524 mentioned in the current amendment is the same as the API lot # 129830 given in the original submission.
6. Based on the above discussion, the DBE does not consider that the firm has submitted appropriate dissolution data to justify for the proposed dissolution specification change at the 15 minute sampling time point.

As per the current DBE policy, in order to justify for any change of the FDA-recommended dissolution specifications of the test product, the firm should provide dissolution data of at least three fresh finished production lots of its test product (both strengths) that are manufactured based on approved manufacturing specifications. The data of full dissolution profile for 12 individual dosage units of each lot manufactured in the same conditions as the bio-lot, using the API of the same particle size (within the approved particle size specification range) should be submitted.

The dissolution data as currently submitted raised a concern that difference in the particle size of the API of the test product could result in difference in *in vivo* performance of the final product as the data have shown that the particle size had direct effect on the dissolution rate of the final product. The firm should submit additional evidence for demonstrating that the change in particle size has no effect on *in vivo* performance or bioequivalence of the test product.

7. At this time, the BE study for ANDA 90164 is considered acceptable. The waiver request for ANDA 90166 is granted. However, the application is **incomplete** pending the firm's submission of additional information and further clarification on the particle size range of the API used for manufacturing the test product, as stated above.

## 6 Deficiency Comment

1. The firm's proposed specification change at the 15 minute time point, from (b) (4) (as previously recommended by the FDA) to (b) (4), which is based on Active Pharmaceutical Ingredient (API) particle size range is not supported by the data submitted in the current amendment.
2. The firm should verify the bio lot's API batch #0130524 mentioned in the current amendment is the same as the bio lot's API batch # 129830 given in the original submission, and explain the lot number discrepancy.
3. The firm should submit additional evidence to show that the difference observed in the particle size of different lots of the API has no effect on in vivo bioequivalence or performance of the test product in order to justify for the requested specification adjustment at the 15 minute sampling time point. In addition, the firm should submit additional dissolution data of at least three fresh finished production lots of its test product (both strengths), which should be manufactured based on approved manufacturing specifications, to support the proposed change in the dissolution specification.

Alternatively, the firm should accept the FDA-recommended dissolution method and specifications:

Medium:	Water with 0.35% Sodium Dodecyl Sulfate
USP Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Rotational Speed:	75 rpm
Volume:	900 mL

Specifications:	15 min: NLT (b) (4)
	60 min: NLT (b) (4)

## 7 Recommendation

The specification change requested by the firm for the 15 minute sampling time point drug release specification from (b) (4) to (b) (4) is incomplete for the reasons cited in the Deficiency Comments above.

The firm should be informed of the above deficiency comments and recommendations.

## 8 Dissolution Consult

None

## 9 Additional Attachments

### Particle Size Specifications for the API and Finished Product for the Test and RLD Products

	API Specifications	Finished Product Specifications	Currently Proposed API Specifications <sup>2</sup>
NDA 12041 <sup>3</sup> NDA 14901 <sup>4</sup>	(b) (4)		
ANDA 90164 <sup>5</sup> ANDA 90166 <sup>6</sup>			

<sup>2</sup> Electronic Document Room, ANDA 90164 and ANDA 90166, Submission Date: 08/01/08 (Current Amendment)b

<sup>3</sup> Electronic Document Room, NDA 12041, Submission Date: 03/28/08

<sup>4</sup> Electronic Document Room, NDA 14901, Submission Date: 08/07/08

<sup>5</sup> Electronic Document Room, ANDA 90164, Submission Date: 11/30/07

<sup>6</sup> Electronic Document Room, ANDA 90166, Submission Date: 11/30/07

## BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-164 and 90-166  
APPLICANT: Sandoz Canada Inc.  
DRUG PRODUCT: Triamcinolone Acetonide Injectable  
Suspension USP, 10 mg/mL and 40 mg/mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. Based on the dissolution data provided by you, there appears to be a direct relationship between the particle size of the active pharmaceutical ingredient (API) and the dissolution rate: The smaller the particle size of the API, the faster the dissolution rate of the finished product. However, you have not provided any evidence to demonstrate that difference in the particle size of the API lots will not affect the in vivo performance/bioequivalence of the test product. In addition, there are currently insufficient data provided by you to justify for an appropriate particle size range which can be considered as acceptable limits of the bio lot particle size.
2. You stated that the particle size distribution observed in different API lots of the test product has also been observed in the reference listed drug (RLD) product. Please provide data to support this statement, i.e., particle size data for API used in the RLD product.

With respect to the particle size data for the finished RLD product: **You did not submit particle size data for any lots of the finished RLD product of the 40 mg/mL strength.** However, you have submitted for the Chemistry review of the ANDA 90166 (in the submission dated November 30, 2007) the particle size data for several finished product lots of the 10 mg/mL of the RLD product, for comparison with a test lot No. 1280605 of the same strength, as follow:

Parameter	Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL	Kenalog® Lot 6K21219:Exp.09-08 Lot 5MO6227:Exp.12-07	Kenalog® Lot 6G15740:Exp.04-08	Kenalog® Lot 5M01726:Exp.11-07
Batch No.	1280605	Lots *6K21219 and **5MO6227	6G15740	5M01726
Size	(b) (4)			
Density [g/mL]				
pH***				
Osmolality [mOsm/kg]				
Particle Size [µm]				
Viscosity [cSt]				
Surface tension [dynes/cm]				
* Lot 6K21219 was used for the following tests: Density, Osmolality, Viscosity and Surface Tension was used for the pH test. ** Lot 5MO6227 was used for the pH and Particle size tests. ***Labeling: pH =5.0-7.5. N/P = Not performed				

Based on the particle size data presented above, although the 10 mg/mL strength of the RLD product showed variations in the particle size distribution profile, it appeared that the particle size profile for this strength of the RLD product was much different and (b) (4) than that of the 10 mg/mL strength of the exhibit lot No. 1280605 of the test product.

Also, comparing the above particle size data with those provided by you for the 40 mg/mL strength of the test product below, it appeared that the particle size distribution profile for the 40 mg/mL strength of the test product was much more variable (than that of the 10 mg/mL strength of the RLD product as seen above). The range of the particle size of the finished test product at the 40 mg/mL was (b) (4) and (b) (4) the range of the particle size of the finished RLD product (at the 10 mg/mL), whereas the range of particle size of the bio batch No. 1370607-1 (40 mg/mL) and the exhibit batch No. 1280605 (10 mg/mL) of the test product was more comparable.

Test	Procedure	Specifications (Drug Substance)	Test results Lots# (Drug Substance)		
			129830	137291	138079
Particle size	PS-0008	d50: (b)(4) d90: (b)(4)	(b)(4)	(b)(4)	(b)(4)
Test	Procedure	Specifications (Product)	Test results Lots# (Drug Product)		
			1370607-1 (1mL bio batch)	1450710 (b)(4)	1120702 (b)(4)
Particle size	PS-0007	d50: (b)(4) d90: (b)(4)	d <sub>50</sub> : (b)(4) d <sub>90</sub> : (b)(4)	d <sub>50</sub> : (b)(4) d <sub>90</sub> : (b)(4)	d <sub>50</sub> : (b)(4) d <sub>90</sub> : (b)(4)

Based on the particle size data provided by you for the finished test product (10 mg/mL and 40 mg/mL) and the finished RLD product (10 mg/mL strength only) above, it is not possible to compare the particle size profiles of the bio lots of the test and RLD products which have demonstrated bioequivalence in the fasting BE study.

3. You did not provide the following necessary information for the currently submitted dissolution data: (1) how many units of the finished lots were tested, and (2) whether the dissolution values as stated were single or mean values.
4. For the dissolution data currently submitted for the 15 minute dissolution time point, three out of four of the dissolution values, (b)(4) (lot# 0070724, 0130524, 0060624, respectively) met the previously FDA-recommended specification [15 min: (b)(4)]. The fourth dissolution value of (b)(4) (lot # 0080724) did not meet the FDA-recommended specification and also does not even meet your new proposed specification [15 min: (b)(4)]. Therefore, these data do not support your proposed change in the dissolution specification at this time point.
5. You state that "(b)(4) lot # 0130524 is the lot used in the manufacture of Sandoz Canada's 40 mg/mL bio batch and 10 mg/mL ANDA batch..." However, based on the information provided in the original ANDA submission (dated 30-Nov-2007), a different drug substance lot number (i.e, #129830) was used to manufacture the test bio lot # 1370607-1. Please verify the API lot #0130524 mentioned in the current amendment is the same as the API lot # 129830 given in the original submission, and/or explain the discrepancy in the API lot numbers reported.

6. Based on the above discussion, the DBE does not consider that you have submitted appropriate and adequate dissolution data to justify for the proposed dissolution specification change at the 15 minute sampling time point.

As per the current DBE policy, in order to justify for any change of the FDA-recommended dissolution specifications of the test product, please submit dissolution data of at least three fresh finished production lots of your test product (of both strengths). These lots should be manufactured based on approved manufacturing specifications. The data of full dissolution profile for 12 individual dosage units of each lot, manufactured in the same conditions as the bio-lot, using the API of the same particle size (with any difference to be within the approved particle size specification range) should be submitted.

7. Alternatively, please accept the following dissolution method and specifications:

Medium:	Water with 0.35% Sodium Dodecyl Sulfate (SDS)
Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Speed:	75 rpm
Volume:	900 mL
<b>Specifications:</b>	<b>15 min: NLT</b> (b) (4)
	60 min: NLT

Sincerely yours,

{See appended electronic signature page}

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

**10 Outcome Page**

**ANDA: 90-164**

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
6193	8/1/2008	Other	Dissolution Amendment	1	1
				<b>Bean Total:</b>	<b>1</b>

**ANDA: 90-166**

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
6192	8/1/2008	Other	Dissolution Amendment	1	1
				<b>Bean Total:</b>	<b>1</b>

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/s/

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Deanah L Mitchell  
9/3/2008 11:04:30 AM  
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April Braddy  
9/3/2008 12:12:16 PM  
BIOPHARMACEUTICS

Hoainhon T. Nguyen  
9/3/2008 01:48:27 PM  
BIOPHARMACEUTICS  
For Dale P. Conner, Pharm. D., Director, Division of  
Bioequivalence I

## DIVISION OF BIOEQUIVALENCE REVIEW

<b>ANDA No.</b>	90164 (40 mg/mL) and 90166 (10 mg/mL)
<b>Drug Product Name</b>	Triamcinolone Acetonide Injectable Suspension USP
<b>Strength(s)</b>	10 mg/mL and 40 mg/mL
<b>Applicant Name</b>	Sandoz Canada Inc.
<b>Address</b>	2555 W. Midway Blvd. P.O. Box 446 (US Agent) Broomfield, Colorado 80038
<b>Applicant's Point of Contact</b>	Ms. Beth Brannan, c/o Sandoz Inc.
<b>Contact's Telephone Number</b>	303-438-4237
<b>Contact's Fax Number</b>	303-438-4600
<b>Original Submission Date(s)</b>	November 30, 2007 (ANDA # 90164 and # 90166 amendment)
<b>Submission Date(s) of Amendment(s) Under Review</b>	September 26, 2008 (ANDA # 90164 and # 90166 amendment)
<b>Reviewer</b>	Deanah L. Mitchell, Ph.D.
<b>OUTCOME DECISION</b>	<b>COMPLETE</b>

### Review of an Amendment

#### 1 Executive Summary

On September 26, 2008, the firm, Sandoz, Inc., submitted a second amendment to its *first generic* application for Triamcinolone Acetonide Injectable Suspension. The amendment is in response to a deficiency letter sent to the firm dated September 10, 2008 from the Division of Bioequivalence (DBE) concerning: (1) a change in the particle size of the Active Pharmaceutical Ingredient (API) specification, (2) incomplete dissolution testing, (3) a discrepancy in API bio-lot numbers, (4) and a change in the dissolution specification<sup>1</sup>.

In the deficiency letter the DBE requested the firm to submit additional evidence to show that the difference observed in the particle size of different lots of the API has no effect on in vivo bioequivalence or performance of the test product in order to justify the requested dissolution specification adjustment at the 15 minute sampling time point, based on the API particle size change.

In the current amendment, the firm did not provide (1) requested justification for changing the particle size of the Active Pharmaceutical Ingredient (API) specification, or (2) additional and complete dissolution testing in new fresh test and reference lots, as requested by the DBE. The firm has provided additional mean dissolution data for several additional RLD lots to correlate with the measured particle size distribution of the RLD lots. The firm has also agreed with the DBE that the dissolution data presented for

<sup>1</sup>DFS, Review/Bioequivalence Review/Biopharmaceutics/N 090164 N 000 AB 08-May-2008.

three test lots thus far, however limited (i.e., on only 3 units of two test lots) met the FDA-recommended specifications. Finally, in the last response to the DBE's Deficiency No. 7, the firm has accepted the FDA-recommended method [900 mL of Water with 0.35% SDS using USP Apparatus II (Paddle) at 75 rpm] and specifications [15 min: NLT (b)(4) and 60 min: NLT (b)(4)]. The firm now proposes to submit additional dissolution data on at least three fresh test lots to justify the proposed dissolution specification change of (b)(4) at 15 minutes in a CBE-30 supplement, unless the data of the fresh lots do not meet the proposed specification.

The DBE acknowledges that Sandoz has accepted the DBE's previously recommended dissolution method and specifications. The DBE also acknowledges that Sandoz will submit dissolution data on 12 units of at least three fresh lots of the test product for each strength to justify any change in the dissolution specifications. However, the DBE requests that any proposed change in dissolution specifications be filed under a Prior Approval Supplement and not a CBE-30.

As recommended previously, the bioequivalence study for the 40 mg/mL strength of the test product remains acceptable. The waiver of *in vivo* BE study requirements for its 10 mg/mL strength suspension (ANDA # 90166) is granted as per the criteria set forth in 21 CFR § 320.22 (d) (2).

The application is complete with respect to the bioequivalence testing.

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### 3 Deficiency Comments

#### 3.1 Deficiency Comment No. 1

1. *Based on the dissolution data provided by you, there appears to be a direct relationship between the particle size of the active pharmaceutical ingredient (API) and the dissolution rate: The smaller the particle size of the API, the faster the dissolution rate of the finished product. However, you have not provided any evidence to demonstrate that difference in the particle size of the API lots will not affect the in vivo performance and bioequivalence of the test product. In addition, there are currently insufficient data provided by you to justify for an appropriate particle size range which can be considered as acceptable limits of the bio lot particle size.*

#### Firm's Response to Deficiency Comment No. 1

**Sandoz has accumulated additional data and included it to this amendment. Additionally, we have filed a revised particle size specification for the drug substance in our minor CMC deficiency response submitted on September 22, 2008. Please find the revised Drug Substance Specifications in ATTACHMENT -1-. This new particle size specification has been proposed along with the use of a revised method (PS-0008, found in ATTACHMENT -1-) which incorporates optimized sample preparation procedures. The proposed specification is:**

**d50:** (b) (4)  
**d90:** (b) (4)

**We believe this specification provides the appropriate control to ensure the limits for API align our commercial production finished product batches with the DBE dissolution specifications. The Drug Product Specifications have also been updated and are presented in ATTACHMENT -2-.**

#### Reviewer's Comment

The firm is proposing new particle size specifications (d50: (b) (4) and d90: (b) (4) (b) (4) that are different from what they proposed in the original submission on November 30, 2007 (d50: (b) (4) and d90 (b) (4) and bioequivalence amendment on August 01, 2008 (d50: (b) (4) and d90: (b) (4)). The firm still has not provided sufficient data to justify that the change in particle size of the API lots will not affect in vivo performance and bioequivalence of the test product. Therefore, the firm's response is **incomplete** with respect to the requested justification for dissolution specification change based on the API particle size change. However, since in the current amendment, the firm has accepted the DBE's previously recommended dissolution method and specifications (See the firm's Response to Deficiency No. 7 below), the proposed change in the API particle size specification alone should be considered by the Division of Chemistry.

**3.2 Deficiency Comment No. 2**

2. *You stated that the particle size distribution observed in different API lots of the test product has also been observed in the reference listed drug (RLD) product. Please provide data to support this statement, i.e., particle size data for API used in the RLD product.*

*With respect to the particle size data for the finished RLD product: You did not submit particle size data for any lots of the finished RLD product of the 40 mg/mL strength. However, you have submitted for the Chemistry review of the ANDA 90166 (in the submission dated November 30, 2007) the particle size data for several finished product lots of the 10 mg/mL of the RLD product, for comparison with a test lot No. 1280605 of the same strength, as follow:*

Parameter	Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL	Kenalog® Lot 6K21219:Exp.09-2008 Lot 5MO6227:Exp.12-2007	Kenalog® Lot 6G15740:Exp.04-2008	Kenalog® Lot 5M01726:Exp.11-2007
Batch No.	(b) (4)			
Size				
Density [g/mL]				
pH				
Osmolality [mOsm/kg]				
Particle Size [µm]				
Viscosity [cSt]				
Surface tension [dynes/cm]				
* Lot 6K21219 was used for the following tests: Density, Osmolality, Viscosity and Surface Tension was used for the pH test. ** Lot 5MO6227 was used for the pH and Particle size tests. ***Labeling: pH=5.0-7.5. N/P = Not performed				

*Based on the particle size data presented above, although the 10 mg/mL strength of the RLD product showed variations in the particle size distribution profile, it appeared that the particle size profile for this strength of the RLD product was much different and (b) (4) than that of the 10 mg/mL strength of the exhibit lot No. 1280605 of the test product.*

*Also, comparing the above particle size data with those provided by you for the 40 mg/mL strength of the test product below, it appeared that the particle size distribution profile for the 40 mg/mL strength of the test product was much more variable (than that of the 10 mg/mL strength of the RLD product as seen above). The range of the particle size of the finished test product at the 40 mg/mL was (b) (4) and*

(b) (4) the range of the particle size of the finished RLD product (at the 10 mg/mL), whereas the range of particle size of the bio batch No. 1370607-1 (40 mg/mL) and the exhibit batch No. 1280605 (10 mg/mL) of the test product was more comparable.

Test	Procedure	Specifications (Drug Substance)	Test results Lots# (Drug Substance)		
			129830	137291	138079
Particle size	PS-0008	d50: (b) (4) d90: (b) (4)	(b) (4)		
Test	Procedure	Specifications (Product)	Test results Lots# (Drug Substance)		
			1370607-1 (1mL biobatch)	1450710 (b) (4)	1120702 (b) (4)
Particle size	PS-0007	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)

Based on the particle size data provided by you for the finished test product (10 mg/mL and 40 mg/mL) and the finished RLD product (10 mg/mL strength only) above, it is not possible to compare the particle size profiles of the bio lots of the test and RLD products which have demonstrated bioequivalence in the fasting BE study.

**Firm’s Response to Deficiency Comment No. 2**

During the pharmaceutical product development, we evaluated the particle size distribution in our active ingredient as compared to the finished dosage formulation. This evaluation has demonstrated that particle size remains consistent throughout manufacturing steps. Our stability data demonstrates that particle size does not change throughout product shelf life. On the basis of this observation, we can propose that the particle size distribution observed in the reference listed drug (RLD) lots would be closely related to the particle size distribution of the API used in the manufacture of these lots. However, since we do not have access to the API lots used in the RLD, we cannot provide test data for these lots as requested by the FDA.

Table 1 presents the particle size distribution observed in 9 lots of Kenalog-40 and 8 lots of Kenalog-10. The test results presented below represent testing with the revised particle size method (PS-0008, found in ATTACHMENT -1-). As such, the values for some of the RLD lots reported below are slightly different from the tables presented in the original ANDA and in your question above. We believe the new method shows only minimal differences and that comparing results using only the new method provides the most appropriate analysis from this point forward.

Table 1. Particle size distribution in the RLD (presented from smallest to largest d50 values).

Kenalog-40	6C18416	6B21109	6F11295* (Biobatch)	6F13031*	6F14176*	6F13034*	8E36425	8F37896*	6F13029*
d50 (µm)	(b) (4)								
d90 (µm)	(b) (4)								
Kenalog-10	5M06227	7M22629*	8C42471	7H28592*	8B32527*	6K21219*	5M01726	6G15740*	
d50 (µm)	(b) (4)								
d90 (µm)	(b) (4)								

\*Dissolution experiments using the Paddle II apparatus were performed with these batches.

The information presented below was provided in our previous amendment however for ease of review it is provided again. Sandoz Canada Inc. has tested the particle size distribution of three additional drug substance (API) lots manufactured by (b) (4) with particle size distribution comparable to the drug substance lot used in the Sandoz Biobatch. The particle size distributions found for these 3 lots of API are presented in Table 2 and are compared to the API used in the Biobatch.

Table 2: Particle size distribution of different drug substance (API) lots

	(b) (4) Lot numbers			
	2196NMO0060624	2196NMO0070724	2196NMO0080724	2196NMO 0130524 (Biobatch API lot 129830)
d50 (µm)	(b) (4)			
d90 (µm)	(b) (4)			

We then measured the particle size distribution observed in lab scale finished product formulated with each of the (b) (4) API lots (Table 3). These measurements confirm that the formulation has virtually no impact on the apparent particle size of the API.

Table 3: Particle size distribution of small scale drug product batches manufactured using three (3) additional API lots (the Biobatch formulation particle sizes are presented for comparison purposes).

FDF Lot	Lab batch 1	Lab batch 2	Lab batch 3	Biobatch 1370607
(b) (4) Lot	2196NMO0060624	2196NMO0070724	2196NMO0080724	2196NMO 0130524 (Biobatch API lot 129830)
d50 (µm)	(b) (4)			
d90 (µm)	(b) (4)			

We note that the Sandoz and RLD Bio batch particle size data are relatively close. Furthermore, the RLD batch selected to perform the bioequivalence study present a particle size distribution at the d50 and d90 median of all of the evaluated RLD lots.

Figure 1 present a linear regression of the dissolution data obtained at 15 minutes using the DBE recommended conditions. There is a relatively good linear relationship between the d90 particle size and the percent (%) dissolution at 15 minutes. Arrows indicate the original and updated particle size limits. The gray area represent the proposed DBE dissolution limits and the squares and circles, the RLD and Sandoz lots data, respectively. The Sandoz data are from dissolution studies obtained with the small scale Lab Batch number 1 and 2, as well as the Biobatch (lot 1370607 40 mg/mL) (indicated with a 1, 2 and 40 respectively). Data from the small scale Lab Batch number 3 is not included since it is outside our proposed limits for particle size distribution. The dissolution data obtained with the 10 mg/mL exhibit lot 1280605 is not represented in Figure 1.

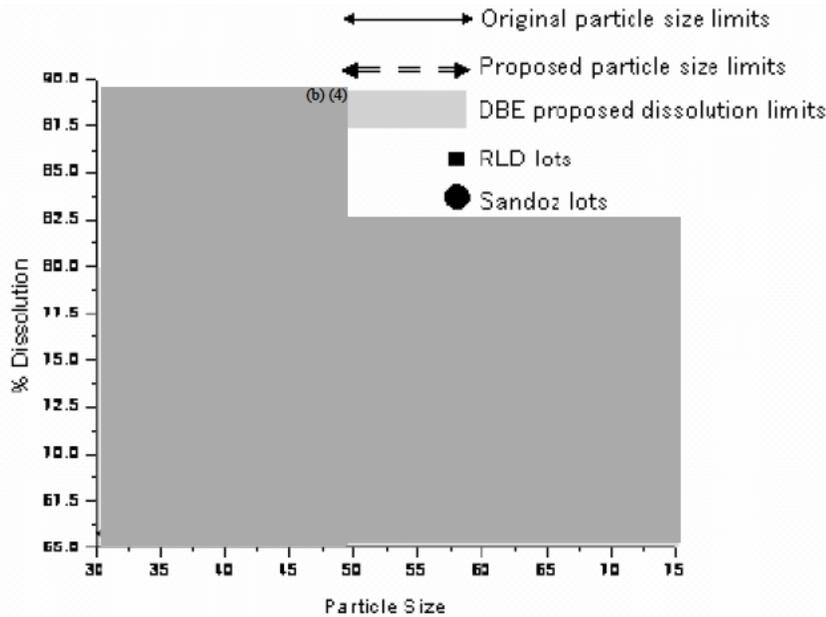


Figure 1: Particle Size (d90) vs. percent (%) Dissolution relationship at 15 minutes.

These results demonstrate that the particle size distribution of the API lots manufactured by (b)(4) are in line with the particle size distribution of the brand product API which present a d50 range of (b)(4) and a d90 range of (b)(4) with an average of (b)(4) and (b)(4) respectively.

## Reviewer's Comment

The firm evaluated the particle size distribution in their active ingredient in comparison to the finished product, which they say remains consistent throughout the manufacturing steps. The firm concluded that the particle size distribution observed in the reference listed drug (RLD) lots would be closely related to the particle size distribution of the API used in the manufacture of these lots. The firm's explanation of how they derived at the particle size distribution observed in different API lots in the RLD is acknowledged. However, the assumption that relationship of the particle size distribution (PSD) between the RLD API and the RLD product is similar to that observed in the test API and test finished product **has not been tested using the PSD data of the RLD API**. It is possible that since the RLD product was manufactured with different process, this manufacturing process can affect the PSD of the RLD product differently. Therefore, the firm's above conclusion statement "*These results demonstrate that the particle size distribution of the API lots manufactured by (b)(4) are in line with the particle size distribution of the brand product API which present a d50 range of (b)(4) and a d90 range of (b)(4) (b)(4) with an average of (b)(4) and (b)(4) respectively*" is considered inadequately supported and confusing.

The plot of PS(D90) versus %dissolution (at 15 minutes) showed the circle (b)(4) for the test biolot No.1370607 (D90=(b)(4) and %dissolution=(b)(4)) showed the RLD square for the RLD biolot No. 6F11295 (D90=(b)(4) %dissolution (b)(4)). The dissolution data for the RLD product lots and other two test lots used in the plot are provided in Table 4 of the firm's response below.

It should be noted that the firm did not submit the dissolution data for the RLD biolot No. 6F11295 in the previous amendments dated May 8, 2008 and June 10, 2008 for the dissolution testing using FDA-recommended dissolution method, for comparison with the test biolot No. 1370607. Instead, the firm used the RLD lot No. 6F13029, for which the %dissolution at 15 minutes was (b)(4) and comparable to that of the test biolot No. 1370607. It is not clear when the firm conducted the dissolution testing for the RLD biolot No. 6F11295 which yielded %dissolution of (b)(4) at 15 minutes (as shown in Table 4 below), and whether at the time of testing, the RLD biolot has expired. The firm should explain the reason for not submitting the dissolution data for the RLD biolot No. 6F11295 earlier, and confirm the dissolution testing date for this RLD biolot.

However, since in the current amendment, the firm has accepted the DBE's previously recommended dissolution method and specifications (See the firm's Response to Deficiency No. 7 below), the above question concerning the dissolution data of the RLD biolot No. 6F11295 is now a moot point.

### **3.3 Deficiency Comment No. 3**

*You did not provide the following necessary information for the currently submitted dissolution data: (1) how many units of the finished lots were tested, and (2) whether the dissolution values as stated were single or mean values.*

#### **Firm's Response to Deficiency Comment No. 3**

**The dissolution data presented were obtained using 3 units per finished lots and the data were mean values.**

#### **Reviewer's Comment**

The firm's clarification of the dissolution data presented in the previous amendment (August 01, 2008) is acknowledged. However, dissolution testing based on 3 units is not adequate. In the current amendment, the firm has included in a table (Table 5) the PSD of the finished lots and the %dissolution at 15 minutes. This table helps clarify the relationship between the PSD of the test finished product lots and the dissolution rates, as compared to the table presented in the previous amendment which showed only the relationship between the PSD of the API used to manufacture these finished lots and the dissolution rates. But for demonstrating how the PSD of the proposed API relates to the PSD of the finished lots and affects the dissolution rates of these lots, the firm should conduct additional dissolution data using at least 12 units of each lot.

### **3.4 Deficiency Comment No. 4**

*For the dissolution data currently submitted for the 15 minute dissolution time point, three out of four of the dissolution values, (b)(4) (lot# 0070724, 0130524, 0060624, respectively) met the previously FDA-recommended specification [15 min: (b)(4)]. The fourth dissolution value of (b)(4) (lot # 0080724) did not meet the FDA-recommended specification and also does not even meet your new proposed specification [15 min: (b)(4)]. Therefore, these data do not support your proposed change in the dissolution specification at this time point.*

#### **Firm's Response to Deficiency Comment No. 4**

**Lot # 0080724 met neither the DBE nor our proposed dissolution limits because its particle size is relatively small. This lot would be rejected by the new proposed particle size limits.**

**For ease of comparison, Table 4 presents the comparative dissolution data and particle sizes at the 15 minutes time points as described in Figure 1 of response number 2. Kenalog-40, Kenalog-10 as well as data obtained with our lots, including biobatches, are compared. Table 5 present corresponding data from small scale drug product batches. Please find in ATTACHMENT -3- the dissolution data for the Kenalog and Sandoz products.**

Table 4. Percent (%) dissolution and d90 particle size relationship. Twelve (12) units were tested for each lots except for the Kenalog-40 Biobatch because only one bottle was left from this lot.

Kenalog-40	6F13031	6F14176	6F11295 (Biobatch)	6F13034	8F37896	6F13029
d90 (µm)	(b) (4)					
% Dissolution	(b) (4)					
Kenalog-10	7M22629	7H28592	8B32527	6K21219		
d90 (µm)	(b) (4)					
% Dissolution	(b) (4)					
Sandoz	1370607 (40)		1280605(10)			
d90 (µm)	(b) (4)		(b) (4)			
% Dissolution	(b) (4)					

Table 5: : Particle size distribution of small scale drug product batches manufactured using three (3) additional API lots (the Biobatch formulation particle sizes are presented for comparison purposes).

FDL Lot	Lab batch 1	Lab batch 2	Lab batch 3	Lab batch 4
(b) (4) Lot	2196NMO006062 4	2196NMO0070724	2196NMO0080724	2196NMO 0130524 (Biobatch API lot 129830)
d90 (µm)	(b) (4)			
% Dissolution	(b) (4)			

### **Reviewer's Comment**

In the firm's response to the DBE's Deficiency Comment No. 4 above, the firm agreed with the DBE's comments. No further comment on this deficiency is needed.

### **3.5 Deficiency Comment No. 5**

You state that "(b) (4) lot # 0130524 is the lot used in the manufacture of Sandoz Canada's 40 mg/mL bio batch and 10 mg/mL ANDA batch..." However, based on the information provided in the original ANDA submission (dated 30-Nov-2007), a different drug substance lot number (i.e., #129830) was used to manufacture the test bio lot # 1370607-

1. Please verify the API lot #0130524 mentioned in the current amendment is the same as the API lot # 129830 given in the original submission, and/or explain the discrepancy in the API lot numbers reported.

### **Firm's Response to Deficiency Comment No. 5**

The lots are identical. In our previous amendment, we referred to the (b) (4) lot number (lot # 0130524). Lot # #129830 is the Sandoz internal lot number- Both lot numbers are identified on the Sandoz COA provided in the original submission, please see the COA in ATTACHMENT -4-.

**Reviewer’s Comment**

The firm’s response is acceptable.

**3.6 Deficiency Comment No. 6**

*Based on the above discussion, the DBE does not consider that you have submitted appropriate and adequate dissolution data to justify for the proposed dissolution specification change at the 15 minute sampling time point.*

*As per the current DBE policy, in order to justify for any change of the FDA-recommended dissolution specifications of the test product, please submit dissolution data of at least three fresh finished production lots of your test product (of both strengths). These lots should be manufactured based on approved manufacturing specifications. The data of full dissolution profile for 12 individual dosage units of each lot, manufactured in the same conditions as the bio-lot, using the API of the same particle size (with any difference to be within the approved particle size specification range) should be submitted.*

**Firm’s Response to Deficiency Comment No. 6**

**Please refer to Sandoz Responses to questions 2 and 4 for justification of our proposed API particle size distribution.**

**Reviewer’s Comment**

Please see Reviewer’s Comment for Deficiency Comment Nos. 2 and 4 above.

**3.7 Deficiency Comment No. 7**

*Alternatively, please accept the following dissolution method and specifications:*

<b>Medium:</b>	<b>Water with 0.35% Sodium Dodecyl Sulfate (SDS)</b>
<b>Apparatus:</b>	<b>USP Apparatus II (Paddle)</b>
<b>Temperature:</b>	<b>37°C ± 0.5°C</b>
<b>Speed :</b>	<b>75 rpm</b>
<b>Volume :</b>	<b>900 mL</b>
<b>Specifications:</b>	<b>15 min: NLT (b) (4)</b>
	<b>60 min: NLT (b) (4)</b>

## **Firm's Response to Deficiency Comment No. 7**

**Sandoz accepts the proposed DBE dissolution method and specifications (Please find the revised Drug Product Specifications in ATTACHMENT-2-).**

**Sandoz would also like to propose filing a CBE-30 to revise the 15 minute timepoint specification to NLT (b)(4) under the following conditions:**

- for three new lots of Sandoz finished product (for both strengths- 6 lots in total) manufactured based on the approved manufacturing specifications**
- 12 point dissolution profile data falls within the range of (b)(4) at 15 minutes**
- using the API of the same particle size (within the approved particle size specification range)**
- If any results do not conform to these criteria, then we will file any further request regarding dissolution in a Prior Approval Supplement.**

## **Reviewer's Comment**

Sandoz has not submitted sufficient dissolution data for the DBE to change the dissolution specification range from (b)(4) to (b)(4). The DBE acknowledges that Sandoz has accepted the DBE's previously recommended dissolution method and specifications. The DBE also acknowledges that Sandoz will submit dissolution data on 12 units of at least three fresh lots of the test product for each strength to justify any change in the dissolution specifications. However, the DBE requests that any proposed change in dissolution specifications be filed under a Prior Approval Supplement and not a CBE-30.

## **4 Reviewer's Overall Comments**

In summary, Sandoz has not submitted sufficient dissolution data for the DBE to change the dissolution specification range from (b)(4) to (b)(4). The DBE acknowledges that Sandoz has accepted the DBE's previously recommended dissolution method and specifications. The DBE also acknowledges that Sandoz will submit dissolution data on 12 units of at least three fresh lots of the test product for each strength to justify any change in the dissolution specifications. However, the DBE requests that any proposed change in dissolution specifications be filed under a Prior Approval Supplement and not a CBE-30.

## **5 Deficiency Comment**

None

## **6 Recommendation**

The DBE acknowledges that Sandoz has accepted the DBE's previously recommended dissolution method and specifications. The DBE also acknowledges

that Sandoz will submit dissolution data on 12 units of at least three fresh lots of the test product for each strength to justify any change in the dissolution specifications. However, the DBE requests that any proposed change in dissolution specifications be filed under a Prior Approval Supplement and not a CBE-30.

## 7 Comments for Other OGD Disciplines

Discipline	Comment
Chemistry	DBE considers the API particle size change a chemistry issue if the change does not affect the dissolution rate of the test product. At this time, since the firm accepts our originally recommended specifications, we consider the test product acceptable with respect to bioequivalence testing.

## 8 Dissolution Consult

None

## 9 Additional Attachments

### KENALOG-40

product: Kenalog 40 mg  
lot: 6F13031

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	86.17625	98.8139167
%RSD	2.79	0.63
min		(b) (4)
max		

product: Kenalog 40 mg  
lot: 6F14176

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	87.773	99.31775
%RSD	4.52	0.64
min		(b) (4)
max		

product: Kenalog 40 mg  
lot: 6F11295

vessel	Timepoint (min)	
	15	60
1		(b) (4)

Only one bottle was left from the Biobatch lot

product: Kenalog 40 mg  
lot: 6F13034

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	82.0278333	95.4936667
%RSD	3.39	1.88
min		(b) (4)
max		

product: Kenalog 40 mg  
lot: 8F37896

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	74.1901667	95.3953333
%RSD	1.05	0.59
min		(b) (4)
max		

product: Kenalog 40 mg  
lot: 6F13029

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	73.571	97.8418333
%RSD	1.67	1.65
min		(b) (4)
max		

# KENALOG-10

product: Kenalog 10 mg  
lot: 7M22629

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	85.0595	96.91275
%RSD	0.66	0.91
min		(b) (4)
max		

product: Kenalog 10 mg  
lot: 7H28592

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	83.316	96.1241667
%RSD	0.62	0.85
min		(b) (4)
max		

product: Kenalog 10 mg  
lot: 8B32527

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	83.97275	100.722
%RSD	0.71	0.64
min		(b) (4)
max		

product: Kenalog 10 mg  
lot: 6K21219

vessel	Timepoint (min)	
	15	60
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
average	82.76975	99.0783333
%RSD	1.19	0.97
min		(b) (4)
max		

product: Sandoz lab batch 1  
40 mg/mL 2196NMO0060624

vessel	Timepoint (min)	
	15	60
1	(b) (4)	
2		
3		
average	69.7	88.3
%RSD	1.4	0.5
min	(b) (4)	
max		

product: Sandoz lab batch 2  
40 mg/mL 2196NMO0070724

vessel	Timepoint (min)	
	15	60
1	(b) (4)	
2		
3		
average	78.8	92.6
%RSD	1.0	0.6
min	(b) (4)	
max		

product: Sandoz lab batch 3  
40 mg/mL 2196NMO0080724

vessel	Timepoint (min)	
	15	60
1	(b) (4)	
2		
3		
average	86.2	95.4
%RSD	0.6	0.2
min	(b) (4)	
max		

# SANDOZ PRODUCT

product: Sandoz 40 mg  
lot: 1370607

vessel	Timepoint (min)	
	15	60
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
<b>average</b>	73.513	90.0215833
<b>%RSD</b>	1.02	2.02
<b>min</b>	(b) (4)	
<b>max</b>		

product: Sandoz 10 mg  
lot: 1280605

vessel	Timepoint (min)	
	15	60
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
<b>average</b>	73.9553333	91.1824167
<b>%RSD</b>	0.63	0.98
<b>min</b>	(b) (4)	
<b>max</b>		

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-164 and 90-166  
APPLICANT: Sandoz Canada Inc.  
DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension  
USP, 10 mg/mL and 40 mg/mL

The Division of Bioequivalence (DBE) has completed its review and has no further question at this time.

1. The DBE acknowledges that Sandoz has accepted the DBE's previously recommended dissolution method and specifications, as follows:

Medium: Water with 0.35% Sodium Dodecyl Sulfate (SDS)  
Apparatus: USP Apparatus II (Paddle)  
Temperature: 37°C ± 0.5°C  
Speed: 75 rpm  
Volume: 900 mL  
Specifications: 15 min: NLT [REDACTED] (b)(4)  
60 min: NLT [REDACTED]

2. The DBE also acknowledges that Sandoz will submit dissolution data on 12 units of at least three fresh lots of the test product for each strength to justify any change in the dissolution specifications in the future.

3. However, please be informed that the DBE requests that any proposed change in dissolution specifications be filed under a Prior Approval Supplement and not a CBE-30 as proposed by you. In addition, if the proposed change in the dissolution specification(s) is due to a change in the particle size of the Active Pharmaceutical Ingredient (API), please submit, in the same supplement or amendment, along with dissolution data for at least three fresh production lots, evidence to show that difference in the particle size of the new API lots will not affect the in vivo performance/bioequivalence of the test product.

Sincerely yours,

{See appended electronic signature page}

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

**10 Outcome Page**

**ANDA: 90-164**

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
7023	9/26/2008	Dissolution Data	Dissolution Amendment	1	1
				Bean Total:	1

**ANDA: 90-166**

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
7024	9/26/2008	Dissolution Data	Dissolution Amendment	1	1
				Bean Total:	1

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/s/

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Deanah L Mitchell  
12/23/2008 11:05:45 AM  
BIOPHARMACEUTICS

April Braddy  
12/23/2008 11:42:26 AM  
BIOPHARMACEUTICS

Hoainhon T. Nguyen  
12/23/2008 12:23:57 PM  
BIOPHARMACEUTICS  
For Dale P. Conner, Pharm. D., Director, Division of  
Bioequivalence I

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 090164**

**MICROBIOLOGY REVIEWS**

# Product Quality Microbiology Review

11 Apr 2008

ANDA: 90-164

**Drug Product Name**

**Proprietary:** N/A

**Non-proprietary:** Triamcinolone Acetonide Injectable Suspension, USP

**Drug Product Priority Classification:** N/A

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Consult Sent	Assigned to Reviewer
11/30/07	12/03/07	N/A	4/2/08

**Submission History (for amendments only)**

None

**Applicant/Sponsor**

**Name:** Sandoz Canada Inc.

**Address:** 145 Jules Leger Street, Boucherville (QC) Canada, J4B 7K8

**Representative:** Beth Brannan

**Telephone:** 303 438 4237

**Name of Reviewer:** Jesse Wells, Ph.D.

**Conclusion:** The submission is **not recommended** for approval on the basis of sterility assurance.

## Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original ANDA
  - 2. SUBMISSION PROVIDES FOR:** Initial marketing of a sterile drug product
  - 3. MANUFACTURING SITE:** Sandoz Canada Inc., 145 Jules-Leger Street, Boucherville (QC), Canada J4B 7K8
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Intramuscular and intra-articular injectable suspension; 40 mg/ mL; (b) (4).
  - 5. METHOD(S) OF STERILIZATION:** (b) (4)
  - 6. PHARMACOLOGICAL CATEGORY:** Corticosteroid
- B. SUPPORTING/RELATED DOCUMENTS:** ANDA 90-166 and associated microbiology review 90-166.doc by J. Wells, dated 4/11/08.
- C. REMARKS:** ANDA 90-166 is a sister application for the current submission and contains the API at 10 mg/mL. Most of the validation information is the same for the two ANDAs.

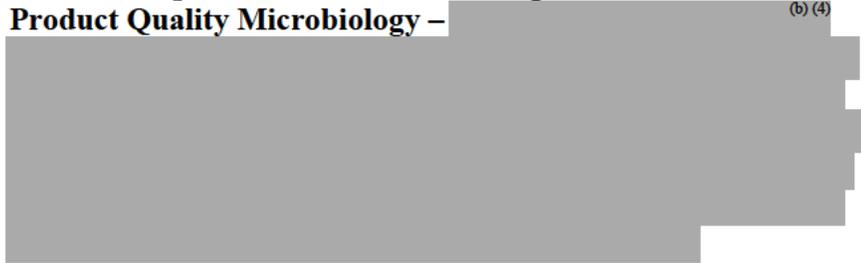
**filename:** 90-164.doc

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** – The submission is not recommended for approval on the basis of sterility assurance. Specific comments and deficiencies can be found in the “Product Quality Microbiology Review” and “List of Microbiology Deficiencies and Comments” sections.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – (b) (4)  

- B. Brief Description of Microbiology Deficiencies – Incomplete** (b) (4)  
  
 information.
- C. Assessment of Risk Due to Microbiology Deficiencies** – The safety risk due to microbiology deficiencies is considered moderate.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_
- B. Endorsement Block**  
 Microbiologist / Jesse Wells, Ph.D.  
 Microbiology Supervisor/Neal Sweeney, Ph.D.
- C. CC Block**  
 cc: Field Copy

Following this page, 24 pages withheld in full (b)(4)

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:**

ANDA: 90-164      APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension, USP

A. Microbiology Deficiencies:

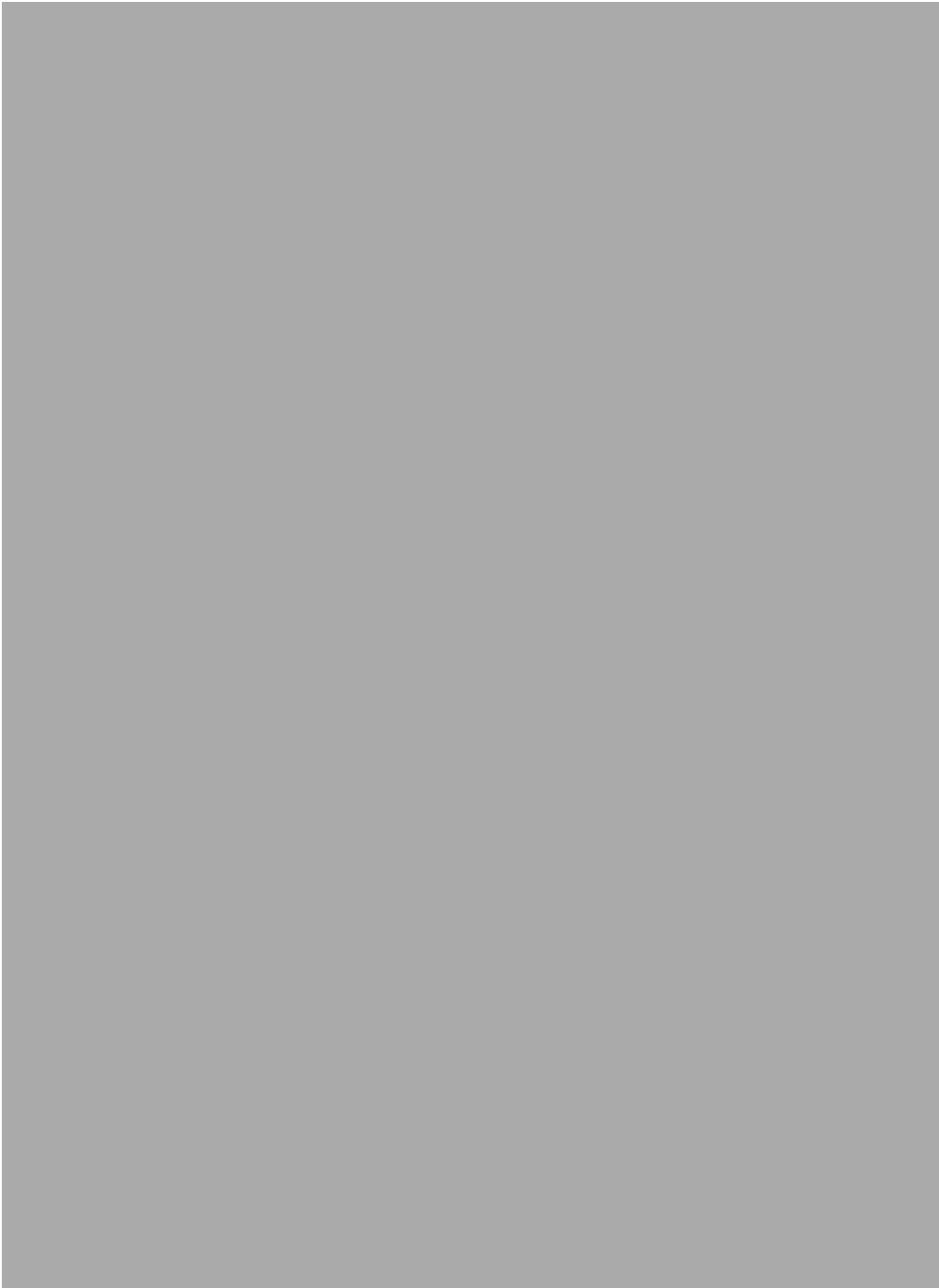
1.

2.

3.

4.

5.



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

Sincerely yours,

*{See appended electronic signature page}*

Neal J. Sweeney, Ph.D.  
Microbiology Supervisor  
Office of Generic Drugs

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/s/

-----  
Jesse Wells  
5/28/2008 07:18:35 AM  
CHEMIST

Kun Shen  
5/28/2008 07:52:26 AM  
MICROBIOLOGIST

Neal Sweeney  
5/28/2008 11:52:14 AM  
MICROBIOLOGIST

# Product Quality Microbiology Review

23 Jul 2008

ANDA: 90-164

## Drug Product Name

**Proprietary:** N/A

**Non-proprietary:** Triamcinolone Acetonide Injectable Suspension, USP

**Drug Product Priority Classification:** N/A

**Review Number:** 2

## Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
7/15/08	7/16/08	N/A	7/22/2008

## Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
11/30/2007	1	4/2/2008

## Applicant/Sponsor

**Name:** Sandoz Canada Inc.

**Address:** 145 Jules Leger Street, Boucherville (QC) Canada, J4B 7K8

**Representative:** Beth Brannan

**Telephone:** 303 438 4237

**Name of Reviewer:** Jesse Wells, Ph.D.

**Conclusion:** The submission is **not recommended** for approval on the basis of sterility assurance.

## Product Quality Microbiology Data Sheet

- A.
  - 1. **TYPE OF SUBMISSION:** Amendment
  - 2. **SUBMISSION PROVIDES FOR:** Response to microbiology deficiencies
  - 3. **MANUFACTURING SITE:** Sandoz Canada Inc., 145 Jules-Leger Street, Boucherville (QC), Canada J4B 7K8
  - 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Intramuscular and intra-articular injectable suspension; 40 mg/ mL; (b) (4).
  - 5. **METHOD(S) OF STERILIZATION:** (b) (4)
  - 6. **PHARMACOLOGICAL CATEGORY:** Corticosteroid
  
- B. **SUPPORTING/RELATED DOCUMENTS:**  
ANDA 90-166a1
  
- C. **REMARKS:** ANDA 90-166 is a sister application for the current submission and contains the API at 10 mg/mL. Most of the original deficiencies and responses are the same for the two ANDAs.

**filename:** 90-164.doc

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** - The submission is not recommended for approval on the basis of sterility assurance. Specific comments and deficiencies can be found in the “Product Quality Microbiology Review” and “List of Microbiology Deficiencies and Comments” sections.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -** (b) (4)
- B. Brief Description of Microbiology Deficiencies – Incomplete**  
(b) (4)
- C. Assessment of Risk Due to Microbiology Deficiencies –** The safety risk due to microbiology deficiencies is considered moderate.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_
- B. Endorsement Block**  
 Microbiologist / Jesse Wells, Ph.D.  
 Microbiology Team Leader/ LCDR Paul Dexter, M.S.
- C. CC Block**  
 cc: Field Copy

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:**

ANDA: 90-164      APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension, USP

Microbiology Deficiencies:

In regard to  (b) (4):

- a)  (b) (4)
- b) 
- c) 
- d) 
- e) 

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

Sincerely yours,

*{See appended electronic signature page}*

LCDR Paul Dexter, M.S.  
Microbiology Team Leader  
Office of Generic Drugs  
Center for Drug Evaluation and Research

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/s/

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Jesse Wells  
8/1/2008 03:02:19 PM  
MICROBIOLOGIST

Bonnie McNeal  
8/1/2008 04:13:14 PM  
MICROBIOLOGIST  
Checked for correct file and submission link. Both ok.

Neal Sweeney  
8/1/2008 04:23:35 PM  
MICROBIOLOGIST

Paul Dexter  
8/4/2008 08:30:31 AM  
MICROBIOLOGIST

# Product Quality Microbiology Review

05 SEP 2008

ANDA: 90-164

## Drug Product Name

**Proprietary:** N/A

**Non-proprietary:** Triamcinolone Acetonide Injectable Suspension, USP

**Drug Product Priority Classification:** N/A

**Review Number:** 3

## Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
8/26/2008	8/27/2008	N/A	9/3/2008

## Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
7/15/2008	2	7/23/2008
11/30/2007	1	4/2/2008

## Applicant/Sponsor

**Name:** Sandoz Canada Inc.

**Address:** 145 Jules Leger Street, Boucherville (QC) Canada, J4B 7K8

**Representative:** Beth Brannan

**Telephone:** 303 438 4237

**Name of Reviewer:** Jesse Wells, Ph.D.

**Conclusion:** The submission is **recommended** for approval on the basis of sterility assurance.

## Product Quality Microbiology Data Sheet

1. **TYPE OF SUBMISSION:** Amendment
  
  2. **SUBMISSION PROVIDES FOR:** Response to microbiology deficiencies
  
  3. **MANUFACTURING SITE:** Sandoz Canada Inc., 145 Jules-Leger Street, Boucherville (QC), Canada J4B 7K8
  
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Intramuscular and intra-articular injectable suspension; 40 mg/ mL; (b) (4)
  
  5. **METHOD(S) OF STERILIZATION:** (b) (4)
  
  6. **PHARMACOLOGICAL CATEGORY:** Corticosteroid
- B. SUPPORTING/RELATED DOCUMENTS:**  
ANDA 90-166a2
- C. REMARKS:** ANDA 90-166 is a sister application for the current submission and contains the API at 10 mg/mL. The deficiencies and responses are the same for the two ANDAs.

**filename:** 90-164a2.doc

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** - The submission is recommended for approval on the basis of sterility assurance.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -** (b) (4)  

- B. Brief Description of Microbiology Deficiencies** - None identified
- C. Assessment of Risk Due to Microbiology Deficiencies** - None; sufficient sterility assurance information is provided.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_
- B. Endorsement Block**  
 Microbiologist/ Jesse Wells, Ph.D.  
 Microbiology Team Leader / LCDR Paul Dexter, M.S.
- C. CC Block**  
 cc: Field Copy

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/s/

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Jesse Wells  
10/20/2008 01:10:30 PM  
MICROBIOLOGIST

Mark Anderson  
10/20/2008 01:22:54 PM  
MICROBIOLOGIST

checked for correct linking

Neal Sweeney  
10/21/2008 11:09:19 AM  
MICROBIOLOGIST

Paul Dexter  
10/21/2008 04:10:26 PM  
MICROBIOLOGIST

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 090164**

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

Sandoz Inc.  
Triamcinolone Acetonide Injectable Suspension, USP  
40 mg/mL  
1.2 Cover Letters

Confidential

Page 2

*ack for filing*  
*5/2/07*  
*S. Mitchell*  
*2/7/08*  
*One*  
*Nov 28*  
*28 February 2008*

Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Internet:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

90164

**ORIGINAL ANDA**  
**(includes electronic media)**

NOV 30 2007

**RE: Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. hereby submits an original Abbreviated New Drug Application for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL ( [REDACTED] <sup>(b) (4)</sup> ) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA in CTD format consists of 26 volumes. Sandoz Canada Inc. is filing an archival copy of the ANDA (in blue jackets) with all the required information. Additionally, the review copy is provided (red and orange jackets) as dictated by the guidelines.

**STERILITY ASSURANCE:** Given that this is a sterile injectable product [REDACTED] <sup>(b) (4)</sup> the sterility assurance data is included in Module 3 with an additional separate review copy (white jackets).

**BIOEQUIVALENCE:** This ANDA includes an *in-vivo* bioequivalence study against the reference listed drug (RLD) included in Module 5. Bio Summary Tables are provided electronically as indicated below.

**METHOD VALIDATION:** The Method Validation information included in Module 3, section 3.2.R.3 is also provided in 2 additional volumes (green jackets) for non-compendial methods.

**FIELD COPY:** As Sandoz Canada Inc. is a foreign manufacturer, a complete copy of Module 3 is provided as the field copy to the Office of Generic Drugs (burgundy jackets).

**RECEIVED**

DEC 03 2007

OGD

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**Electronic Media:** Sandoz is providing the following electronic media on 4 CDs as follows:

1. MODULE 2- Quality Overall Summary: contains the QOS in pdf & MS Word Format
2. BIO SUMMARY TABLES 1-16: MS Word and pdf Format
3. BIO SAS Transport Files
4. ELECTRONIC LABELING SUBMISSION contains draft physician insert and draft container labels in pdf format

If there are any comments or questions about this application, please contact me at 303-438-4237.

Sincerely,

Sandoz Inc.



Beth Brannan, Director  
Regulatory Affairs

cc: Peggy Levy (Module 1)

MEMORANDUM

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

DATE : January 12, 2007

TO : Director  
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch  
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA90-164 for Triamcinolone Acetonide Injectable Suspension 40 mg/mL to determine if the application is substantially complete for filing.

Sandoz Canada Inc. has submitted ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension 40 mg/mL. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Sandoz Canada Inc. on November 30, 2007 for its Triamcinolone AcetonideI Injectable Suspension product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

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Eda Howard  
1/14/2008 10:07:22 AM  
APPLICATIONS EXA

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA  
FOR APPLICATION COMPLETENESS**

**ANDA#** 90164      **FIRM NAME** Sandoz Inc.

**DRUG NAME** Triamcinolone Acetonide Injectable Suspension USP

**DOSAGE FORM** 40 mg/mL

**SUBJ:** Request for examination of:

Requested by: \_\_\_\_\_ Date: \_\_\_\_\_  
Chief, Regulatory Support Team, (HFD-615)

<b>Summary of Findings by Division of Bioequivalence</b>	
<input checked="" type="checkbox"/>	<b>Study meets statutory requirements</b>
<input type="checkbox"/>	<b>Study does NOT meet statutory requirements</b>
	<b>Reason:</b>
<input type="checkbox"/>	<b>Waiver meets statutory requirements</b>
<input type="checkbox"/>	<b>Waiver does NOT meet statutory requirements</b>
	<b>Reason:</b>

**RECOMMENDATION:**     **COMPLETE**     **INCOMPLETE**

Reviewed by: \_\_\_\_\_ Date: \_\_\_\_\_  
Svetlana Cherstniakova  
Reviewer

\_\_\_\_\_ Date: \_\_\_\_\_  
Chandra Chaurasia  
Team Leader

<b>Item Verified:</b>	<b>YES</b>	<b>NO</b>	<b>Required Amount</b>	<b>Amount Sent</b>	<b>Comments</b>
Protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P305: fasting study
Assay Methodology	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, Vol XIII-XVII
Procedure SOP	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Section 16.5, 16.6
Methods Validation	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Section 16.5, 16.6
Study Results Ln/Lin	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P5
Adverse Events	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P45
IRB Approval	<input checked="" type="checkbox"/>	<input type="checkbox"/>			July 15, 2006 (Module 5.3.1.4, P274)
Dissolution Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.3, P119
Pre-screening of Patients	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P29, Section 14.1
Chromatograms	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Vol XIII-XVII
Consent Forms	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P313
Composition	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 2.3 QOS, P20
Summary of Study	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P5
Individual Data & Graphs, Linear & Ln	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P91-215
PK/PD Data Disk Submitted)	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Xpt files, EDR
Randomization Schedule	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P55
Protocol Deviations	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P36, Section 16.2.6
Clinical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			EDR
Analytical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			EDR
Study Investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>			EDR

Medical Records	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, Vol III-XII
Clinical Raw Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, Vol III-XII
Test Article Inventory	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.3, P2
BIO Batch Size	<input checked="" type="checkbox"/>	<input type="checkbox"/>			(b) (4) Module 5.3.1.3
Assay of Active Content Drug	<input checked="" type="checkbox"/>	<input type="checkbox"/>			101.5%, Module 2.3 QOS
Content Uniformity	<input checked="" type="checkbox"/>	<input type="checkbox"/>			41.36 mg/mL, 1.5%, Module 2.3
Date of Manufacture	<input checked="" type="checkbox"/>	<input type="checkbox"/>			07-05-2006
Exp. Date of RLD	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Dec 2007
BioStudy Lot Numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>			1370607-1, Module 5.3.1.4, P37
Statistics	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P34
Summary results provided by the firm indicate studies pass BE criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Module 5.3.1.4, P42
Waiver requests for other strengths / supporting data	<input type="checkbox"/>	<input checked="" type="checkbox"/>			

Additional Comments regarding the ANDA:

This is paper and electronic submission. The RLD is Kenalog-40® hold by Apothecon (NDA 014901 approved on September 30, 1964). In control correspondence OGD # 02-037 ( (b) (4) August 22, 2002) OGD provides the following comments:

To obtain an AB rating on the proposed Triamcinolone Acetonide Injection USP, 40 mg/mL, the Division of Bioequivalence (DBE) recommends the following:

1. An in-vivo bioequivalence (BE) study comparing your Triamcinolone Acetonide Injection, 40 mg/mL, to the reference listed drug (RLD), Kenalog-40®. Only the parent compound, triamcinolone acetonide, needs to be measured to establish bioequivalence.
2. The formulation of the test product should be quantitatively and qualitatively

identical to that of the RLD.

In this application the firm conducted fasting BE study. SAS data files are available in EDR. As reported by the firm in the BE Summary Report, the results of the BE study are within the acceptable range for the relevant PK measures: the results (point estimate, 90% CI) for triamcinolone acetonide (N=125) are as follows: LAUC0-t 1.03, 95.05%-111.40%, LAUC0-inf 0.95, 87.9%-103.54%, LCmax 1.00, 82.22%-122.23%. As per Module 2.3.P.1, P.21, there are no differences between the Sandoz Canada formulation and the RLD with respect to excipients quantitatively or qualitatively except the benzyl alcohol content. The benzyl alcohol is reduced to 0.9405% w/v compared to 0.99% w/v in the RLD. This reduction has no significant impact on the preservative effectiveness and falls under differences permitted for inactive ingredients under 21 CFR 314.94 (9)(iii).

The application is acceptable for filing.

### **Completed Assignment for 90164 ID: 4570**

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*Productivity:*

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
4570	11/30/2007	Paragraph 4	Paragraph 4 Checklist	1	1
				<b>Bean Total:</b>	<b>1</b>

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

/s/

-----  
Chandra S. Chaurasia  
1/31/2008 09:16:23 AM



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

## OVERNIGHT DELIVERY

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

TELEPHONE AMENDMENT  
(Electronic Submission)

FEB 26 2008

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Telephone Amendment – Items needed for Acceptance**

## EXPEDITED REVIEW REQUEST

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting an amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the conversation on February 26, 2008 between Sandra Middleton of FDA and Alison Sherwood of Sandoz Inc. Accordingly we are providing the following:

### **Expedited Review Request:**

Sandoz would like to make a request for Expedited Review of ANDA 90-164 on the basis of MAPP 5240.3 which states that first generic products for which there are no blocking patents or exclusivities on the RLD may be identified for expedited review and on FDA's G.I.V.E (Generic Initiative for Value and Efficiency)

### **Additional Items for Acceptance:**

- 1) Enclosed is a copy of the section 3.2.P.4.1.8- Specifications – Nitrogen which was missing from the original submission. This section contains the specifications and COAs from Sandoz Canada Inc as well as the manufacturers COA.
- 2) Sandoz Canada Inc. is requesting an expiry date for the drug product of 24 months when stored at controlled room temperature.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.



# SANDOZ

Document	ANDA 90-164
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Specification Nitrogen	cmc folder specification_nitrogen.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/ags

cc. Maria Garofalo (CL)

# ANDA CHECKLIST FOR CTD or eCTD FORMAT FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD)

Format please go to: <http://www.fda.gov/cder/regulatory/ersr/eectd.htm>

\*For a Comprehensive Table of Contents Headings and Hierarchy please go to:

<http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>

\*\* For more CTD and eCTD informational links see the final page of the ANDA Checklist

\*\*\* A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage <http://www.fda.gov/cder/ogd/> \*\*\*

ANDA #: 90-164

FIRM NAME: SANDOZ CANADA INC.

PIV: NO

Electronic or Paper Submission: PAPER (CTD FORMAT)

**RELATED APPLICATION(S):** SEE 90-166 FOR TRIAMCINOLONE ACETONIDE INJECTABLE SUSPENSION USP, 10 MG/ML FROM SANDOZ CANADA INC. PN 12/3/07 (RLD KENALOG-10)

**First Generic Product Received?** YES

<b>Bio Assignments:</b>		<input checked="" type="checkbox"/> <b>Micro Review !!!Yes, MICRO Review NEEDED!!!</b>
<input checked="" type="checkbox"/> <b>BPH</b>	<input type="checkbox"/> <b>BCE</b>	
<input type="checkbox"/> <b>BST</b>	<input checked="" type="checkbox"/> <b>BDI</b>	

**DRUG NAME:** TRIAMCINOLONE ACETONIDE

**DOSAGE FORM:** INJECTABLE SUSPENSION USP, 40 MG/ML

**Random Queue:** 5

Chem Team Leader: Bykadi, Raj PM: Benjamin Danso Labeling Reviewer: Ruby Wu

<b>Letter Date:</b> NOVEMBER 30, 2007	<b>Received Date:</b> DECEMBER 3, 2007
<b>Comments:</b> EC - 1 YES	<b>On Cards:</b> YES
<b>Therapeutic Code:</b> 4025010 CORTICOSTEROIDS	
<b>Archival copy:</b> PAPER (CTD FORMAT)	<b>Sections</b> I
<b>Review copy:</b> YES Not applicable to electronic sections	E-Media Disposition: YES SENT TO EDR
<b>PART 3 Combination Product Category</b> N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

<b>Reviewing CSO/CST</b> Sandra T. Middleton  <b>Date</b> 2/27/2008	<b>Recommendation:</b>  <input checked="" type="checkbox"/> <b>FILE</b> <input type="checkbox"/> <b>REFUSE to RECEIVE</b>
<b>Supervisory Concurrence/Date:</b> _____ <b>Date:</b> _____	

**ADDITIONAL COMMENTS REGARDING THE ANDA:**

2/21/2008 – Requested the following:

- Debarment certification from Sandoz Canada, Inc. with original signature - **Sandoz Inc. filed a letter of non-repudiation on behalf of Sandoz and all Sandoz affiliates on November 30, 2007.**
- Sample statement for the API and finish product - **provided on page 3 of section 3.2.S.4.3 - volume 1 of module 3**
- Expiration date for the stability **submitted 2/26/2008**
- COA for nitrogen - **submitted 2/26/2008**
- Advise that they could qualify for expedite review based on PI certification and no generic on the market – must request in writing – **submitted 2/26/2008**

**MODULE 1  
ADMINISTRATIVE**

ACCEPTABLE

<b>1.1</b>	<b>1.1.2</b> <b>Signed and Completed Application Form (356h) (original signature)</b> (Check Rx/OTC Status) RX YES	<input checked="" type="checkbox"/>
<b>1.2</b>	<b>Cover Letter</b> Dated: NOVEMBER 30, 2007	<input checked="" type="checkbox"/>
*	<b>Table of Contents (paper submission only) YES</b>	<input checked="" type="checkbox"/>
<b>1.3.2</b>	<b>Field Copy Certification (original signature) YES</b> (N/A for E-Submissions)	<input checked="" type="checkbox"/>
<b>1.3.3</b>	<b>Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:</b> 1. Debarment Certification (original signature) YES – <b>need original signature</b> 2. List of Convictions statement (original signature)	<input type="checkbox"/>
<b>1.3.4</b>	<b>Financial Certifications</b> Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	<input checked="" type="checkbox"/>
<b>1.3.5</b>	<b>1.3.5.1</b> <b>Patent Information</b> Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations <b>1.3.5.2</b> <b>Patent Certification</b> 1. Patent number(s) NONE 2. Paragraph: (Check all certifications that apply) MOU <input type="checkbox"/> PI <input checked="" type="checkbox"/> PII <input type="checkbox"/> PIII <input type="checkbox"/> PIV <input type="checkbox"/> No Relevant Patents <input type="checkbox"/> 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES - NO exclusivities	<input checked="" type="checkbox"/>

1.4.1	<b>References</b> Letters of Authorization <ol style="list-style-type: none"> <li>1. DMF letters of authorization <ol style="list-style-type: none"> <li>a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES # (b) (4)</li> <li>b. Type III DMF authorization letter(s) for container closure YES</li> </ol> </li> <li>2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES</li> </ol>	☒
1.12.11	<b>Basis for Submission</b> NDA#: 14-901 Ref Listed Drug: KENALOG-40 Firm: APOTHECON ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

**MODULE 1 (Continued)**  
**ADMINISTRATIVE**

ACCEPTABLE

1.12.12	<b>Comparison between Generic Drug and RLD-505(j)(2)(A)</b> 1. Conditions of use YES 2. Active ingredients YES 3. Inactive ingredients YES 4. Route of administration YES 5. Dosage Form YES 6. Strength YES	☒
1.12.14	<b>Environmental Impact Analysis Statement</b> YES	☒
1.12.15	<b>Request for Waiver</b> Request for Waiver of In-Vivo BA/BE Study(ies): Paper, NA	☐
1.14.1	<b>Draft Labeling (Mult Copies N/A for E-Submissions)</b> <b>1.14.1.1</b> 4 copies of draft (each strength and container) YES <b>1.14.1.2</b> 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES <b>1.14.1.3</b> 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒

<b>1.14.3</b>	<b>Listed Drug Labeling</b> <b>1.14.3.1</b> 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES <b>1.14.3.3</b> 1 RLD label and 1 RLD container label YES  NDC 0781-3245-72                      40 mg/mL, 1 mL vial  <sup>(b) (4)</sup>	<input checked="" type="checkbox"/>
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2.3	<p><b>Quality Overall Summary</b> E-Submission: <input checked="" type="checkbox"/> PDF (archive) <input type="checkbox"/> Word Processed e.g., MS Word</p> <p>A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage <a href="http://www.fda.gov/cder/ogd/">http://www.fda.gov/cder/ogd/</a></p> <p><b>Question based Review (QbR)</b> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><b>2.3.S</b> <b>Drug Substance (Active Pharmaceutical Ingredient) YES</b></p> <ul style="list-style-type: none"><li>2.3.S.1 General Information</li><li>2.3.S.2 Manufacture</li><li>2.3.S.3 Characterization</li><li>2.3.S.4 Control of Drug Substance</li><li>2.3.S.5 Reference Standards or Materials</li><li>2.3.S.6 Container Closure System</li><li>2.3.S.7 Stability</li></ul> <p><b>2.3.P</b> <b>Drug Product YES</b></p> <ul style="list-style-type: none"><li>2.3.P.1 Description and Composition of the Drug Product</li><li>2.3.P.2 Pharmaceutical Development<ul style="list-style-type: none"><li>2.3.P.2.1 Components of the Drug Product<ul style="list-style-type: none"><li>2.3.P.2.1.1 Drug Substance</li><li>2.3.P.2.1.2 Excipients</li></ul></li><li>2.3.P.2.2 Drug Product</li><li>2.3.P.2.3 Manufacturing Process Development</li><li>2.3.P.2.4 Container Closure System</li></ul></li><li>2.3.P.3 Manufacture</li><li>2.3.P.4 Control of Excipients</li><li>2.3.P.5 Control of Drug Product</li><li>2.3.P.6 Reference Standards or Materials</li><li>2.3.P.7 Container Closure System</li><li>2.3.P.8 Stability</li></ul>	<input type="checkbox"/>
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2.7	<b>Clinical Summary (Bioequivalence)</b> <b>E-Submission: <input checked="" type="checkbox"/> PDF (archive) <input type="checkbox"/> Word Processed e.g., MS Word</b>  <b>2.7.1</b> <b>Summary of Biopharmaceutic Studies and Associated Analytical Methods</b> <b>2.7.1.1</b> <b>Background and Overview YES</b> <b>2.7.1.2</b> <b>Summary of Results of Individual Studies YES</b> <b>2.7.1.3</b> <b>Comparison and Analyses of Results Across Studies</b> 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies YES Table 2. Statistical Summary of the Comparative BA Data YES Table 4. Summary of In Vitro Dissolution Studies YES <b>2.7.1.4</b> <b>Appendix</b>	☒
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**MODULE 3**

**3.2.S DRUG SUBSTANCE**

ACCEPTABLE

3.2.S.1	<b>General Information</b> <b>3.2.S.1.1</b> <b>Nomenclature YES</b> <b>3.2.S.1.2</b> <b>Structure YES</b> <b>3.2.S.1.3</b> <b>General Properties YES</b>	☒
3.2.S.2	<b>Manufacturer</b> <b>3.2.S.2.1</b> <b>Manufacturer(s) (This section includes contract manufacturers and testing labs)</b> <b>Drug Substance (Active Pharmaceutical Ingredient)</b> 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES # <span style="background-color: #cccccc; padding: 0 5px;">(b) (4)</span> 4. CFN or FEI numbers	☒
3.2.S.3	<b>Characterization</b>	☒

<p><b>3.2.S.4</b></p>	<p><b>Control of Drug Substance (Active Pharmaceutical Ingredient)</b></p> <p><b>3.2.S.4.1</b>  <b>Specification</b>  Testing specifications and data from drug substance manufacturer(s) YES</p> <p><b>3.2.S.4.2</b>  <b>Analytical Procedures</b> YES</p> <p><b>3.2.S.4.3</b>  <b>Validation of Analytical Procedures</b></p> <p>1. Spectra and chromatograms for reference standards and test samples YES</p> <p>2. Samples-Statement of Availability and Identification of:</p> <p>a. Drug Substance YES</p> <p>b. Same lot number(s) <b>NO</b></p> <p><b>3.2.S.4.4</b>  <b>Batch Analysis</b></p> <p>1. COA(s) specifications and test results from drug substance mfgr(s) YES</p> <p>2. Applicant certificate of analysis YES</p> <p><b>3.2.S.4.5</b>  <b>Justification of Specification</b></p>	<input type="checkbox"/>
<p><b>3.2.S.5</b></p>	<p><b>Reference Standards or Materials</b></p>	<input checked="" type="checkbox"/>
<p><b>3.2.S.6</b></p>	<p><b>Container Closure Systems</b></p>	<input checked="" type="checkbox"/>
<p><b>3.2.S.7</b></p>	<p><b>Stability</b></p>	<input checked="" type="checkbox"/>

**MODULE 3**

**3.2.P DRUG PRODUCT**

ACCEPTABLE

<p><b>3.2.P.1</b></p>	<p><b>Description and Composition of the Drug Product</b>                  1) Unit composition YES                  2) Inactive ingredients are appropriate per IIG YES – Q1 and Q2 to the RLD</p>	<p><input checked="" type="checkbox"/></p>
<p><b>3.2.P.2</b></p>	<p><b>Pharmaceutical Development</b>                  Pharmaceutical Development Report YES</p>	<p><input checked="" type="checkbox"/></p>
<p><b>3.2.P.3</b></p>	<p><b>Manufacture</b>  <b>3.2.P.3.1</b>  <b>Manufacture(s)</b> (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)                  1. Name and Full Address(es) of the Facility(ies) YES                  2. CGMP Certification: <b>NEED cGMP from applicant</b>                  3. Function or Responsibility YES                  4. CFN or FEI numbers YES  <b>3.2.P.3.2</b>  <b>Batch Formula</b>                  Batch Formulation YES  <b>3.2.P.3.3</b>  <b>Description of Manufacturing Process and Process Controls</b>                  1. Description of the Manufacturing Process YES                  2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b)(4)                  3. If sterile product: Aseptic fill / Terminal sterilization (b)(4)                  4. Reprocessing Statement YES  <b>3.2.P.3.4</b>  <b>Controls of Critical Steps and Intermediates</b>  <b>3.2.P.3.5</b>  <b>Process Validation and/or Evaluation</b>                  1. Microbiological sterilization validation YES                  2. Filter validation (if aseptic fill) Not required per Micro – Rona LaBlanc 2/21/2008</p>	<p><input type="checkbox"/></p>
<p><b>3.2.P.4</b></p>	<p><b>Controls of Excipients (Inactive Ingredients) YES</b>                  Source of inactive ingredients identified YES  <b>3.2.P.4.1</b>  <b>Specifications</b>                  1. Testing specifications (including identification and characterization) YES                  2. Suppliers' COA (specifications and test results) YES  <b>3.2.P.4.2</b>  <b>Analytical Procedures - NA</b>  <b>3.2.P.4.3</b>  <b>Validation of Analytical Procedures NA</b>  <b>3.2.P.4.4</b>  <b>Justification of Specifications</b>                  Applicant COA</p>	<p><input checked="" type="checkbox"/></p>

**MODULE 3**  
**3.2.P DRUG PRODUCT**

ACCEPTABLE

<p><b>3.2.P.5</b></p>	<p><b>Controls of Drug Product</b>  <b>3.2.P.5.1</b>  <b>Specification(s) YES</b>  <b>3.2.P.5.2</b>  <b>Analytical Procedures YES</b>  <b>3.2.P.5.3</b>  <b>Validation of Analytical Procedures</b>  <b>Samples - Statement of Availability and Identification of:</b>  1. Finished Dosage Form YES  2. Same lot numbers YES  <b>3.2.P.5.4</b>  <b>Batch Analysis</b>  Certificate of Analysis for Finished Dosage Form YES  <b>3.2.P.5.5</b>  <b>Characterization of Impurities 3.2.S.3.2</b>  <b>3.2.P.5.6</b>  <b>Justification of Specifications</b></p>	<p><input checked="" type="checkbox"/></p>
<p><b>3.2.P.7</b></p>	<p><b>Container Closure System</b>  1. Summary of Container/Closure System (if new resin, provide data) YES  2. Components Specification and Test Data YES  3. Packaging Configuration and Sizes YES  4. Container/Closure Testing YES  5. Source of supply and suppliers address YES</p>	<p><input checked="" type="checkbox"/></p>
<p><b>3.2.P.8</b></p>	<p><b>3.2.P.8.1</b>  <b>Stability (Finished Dosage Form)</b>  1. Stability Protocol submitted YES  2. Expiration Dating Period NO – <b>NEED TO REQUEST EXPIRATION DATE</b>  <b>3.2.P.8.2</b>  <b>Post-approval Stability and Conclusion</b>  Post Approval Stability Protocol and Commitments YES  <b>3.2.P.8.3</b>  <b>Stability Data</b>  1. 3 month accelerated stability data YES  2. Batch numbers on stability records the same as the test batch YES</p>	<p><input type="checkbox"/></p>

**MODULE 3**

**3.2.R Regional Information**

ACCEPTABLE

<p><b>3.2.R</b>  <b>(Drug Substance)</b></p>	<p><b>3.2.R.1.S</b>  <b>Executed Batch Records for drug substance (if available) IN DMF</b>  <b>3.2.R.2.S</b>  <b>Comparability Protocols NA</b>  <b>3.2.R.3.S</b>  <b>Methods Validation Package YES</b>  Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)  (Required for Non-USP drugs)</p>	<p><input checked="" type="checkbox"/></p>
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**MODULE 3**

**3.2.R Regional Information**

ACCEPTABLE

<p><b>3.2.R (Drug Product)</b></p>	<p><b>3.2.R.1.P.1 Executed Batch Records</b> Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES – (b) (4) SEE BELOW</p> <p><b>3.2.R.1.P.2 Information on Components YES</b></p> <p><b>3.2.R.2.P Comparability Protocols YES</b></p> <p><b>3.2.R.3.P Methods Validation Package YES</b> Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)</p>	<p><input checked="" type="checkbox"/></p>
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*What is the reconciliation of the exhibit batch?*

A summary of the batch reconciliation data for the ANDA exhibit batches is provided below. For batch records of the ANDA exhibit batches refer to Module 3.2 R.1.P1 Executed Batch records

Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL	Lot#	Lot #	Lot #
	1370607-1	1450710	1120702

(b) (4)



**MODULE 5  
CLINICAL STUDY REPORTS**

ACCEPTABLE

5.2	<b>Tabular Listing of Clinical Studies</b>	<input checked="" type="checkbox"/>																																								
5.3.1 (complete study data)	<p><b>Bioavailability/Bioequivalence</b></p> <p><b>1. Formulation data same?</b></p> <p>a. Comparison of all Strengths (check proportionality of multiple strengths) NA</p> <p>b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) YES</p> <p><b>2. Lot Numbers of Products used in BE Study(ies): Study # 3270 Lot# 1370607-1</b></p> <p><b>3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)</b></p>	<input checked="" type="checkbox"/>																																								
	<p><b>5.3.1.2</b></p> <p><b>Comparative BA/BE Study Reports</b></p> <p>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)</p> <p>2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples</p> <p><b>5.3.1.3</b></p> <p><b>In Vitro-In-Vivo Correlation Study Reports</b></p> <p>1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data</p> <p><b>5.3.1.4</b></p> <p><b>Reports of Bioanalytical and Analytical Methods for Human Studies</b></p> <p>1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation</p> <p><b>5.3.7</b></p> <p><b>Case Report Forms and Individual Patient Listing</b></p>	<input type="checkbox"/>																																								
5.4	<b>Literature References</b>																																									
	<b>Possible Study Types:</b>																																									
Study Type	<p><b>IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) FASTING ON 40 MG - First generic looked at by DBE for completeness found AC 1/31/2008</b></p> <p>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES</p> <p>2. EDR Email: Data Files Submitted: YES SENT TO EDR</p> <p>3. In-Vitro Dissolution: YES</p> <p>Table 3 Statistical Summary of the Comparative Bioavailability Data</p> <table border="1" data-bbox="365 1724 1406 1875"> <thead> <tr> <th colspan="5">Triamcinolone Acetonide 40 mg/mL Injectable Solution</th> </tr> <tr> <th colspan="5">Dose (60 mg)</th> </tr> <tr> <th colspan="5">Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals</th> </tr> <tr> <th colspan="5">Fasted Bioequivalence Study (3270)</th> </tr> <tr> <th>Parameter</th> <th>Test</th> <th>Reference</th> <th>Ratio of Means</th> <th>90% Confidence Interval</th> </tr> </thead> <tbody> <tr> <td>AUC<sub>0-t</sub></td> <td>1362.34</td> <td>1323.91</td> <td>102.90%</td> <td>95.05% to 111.40%</td> </tr> <tr> <td>AUC<sub>∞</sub></td> <td>1447.61</td> <td>1517.39</td> <td>95.40%</td> <td>87.90% to 103.54%</td> </tr> <tr> <td>C<sub>max</sub></td> <td>3.04</td> <td>3.03</td> <td>100.25%</td> <td>82.22% to 122.23%</td> </tr> </tbody> </table>	Triamcinolone Acetonide 40 mg/mL Injectable Solution					Dose (60 mg)					Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					Fasted Bioequivalence Study (3270)					Parameter	Test	Reference	Ratio of Means	90% Confidence Interval	AUC <sub>0-t</sub>	1362.34	1323.91	102.90%	95.05% to 111.40%	AUC <sub>∞</sub>	1447.61	1517.39	95.40%	87.90% to 103.54%	C <sub>max</sub>	3.04	3.03	100.25%	82.22% to 122.23%	<input type="checkbox"/>
Triamcinolone Acetonide 40 mg/mL Injectable Solution																																										
Dose (60 mg)																																										
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals																																										
Fasted Bioequivalence Study (3270)																																										
Parameter	Test	Reference	Ratio of Means	90% Confidence Interval																																						
AUC <sub>0-t</sub>	1362.34	1323.91	102.90%	95.05% to 111.40%																																						
AUC <sub>∞</sub>	1447.61	1517.39	95.40%	87.90% to 103.54%																																						
C <sub>max</sub>	3.04	3.03	100.25%	82.22% to 122.23%																																						

Study Type	<p><b>IN-VIVO BE STUDY with CLINICAL ENDPOINTS</b> NO</p> <ol style="list-style-type: none"> <li>1. Properly defined BE endpoints (eval. by Clinical Team)</li> <li>2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25).</li> <li>3. Summary results indicate superiority of active treatments (test &amp; reference) over vehicle/placebo (<math>p &lt; 0.05</math>) (eval. by Clinical Team)</li> <li>4. EDR Email: Data Files Submitted</li> </ol>	<input type="checkbox"/>
Study Type	<p><b>IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays)</b> NO</p> <ol style="list-style-type: none"> <li>1. Study(ies) meets BE criteria (90% CI of 80-125)</li> <li>2. EDR Email: Data Files Submitted:</li> <li>3. In-Vitro Dissolution:</li> </ol>	<input type="checkbox"/>
Study Type	<p><b>NASALLY ADMINISTERED DRUG PRODUCTS</b> NO</p> <ol style="list-style-type: none"> <li>1. <u>Solutions</u> (Q1/Q2 sameness): <ol style="list-style-type: none"> <li>a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming &amp; Repriming, Tail Off Profile)</li> </ol> </li> <li>2. <u>Suspensions</u> (Q1/Q2 sameness): <ol style="list-style-type: none"> <li>a. <u>In-Vivo PK Study</u> <ol style="list-style-type: none"> <li>1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC)</li> <li>2. EDR Email: Data Files Submitted</li> </ol> </li> <li>b. <u>In-Vivo BE Study with Clinical End Points</u> <ol style="list-style-type: none"> <li>1. Properly defined BE endpoints (eval. by Clinical Team)</li> <li>2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125)</li> <li>3. Summary results indicate superiority of active treatments (test &amp; reference) over vehicle/placebo (<math>p &lt; 0.05</math>) (eval. by Clinical Team)</li> <li>4. EDR Email: Data Files Submitted</li> </ol> </li> <li>c. <u>In-Vitro Studies</u> (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming &amp; Repriming, Tail Off Profile)</li> </ol> </li> </ol>	<input type="checkbox"/>
Study Type	<p><b>TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)</b> NO</p> <ol style="list-style-type: none"> <li>1. Pilot Study (determination of ED50)</li> <li>2. Pivotal Study (study meets BE criteria 90%CI of 80-125)</li> </ol>	<input type="checkbox"/>
Study Type	<p><b>TRANSDERMAL DELIVERY SYSTEMS</b> NO</p> <ol style="list-style-type: none"> <li>1. <u>In-Vivo PK Study</u> <ol style="list-style-type: none"> <li>1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC)</li> <li>2. In-Vitro Dissolution</li> <li>3. EDR Email: Data Files Submitted</li> </ol> </li> <li>2. <u>Adhesion Study</u></li> <li>3. <u>Skin Irritation/Sensitization Study</u></li> </ol>	<input type="checkbox"/>

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/s/

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Martin Shimer  
3/4/2008 11:05:19 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville, MD 20857

ANDA 90-164

Sandoz Inc.  
U.S. Agent for: Sandoz Canada Inc.  
Attention: Beth Brannan  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Dear Madam:

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

Reference is the telephone conversation dated February 21, 2008 and your e-mails dated February 22 and 26, 2008.

NAME OF DRUG: Triamcinolone Acetonide Injection Suspension, 40 mg/mL,  
1 mL (b)(4) vials

DATE OF APPLICATION: November 30, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 3, 2007

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:

Benjamin Danso  
Project Manager  
(240) 276-8527

Sincerely yours,

*{See appended electronic signature page}*

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

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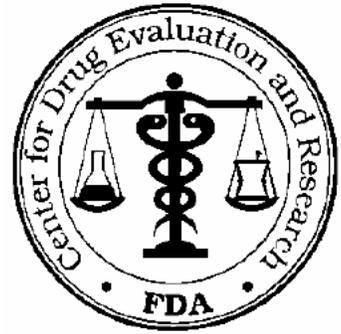
/s/

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Martin Shimer  
3/4/2008 11:10:51 AM  
Signing for Wm Peter Rickman

# Labeling Comments

ANDA 90-164

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North I  
7520 Standish Place  
Rockville, MD 20855-2773



TO: Sandoz Canada Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Agent

FAX: 303-438-4600

FROM: Ruby Wu (240-276-8952)

Dear Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Injectable Suspension, USP, 40 mg/mL (1 mL, 5 mL and 10 mL vials).

Pages (including cover): 3

**SPECIAL INSTRUCTIONS:**

*Labeling comments*

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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

---

<b>ANDA Number</b>	90-164
<b>Date of Submission</b>	November 30, 2007 (original)
<b>Applicant</b>	Sandoz Canada Inc.
<b>Drug Name</b>	Triamcinolone Acetonide Injectable Suspension, USP
<b>Strength(s)</b>	40 mg/mL (1 mL, (b) (4) vials)

---

**Labeling Deficiencies:**

1. CONTAINER LABELS (1 mL, (b) (4) vials)
  - a. Assure that the text is at least 4 point type.
  - b. Please add "Contains Benzyl Alcohol as a Preservative"
  - c. 1 mL vial: revise "For Intramuscular Use Only" to read "For Intramuscular Use"
  - d. (b) (4)
  - e.
  - f.

2. CARTON (1 vial)
  - a. Please add "Contains Benzyl Alcohol as a Preservative"
  - b. Top lid: add the net quantity statement.
  - c. "...sodium hydroxide or hydrochloric..."
  - d. (b) (4)
  - e.

3. PHYSICIAN INSERT
  - a. TITLE:
    - i. Assure that "NOT FOR INTRAVENOUS..." starts on a new line.
    - ii. Add the phrase "Rx only" to a location just under the TITLE of the package insert.
  - b. INDICATIONS AND USAGE: "Nervous system" [spelling]
  - c. PRECAUTIONS, Drug Interactions: "Hepatic enzyme inducers" [spelling]

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling 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://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

*{See appended electronic signature page}*

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

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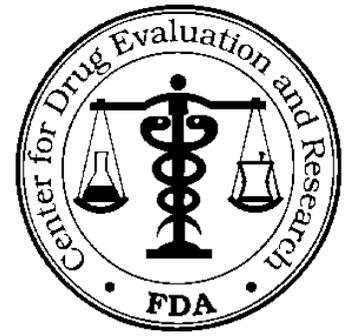
/s/

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John Grace  
3/11/2008 10:17:14 AM

# BIOEQUIVALENCY AMENDMENT

ANDA 90-164 and 90-166

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Sandoz, Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Keri Suh

PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 30, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL and 40 mg/mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached one page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. **Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

## **SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-164 (40 mg/mL) and 90-166 (10 mg/mL)  
APPLICANT: Sandoz Canada, Inc.  
DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension USP,  
10 mg/mL and 40 mg/mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. Your proposed dissolution method is not acceptable. Please conduct additional comparative dissolution testing on 12 individual dosage units for the test and reference products using the following DBE-recommended method:

Additional dissolution testing should be conducted in 900 mL of water using USP apparatus II (paddle) at 75 rpm and in different pH media, i.e. pH 1.2, pH 4.5 and pH 6.8 buffers, at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . It is acceptable to add a small amount of surfactant if necessary. The sampling times are 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 minutes until at least 80% of the drug is dissolved.

2. Please submit long term storage stability data that exceeds 128 days.

3. You have submitted chromatograms from 24 subjects. 20% of chromatograms= 20% x 125 analyzed subject= 25 subject chromatograms. For future studies, please submit 20% of the total chromatograms.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

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Barbara Davit  
3/25/2008 11:34:21 AM  
Signing for Dale P Conner



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**BIO AMENDMENT**  
(Electronic Submission)

MAY 8 2008

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Bio Amendment – Response to March 25, 2008 Deficiency Letter (Dissolution)**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting an amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the bioequivalence deficiency letter dated March 25, 2008. Enclosed please find a complete response to this request. The information provided in this amendment is identical to the information being submitted at this time to ANDA 90-166 for our 10mg/mL ANDA.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

<b>Document</b>	<b>ANDA 90-164</b>
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Bio Deficiency Response	cmc folder bioresponse.pdf (bookmarked)

This information is submitted for your review and approval.



**SANDOZ**

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

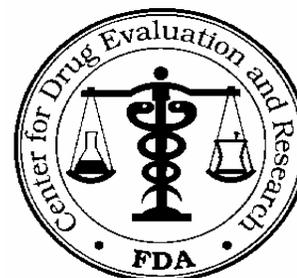
Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/ags

cc. Maria Garofalo (CL)

**FAX – Microbiology Deficiencies Enclosed**

Office of Generic Drugs, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville MD 20855-2773 (240-276-8408)



<b>TO:</b> Beth Brannan, Director, Regulatory Affairs	<b>FROM:</b> Kun Shen
Sandoz Canada, Inc.	Microbiology Project Manager
<b>PHONE:</b> 303-438-4237	<b>PHONE:</b> (240) 276-8722
<b>FAX:</b> 303-438-4600	<b>FAX:</b> (240) 276-8428

Total number of pages, excluding this cover sheet: 4

**SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

**Microbiology Deficiencies:**

Enclosed are the microbiology deficiencies for **ANDA 90-164, Triamcinolone Acetonide Injectable Suspension (40 mg/mL), USP**. The submission reviewed was submitted on 11/30/2007. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Kun Shen, Bonnie McNeal or Mark Anderson.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.** If you are not the addressee, or person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

**LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:**

ANDA: 90-164      APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension (40 mg/mL), USP

A.      Microbiology Deficiencies:

1.

2.

3.

4.

5.

(b) (4)

Following this page, 1 page withheld in full (b)(4)

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

Sincerely yours,

*{See appended electronic signature page}*

Neal J. Sweeney, Ph.D.  
Microbiology Supervisor  
Office of Generic Drugs

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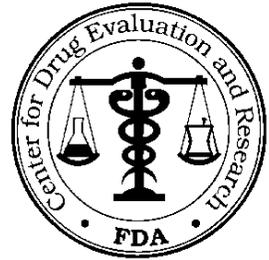
/s/

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Neal Sweeney  
5/28/2008 11:52:49 AM

## MINOR AMENDMENT

ANDA 90-164

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 30, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Injectable Suspension USP, 40 mg/ mL .

### **SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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# CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-164            APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT:        Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL

A. The deficiencies presented below represent MINOR deficiencies.

1. DMF <sup>(b) (4)</sup> is inadequate. The Holder has been notified. Please ensure that there is a response.

2. Please conduct a literature search to verify if any <sup>(b) (4)</sup>

3. <sup>(b) (4)</sup>

4. <sup>(b) (4)</sup>

5. <sup>(b) (4)</sup>

6. <sup>(b) (4)</sup>

7. <sup>(b) (4)</sup>

8. <sup>(b) (4)</sup>

9. <sup>(b) (4)</sup>

10. <sup>(b) (4)</sup>

11. <sup>(b) (4)</sup>

12  
13  
14  
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16  
17  
18

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.
  2. Your Sterility Assurance information is pending review. Deficiencies, if any, will be communicated separately.
  3. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
  4. Your reply should also address the labeling deficiencies provided to you by facsimile on 03/11/2008.
  5. Please provide any additional long term stability data that may be available.
  6. USP<467> becomes official on July 1<sup>st</sup>, 2008. Compliance information will need to be provided to the ANDA unless it is approved prior to that date.

Sincerely yours,

*{See appended electronic signature page}*

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

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/s/

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Michael Smela  
6/6/2008 08:55:36 AM  
For Rashmikant M. Patel, Ph.D.



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**BIO TELEPHONE AMENDMENT  
(Electronic Submission)**

JUN 10 2009

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Bio Telephone Amendment – Response to May 29, 2008 Request (Dissolution)**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting an amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the telephone request made by Nam Chun on May 29, 2008. Enclosed please find the 12 unit dissolution profiles using 900mL water and 0.35% SDS as the media for both test and reference 40 mg/mL and 10 mg/mL strengths. The information provided in this amendment is identical to the information being submitted at this time to ANDA 90-166 for our 10mg/mL ANDA.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	ANDA 90-164
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Telephone amendment	cmc folder disso amendment.pdf (bookmarked)

This information is submitted for your review and approval.



Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

*Beth Brannan for*

Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/ags

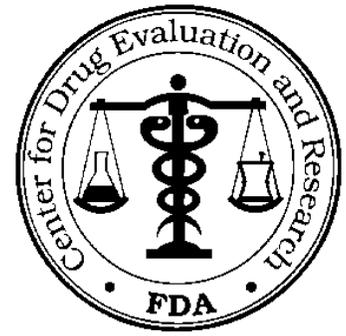
cc. Maria Garofalo (CL)

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# BIOEQUIVALENCY AMENDMENT

ANDA 90-164 & 90-166

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Nam Chun

FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 30, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Injectable Suspension, 10 mg/mL and 40 mg/mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached one page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. **Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

## **SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCY

ANDA: 90-164 and 90-166  
APPLICANT: Sandoz Canada Inc.  
DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension,  
10 mg/mL and 40 mg/mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiency has been identified:

The dissolution testing using the FDA-recommended method is acceptable. Based on the submitted dissolution data, the DBE recommends the below specifications for the test product. Please acknowledge the following FDA-recommended method and specifications for your Triamcinolone Acetonide Injectable Suspension, 10 mg/mL and 40 mg/mL:

Medium:	Water with 0.35% Sodium Dodecyl Sulfate (SDS)
Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Speed:	75 rpm
Volume:	900 mL
Specifications:	15 min: NLT <span style="background-color: gray; color: gray;">(b) (4)</span>
	60 min: NLT <span style="background-color: gray; color: gray;">(b) (4)</span>

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence I  
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.**  
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/s/

-----  
Dale Conner

6/24/2008 02:31:47 PM



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**MINOR AMENDMENT**  
(microbiology)  
(Electronic Submission)

**JUL 15 2008**

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Minor Amendment – Response to Microbiology Deficiencies of May 28, 2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting an amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the deficiency letter dated May 28, 2008. Provided is a complete response to all items.

With this amendment, Sandoz Canada is adding a pre-washed, ready to sterilize rubber stopper to this ANDA. The rubber stopper remains the same however. Sandoz Canada intends to purchase these stoppers already washed according to (b) (4) DMF (b) (4). A DMF letter of authorization is enclosed.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	ANDA 90-164
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
minor amendment- response to micro deficiencies	cmc folder micro amendment.pdf (bookmarked)

This information is submitted for your review and approval.



Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/ags

cc. Maria Garofalo (CL)



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**AMENDMENT**  
(including electronic labeling)

July 17, 2008

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension, USP  
40 mg/mL (1 mL (b)(4) vials)  
Amendment – Labeling – Response to Deficiency Letter received June 26,  
2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. is hereby submitting an amendment to unapproved Abbreviated New Drug Application 90-164 for Triamcinolone Acetonide Injectable Suspension, USP in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the communication dated March 11, 2008 which Sandoz received via fax on June 26, 2008. The following is provided in response to the FDA comments (*in italics*):

1. *CONTAINER:LABELS* (1 mL (b)(4) vials)
  - a. *Assure that the text is at least 4 point type.*
  - b. *Please add "Contains Benzyl Alcohol as a Preservative"*
  - c. *1mL vial: revise "For Intramuscular Use Only" to read "For Intramuscular Use"*
  - d.  (b)(4)
  - e.
  - f.



# SANDOZ

## Sandoz Response:

- a. Sandoz confirms that the text is at least 4 point type.
- b. Sandoz has added "Contains Benzyl Alcohol as a Preservative" on the <sup>(b) (4)</sup> vial labels. However, space does not permit the statement to be added to the 1 mL vial label.
- c. Sandoz has revised the "For Intramuscular Use" statement as requested.

- d. <sup>(b) (4)</sup>
- e.
- f. <sup>(b) (4)</sup>

## 2. *CARTON (1 vial)*

- a. *Please add "Contains Benzyl Alcohol as a Preservative"*
- b. *Top lid: add the net quantity statement.*
- c. *"...sodium hydroxide or hydrochloric..."*

- d. <sup>(b) (4)</sup>
- e.

## Sandoz Response:

- a. Sandoz has added "Contains Benzyl Alcohol as a Preservative"
- b. Sandoz has added the net quantity statement to the top lid as requested.
- c. Sandoz has changed sodium hydroxide of hydrochloric..." to "...sodium hydroxide or hydrochloric..." as requested. Note that Sandoz has changed "...may be present..." to "...may have been added..." to be consistent with triamcinolone acetonide injectable suspension 10 mg, ANDA 90-166.

- d. <sup>(b) (4)</sup>
- e.

## 3. *PHYSICIAN INSERT*

### a. *TITLE*

- i. *Assure that 'NOT FOR INTRAVENOUS...' starts on a new line.*
- ii. *Add the phrase "Rx only" to a location just under the TITLE of the package insert.*



- b. *INDICATIONS AND USAGE: "Nervous system" (spelling)*
- c. *PRECAUTIONS, Drug Interactions: "Hepatic enzyme inducers" [spelling]*

**Sandoz Response:**

- a. i. Sandoz has started "NOT FOR INTRAVENOUS..." on a new line.  
 ii. Sandoz has added "Rx only" under the product name on the final print physician insert.
- b. Sandoz has corrected the spelling of "Nervous System" in INDICATIONS AND USAGE.
- c. Sandoz has corrected the spelling of "Hepatic Enzyme Inducers" in PRECAUTIONS, Drug Interactions.

(b) (4)

The revised labeling is attached electronically. Included on the CD are the following files:

<b>Document</b>	<b>File Name on CD ANDA 90-164</b>
356h form	356h.pdf
Cover Letter	Cover Letter.pdf
Physician Insert in SPL	SPL folder
Physician Insert in MSWord format	Triamcinolone Acetonide 40 mg/mL.doc
Physician Insert in pdf format	Triamcinolone Acetonide 40 mg/mL 8.5x11.pdf
Side by Side Comparison of previously filed and current proposed Physician Insert	SideBySide.doc
Final Print Physician Insert – actual size	Triamcinolone Acetonide 40 mg/mL Actual Size 07-2008.pdf
1 mL vial label	3245-72 Vial 07-2008.pdf
1 x 1 mL carton	3245-72 Carton 07-2008.pdf
	(b) (4)



We can confirm that this submission is virus free. Sandoz filed a non-repudiation agreement to the FDA on November 30, 2007. However, we are providing hard copies of our cover letter and FDA form 356(h) with original signatures.

Please note that we are providing this supplement in electronic format only. One CD is provided in the archival copy of this supplement. Therefore, if you should have any questions regarding this submission, please contact me (303) 438-4237.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/pln

cc: Maria Garofalo (whole submission)



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**BIO AMENDMENT**  
(Electronic Submission)

AUG 1 2008

**RE: ✓ ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
ANDA 90-166 Triamcinolone Acetonide Injectable Suspension USP 10 mg/mL  
Bio Telephone Amendment – Response to June 24, 2008 Request (Dissolution)**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting an amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the bioequivalency deficiency dated June 24, 2008. A complete response to this request is provided.

**Bioequivalence deficiencies:**

The Division of Bioequivalence (DBE) has completed its review and the following deficiency has been identified:

The dissolution testing using the FDA-recommended method is acceptable. Based on the submitted dissolution data, the DBE recommends the below specifications for the test product. Please acknowledge the following FDA-recommended method and specifications for your Triamcinolone Acetonide Injectable Suspension, 10 mg/mL and 40 mg/mL:

Medium:	Water with 0.35% Sodium Dodecyl Sulfate (SDS)
Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Speed:	75 rpm
Volume:	900 mL
Specifications:	15 min: NLT <span style="background-color: gray; color: white; padding: 0 5px;">(b) (4)</span> 60 min: NLT <span style="background-color: gray; color: white; padding: 0 5px;">(b) (4)</span>



**Sandoz Canada Response:**

We accept the DBE-recommended method for dissolution testing of Triamcinolone Acetonide Injectable Suspension USP 10 and 40 mg/mL using USP Apparatus II. However, we would like to propose a modification of the 15 minute specification from (b) (4) to (b) (4)

Sandoz Canada received a request in our chemistry deficiency letter dated June 6, 2008 with respect to the control of particle size of the API. In response to this request Sandoz Canada is proposing the following drug substance particle size specifications:

D<sub>50</sub>: (b) (4)  
D<sub>90</sub>: (b) (4)

The limits for the particle size distribution have been proposed based on four drug substance lots manufactured by (b) (4). These limits allow for the manufacturer's process capability and this particle size distribution has also been observed in the RLD. Sandoz Canada Inc. performed a series of dissolution tests with the Paddle II apparatus using FDF samples manufactured with these different lots of API with particle sizes spanning the specification limit range. The results of this study are presented in Table 1.

Table 1: Dissolution results obtained with lots spanning the limit range for API particle size

(b) (4)	d50 (µm)	d90 (µm)	disso % 15 min	disso % 60 min
<b>Lot Numbers</b>				
Lot 0080724	(b) (4)			
Lot 0070724				
Lot 0130524 *				
Lot 0060624				

\* (b) (4) lot 0130524 is the lot used in the manufacture of Sandoz Canada's 40 mg/mL bio batch and 10 mg/mL ANDA batch, results in this table reflect an optimized particle size method which will be filed in the CMC deficiency response.

On the basis of these results, Sandoz Canada Inc. would like to propose the following:  
A limit of (b) (4) at 15 minutes.

The information provided in this amendment is identical to the information being submitted at this time to ANDA 90-166 for our 10mg/mL ANDA.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.



**SANDOZ**

<b>Document</b>	<b>ANDA 90-164</b>
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/ags

cc. Maria Garofalo (CL & 356h)

**FAX – Microbiology Deficiencies Enclosed**

Office of Generic Drugs, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville MD 20855-2773 (240-276-8408)



<b>TO:</b> Beth Brannan, Director, Regulatory Affairs	<b>FROM:</b> Bonnie McNeal
Sandoz Inc.	Microbiology Project Manager
<b>PHONE:</b> 303-438-4237	<b>PHONE:</b> (240) 276-8831
<b>FAX:</b> 303-438-4600	<b>FAX:</b> (240) 276-8766

Total number of pages, excluding this cover sheet:  3

**SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

**Microbiology Deficiencies:**

Enclosed are the microbiology deficiencies for ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP. The submission reviewed was submitted on July 15, 2008. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Bonnie McNeal or Mark Anderson.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.** If you are not the addressee, or person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

**LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:**

ANDA: 90-164      APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension, USP

Microbiology Deficiencies:

In regard to  (b) (4):

- a)  (b) (4)
- b) 
- c) 
- d) 
- e) 

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

Sincerely yours,

*{See appended electronic signature page}*

LCDR Paul Dexter, M.S.  
Microbiology Team Leader  
Office of Generic Drugs  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
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/s/

-----  
Paul Dexter

8/4/2008 08:35:10 AM

# Memorandum

Division of Chemistry 1  
Office of Generic Drugs  
Office of Pharmaceutical Science  
Center For Drug Evaluation And Research  
Food And Drug Administration

To: The File

From: Michael Smela, Jr.  
Team Leader, Team 2

Re: ANDA 90164 & 90166

Memo of Telecom:

I left a message for Allison Sherwood (303-438-4513) in response to a voice mail left for Esther Chuh. She questioned the deficiency whereby we requested they change the UDU and Redispersibility limits to 90.0-115.0% thinking that perhaps we did not mean UDU because they are following current <905>.

I said the deficiency is correct as it was worded because the DP USP monograph does not reference <905> and therefore all vials must meet the USP assay limit of 90.0-115.0% thru the shelf life.

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/s/

-----  
Michael Smela  
8/4/2008 09:21:17 AM  
CHEMIST



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**MINOR AMENDMENT**  
(microbiology)  
(Electronic Submission)

**AUG 26 2008**

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Minor Amendment – Response to Microbiology Deficiencies of August 4, 2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting an amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the deficiency letter dated August 4, 2008. Provided is a complete response to all items.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

<b>Document</b>	<b>ANDA 90-164</b>
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
minor amendment- response to micro deficiencies	cmc folder micro amendment.pdf (bookmarked)

This information is submitted for your review and approval.



Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Beth Brannan, Director  
Regulatory Affairs

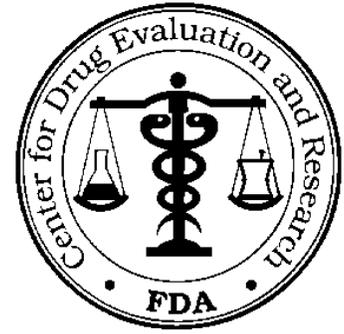
Enclosures  
BB/ags

cc. Maria Garofalo (CL)

# BIOEQUIVALENCY AMENDMENT

ANDA 90-164 & 90-166

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Nam Chun

FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 30, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Injectable Suspension, 10 mg/mL and 40 mg/mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached four pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. **Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

## **SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-164 and 90-166  
APPLICANT: Sandoz Canada Inc.  
DRUG PRODUCT: Triamcinolone Acetonide Injectable Suspension USP,  
10 mg/mL and 40 mg/mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. Based on the dissolution data provided by you, there appears to be a direct relationship between the particle size of the active pharmaceutical ingredient (API) and the dissolution rate: The smaller the particle size of the API, the faster the dissolution rate of the finished product. However, you have not provided any evidence to demonstrate that difference in the particle size of the API lots will not affect the in vivo performance and bioequivalence of the test product. In addition, there are currently insufficient data provided by you to justify for an appropriate particle size range which can be considered as acceptable limits of the bio lot particle size.
2. You stated that the particle size distribution observed in different API lots of the test product has also been observed in the reference listed drug (RLD) product. Please provide data to support this statement, i.e., particle size data for API used in the RLD product.

With respect to the particle size data for the finished RLD product: ***You did not submit particle size data for any lots of the finished RLD product of the 40 mg/mL strength.*** However, you have submitted for the Chemistry review of the ANDA 90166 (in the submission dated November 30, 2007) the particle size data for several finished product lots of the 10 mg/mL of the RLD product, for comparison with a test lot No. 1280605 of the same strength, as follow:

Parameter	Triamcinolone Acetonide Injectable Suspension USP, 10 mg/mL	Kenalog®	Kenalog®	Kenalog®
		Lot 6K21219:Exp.09-08 Lot 5MO6227:Exp.12-07	Lot 6G15740:Exp.04-08	Lot 5M01726:Exp.11-07
Batch No.	1280605	Lots *6K21219 and **5MO6227	6G15740	5M01726
Size	(b) (4)			
Density [g/mL]				
pH***				
Osmolality [mOsm/kg]				
Particle Size [µm]				
Viscosity [cSt]				
Surface tension [dynes/cm]				
* Lot 6K21219 was used for the following tests: Density, Osmolality, Viscosity and Surface Tension was used for the pH test. ** Lot 5MO6227 was used for the pH and Particle size tests. ***Labeling: pH =5.0-7.5. N/P = Not performed				

Based on the particle size data presented above, although the 10 mg/mL strength of the RLD product showed variations in the particle size distribution profile, it appeared that the particle size profile for this strength of the RLD product was much different and (b) (4) than that of the 10 mg/mL strength of the exhibit lot No. 1280605 of the test product.

Also, comparing the above particle size data with those provided by you for the 40 mg/mL strength of the test product below, it appeared that the particle size distribution profile for the 40 mg/mL strength of the test product was much more variable (than that of the 10 mg/mL strength of the RLD product as seen above). The range of the particle size of the finished test product at the 40 mg/mL was (b) (4) and (b) (4) the range of the particle size of the finished RLD product (at the 10 mg/mL), whereas the range of particle size of the bio batch No. 1370607-1 (40 mg/mL) and the exhibit batch No. 1280605 (10 mg/mL) of the test product was more comparable.

Test	Procedure	Specifications (Drug Substance)	Test results Lots# (Drug Substance)		
			129830	137291	138079
Particle size	PS-0008	d50: (b) (4) d90: (b) (4)	(b) (4)		
Test	Procedure	Specifications (Product)	Test results Lots# (Drug Product)		
			1370607-1 (1mL, bio batch)	1450710 (b) (4)	1120702 (b) (4)
Particle size	PS-0007	d50 (b) (4) d90 (b) (4)	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)	d50: (b) (4) d90: (b) (4)

Based on the particle size data provided by you for the finished test product (10 mg/mL and 40 mg/mL) and the finished RLD product (10 mg/mL strength only) above, it is not possible to compare the particle size profiles of the bio lots of the test and RLD products which have demonstrated bioequivalence in the fasting BE study.

3. You did not provide the following necessary information for the currently submitted dissolution data: (1) how many units of the finished lots were tested, and (2) whether the dissolution values as stated were single or mean values.
4. For the dissolution data currently submitted for the 15 minute dissolution time point, three out of four of the dissolution values, (b)(4) (lot# 0070724, 0130524, 0060624, respectively) met the previously FDA-recommended specification [15 min: (b)(4)]. The fourth dissolution value of (b)(4) (lot # 0080724) did not meet the FDA-recommended specification and also does not even meet your new proposed specification [15 min: (b)(4)]. Therefore, these data do not support your proposed change in the dissolution specification at this time point.
5. You state that "(b)(4) lot # 0130524 is the lot used in the manufacture of Sandoz Canada's 40 mg/mL bio batch and 10 mg/mL ANDA batch..." However, based on the information provided in the original ANDA submission (dated 30-Nov-2007), a different drug substance lot number (i.e., #129830) was used to manufacture the test bio lot # 1370607-1. Please verify the API lot #0130524 mentioned in the current amendment is the same as the API lot # 129830 given in the original submission, and/or explain the discrepancy in the API lot numbers reported.
6. Based on the above discussion, the DBE does not consider that you have submitted appropriate and adequate dissolution data to justify for the proposed dissolution specification change at the 15 minute sampling time point.

As per the current DBE policy, in order to justify for any change of the FDA-recommended dissolution specifications of the test product, please submit dissolution data of at least three fresh finished production lots of your test product (of both strengths). These lots should be manufactured based on approved manufacturing specifications. The data of full dissolution profile for 12 individual dosage units of each lot, manufactured in the same conditions as the bio-lot, using the API of the same particle size (with any difference to be within the approved particle size specification range) should be submitted.

7. Alternatively, please accept the following dissolution method and specifications:

Medium:	Water with 0.35% Sodium Dodecyl Sulfate (SDS)
Apparatus:	USP Apparatus II (Paddle)
Temperature:	37°C ± 0.5°C
Speed:	75 rpm
Volume:	<b>900 mL</b>
<b>Specifications:</b>	<b>15 min: NLT</b> <span style="background-color: gray; color: gray;">(b) (4)</span>
	60 min: NLT <span style="background-color: gray; color: gray;">(b) (4)</span>

Sincerely yours,

{See appended electronic signature page}

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

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**This is a representation of an electronic record that was signed electronically and  
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/s/

-----  
Dale Conner

9/10/2008 08:45:07 AM



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**MINOR AMENDMENT  
(Chemistry)  
(Electronic Submission)**

**SEP 22 2008**

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Minor Amendment – Response to Deficiency Letter dated June 6, 2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting a minor amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the deficiency letter dated June 6, 2008. Enclosed please find a complete response to the comments provided.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

<b>Document</b>	<b>ANDA 90-164</b>
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Minor Amendment- Response to June 6, 2008 Deficiencies	cmc folder minor amendment.pdf (bookmarked)



This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/ags

cc. Maria Garofalo (CL)



Beth Brannan, Director  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Email:  
Beth.Brannan@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**BIO AMENDMENT**  
(Electronic Submission)

SEP 26 2008

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Bio Amendment – Response to September 10, 2008 Deficiency Letter (Dissolution)**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting an amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the bioequivalence deficiency letter dated September 10, 2008. Enclosed please find a complete response to this request. The information provided in this amendment is identical to the information being submitted at this time to ANDA 90-166 for our 10mg/mL ANDA.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	ANDA 90-164
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Bio Deficiency Response	cmc folder bio amendment.pdf (bookmarked)

This information is submitted for your review and approval.



Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Beth Brannan, Director  
Regulatory Affairs

Enclosures  
BB/ags

cc. Maria Garofalo (CL)

## COMPLETE RESPONSE -- MINOR

ANDA 90-164

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Sandoz Canada Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 30, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL.

Reference is also made to your amendment dated September 22, 2008.

### **SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

## CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-164                      APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT:            Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL

A. The deficiencies presented below represent MINOR deficiencies.

1. DMF <sup>(b) (4)</sup> is inadequate. The Holder has been notified. Please ensure that there is a response. <sup>(b) (4)</sup>

2. <sup>(b) (4)</sup>

3. <sup>(b) (4)</sup>

4. <sup>(b) (4)</sup>

5. <sup>(b) (4)</sup>

6. <sup>(b) (4)</sup>

7. <sup>(b) (4)</sup>

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

1. An acceptable compliance evaluation is necessary for approval and the evaluation is pending.
2. Your microbiology and bioequivalence information are pending review. Deficiencies, if any, will be provided under separate cover.

Sincerely yours,

*{See appended electronic signature page}*

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

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/s/

-----  
Michael Smela  
11/4/2008 09:04:14 AM  
For Rashmikant M. Patel, Ph.D.



Alison Sherwood, Manager  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4513  
Fax +1 303 438-4600  
Email:  
alison.sherwood@sandoz.com

## OVERNIGHT DELIVERY

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

MINOR AMENDMENT  
(Chemistry)  
(Electronic Submission)

DEC 12 2008

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Minor Amendment – Response to Deficiency Letter dated November 4, 2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting a minor amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the deficiency letter dated November 4, 2008. Enclosed please find a complete response to the comments provided.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	ANDA 90-164
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Minor Amendment- Response to Nov 4, 2008 Deficiencies	cmc folder minoramendment.pdf (bookmarked)



This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Alison Sherwood, Manager  
Regulatory Affairs

Enclosures

cc. Daniel Abran (CL)



Alison Sherwood, Manager  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
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Broomfield, CO 80038-0446

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alison.sherwood@sandoz.com

90-164

MC

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**New Correspondence**

January 14, 2009

RE ANDAs: See Attached list

Dear Director:

On behalf of Sandoz Canada, we wish to provide you with New Correspondence announcing a change in the responsible agent for the attached list of product applications.

Effective November 17, 2008, the contact name for this application has changed from Beth Brannan to Alison Sherwood, who can be reached at (303) 438-4513. The agent address did not change. Reference is made to a telephone conversation between Tom Hinchliff (FDA) and Jean Pederson (Sandoz) on November 20, 2008. Per Tom, a 356h is not required to be submitted, and that a cover letter with the attached list of products is all that is needed, plus one CD and a copy of the letter for each application. Therefore, one copy of this letter is enclosed for each ANDA provided on the list. Also enclosed is one CD containing a copy of this entire submission.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Alison Sherwood, Manager  
Regulatory Affairs

Enclosures: List of Applications

AS/sc

**RECEIVED**

JAN 15 2009

**OGD**



Alison Sherwood,  
Manager  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4513  
Fax +1 303 438-4600

Sandoz Canada Products

ANDA	Product NAME
	(b) (4)
78-075	Brimonidine Tartrate Ophthalmic Solution, 0.2%
40-481	Digoxin for Injection, 0.25mg/mL
78-748	Dorzolamide Hydrochloride Ophthalmic Solution 22.3mg/mL (2%)
78-749	Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution 22.3mg/mL
	(b) (4)
40-628	Estradiol Valerate Injection USP, 10mg/mL, 20mg/mL, 40mg/mL
77-155	Fenoldopam Mesylate Injection USP, 10mg (base) / mL
77-071	Flumazenil Injection USP, 0.1mg/mL
78-534	Granisetron Hydrochloride Injection 0.1mg/mL (1mL single use vial)
78-531	Granisetron Hydrochloride Injection 1mg/mL (1mL single use and 4mL multi use)
76-463	Haloperidol Decanoate Injection, 50mg/mL and 100mg/mL
76-464	Haloperidol Injection 5mg/mL
40-648	Isoniazid Injection USP 100 mg/mL
76-271	Ketorolac Tromethamine injection, USP, 15mg/mL, 30 mg/mL
78-711	Medroxyprogesterone Acetate Injectable Suspension USP 150mg/mL
40-719	Methylprednisolone Acetate Injectable Suspension USP 40mg/mL and 80mg/mL
40-794	Methylprednisolone Acetate Injectable Suspension USP 40mg/mL and 80mg/mL
77-360	Metoprolol Tartrate Injection USP, 1 mg/mL, 5mL vials
77-551	Ondansetron Injection USP, 2mg / mL, 2mL vial
77-430	Ondansetron Injection USP, 2mg/mL 20mL vials
40-593	Promethazine Hydrochloride Injection, USP 25mg /mL and 50mg /mL
76-400	Propranolol Hydrochloride Injection 1mg/mL
79-195	Rocuronium Bromide Injection 10mg/mL
	(b) (4)
78-067	Sumatriptan Succinate Injection 12mg/mL, 8mg/mL
40-615	Testosterone Cypionate Injection, USP 100 mg/mL and 200 mg/mL
90-166	Triamcinolone Acetonide Injectable Suspension USP 10mg/mL
90-164	Triamcinolone Acetonide Injectable Suspension USP 40mg/mL

## COMPLETE RESPONSE -- MINOR

ANDA 90-164

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Sandoz Canada Inc.

TEL: 303-438-4513

ATTN: Allison Sherwood, Regulatory Affairs

FAX: 303-438-4600

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 30, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL.

Reference is also made to your amendments dated December 12, 2008 and January 14, 2009.

### **SPECIAL INSTRUCTIONS:**

**Please submit your response in electronic format.**

**This will improve document availability to review staff.**

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

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## CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-164      APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT:      Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL

The deficiency presented below represents Minor deficiency.

A. Deficiency:

Please provide updated drug product specifications for 40 mg/mL (1 ml fill size).

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

DMF <sup>(b) (4)</sup> is inadequate. <sup>(b) (4)</sup>  
<sup>(b) (4)</sup>. This comment also pertains to your related application (ANDA #90166).

Sincerely yours,

*{See appended electronic signature page}*

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

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/s/

-----  
Paul Schwartz  
2/9/2009 01:04:26 PM  
Signed for R. Patel



Alison Sherwood, Manager  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
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alison.sherwood@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**MINOR AMENDMENT**  
(Chemistry)  
(Electronic Submission)

FEB 19 2009

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
Minor Amendment – Response to Deficiency Letter dated February 10, 2009**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting a minor amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the deficiency letter dated February 10, 2009. Enclosed please find a complete response to the comments provided.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

<b>Document</b>	<b>ANDA 90-164</b>
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Minor Amendment- Response to Feb 10, 2009 Deficiencies	cmc folder minoramendment.pdf (bookmarked)



This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

A handwritten signature in blue ink that reads 'Alison Sherwood'.

Alison Sherwood, Manager  
Regulatory Affairs

Enclosures

cc. Daniel Abran (CL)

## RECORD OF TELEPHONE CONVERSATION

<p>We called the firm for the following reasons:</p> <ol style="list-style-type: none"> <li>1. The particle size limits for Triamcinolone Acetonide injectable Suspensions are inadequate. Please provide an updated drug product release and stability specifications for the 10 and 40 mg/mL products [REDACTED] (b) (4).</li> <li>2. Please revise [REDACTED] (b) (4) [REDACTED] ).</li> <li>3. Please provide comparative [REDACTED] (b) (4) Particle Size results for the ANDA and RLD lots.</li> </ol> <p>Sandoz acknowledged our concerns and agreed to response these questions in a telephone amendment.</p>	<p style="text-align: center;"><b>DATE:</b> April 24, 2009</p> <hr/> <p style="text-align: center;"><b>ANDA NUMBER</b> 90-164 90-166</p> <hr/> <p style="text-align: center;"><b>TELECON INITIATED BY</b> FDA</p> <hr/> <p style="text-align: center;"><b>PRODUCT NAME:</b> Triamcinolone Acetonide Inj. Suspension, 10 mg/mL and 40 mg/ml</p> <hr/> <p style="text-align: center;"><b>FIRM NAME:</b> Sandoz Inc</p> <hr/> <p style="text-align: center;"><b>FIRM REPRESENTATIVES:</b> ALISON SHERWOOD KALPANA RAO VANAM MARK BABCOCK DANIEL ABRAN YVES LEBLANC</p> <hr/> <p style="text-align: center;"><b>PHONE NUMBER:</b> 303 4384513</p> <hr/> <p style="text-align: center;"><b>FDA REPRESENTATIVE(S)</b> Bing Cai Radhika Rajagopalan Paul Schwartz</p> <hr/> <p style="text-align: center;">SIGNATURES:</p> <p style="text-align: center;">_____ Bing Cai</p> <p style="text-align: center;">_____ Radhika Rajagopalan</p> <hr/> <p style="text-align: center;">_____ Paul Schwartz</p> <hr/>
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/s/

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Bing Cai  
5/26/2009 09:53:44 AM  
CHEMIST

Radhika Rajagopalan  
5/26/2009 10:40:27 AM  
CHEMIST  
None  
None

Paul Schwartz  
5/27/2009 04:36:08 PM  
CHEMIST



Alison Sherwood, Manager  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
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**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**FAX AMENDMENT**  
(Chemistry)  
(Electronic Submission)

**MAY 12 2009**

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL  
ANDA 90-166 Triamcinolone Acetonide Injectable Suspension USP 10 mg/mL  
Fax Amendment – Response to FDA Teleconference Request**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., Sandoz Inc., as the U.S. Authorized Agent, is hereby submitting a minor amendment to pending Abbreviated New Drug Application ANDA 90-164 for Triamcinolone Acetonide Injectable Suspension USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the teleconference between FDA and Sandoz personnel on April 24, 2009. The FDA participants were Bing Cai, Paul Swartz, and Radhika Rajagopalan. The Sandoz participants were Alison Sherwood, Kalpana Rao Vanam, March Babcock, Daniel Abran, and Yves LeBlanc. Enclosed is a complete response to all the items requested.

**A. DEFICIENCIES**

The comments and suggestions brought forth by Drs. Radhika Rajagopalan, Paul Schwartz and Bing Cai in a teleconference with Sandoz's representatives have been compiled and rewritten as FDA comments.

- 1. FDA Comment: The particle size limits for Triamcinolone Acetonide injectable Suspensions are inadequate. Please provide an updated drug product release and stability specifications for the 10 and 40 mg/mL products** (b) (4)

**Sandoz Response:** The updated drug product release and stability specifications for the 10 and the 40 mg/mL Triamcinolone Acetonide Injectable Suspension USP as well as their associated post-approval stability protocols can be found in ATTACHMENT -1-. A

Following this page, 2 pages withheld in full (b)(4)



**SANDOZ**

(b) (4)

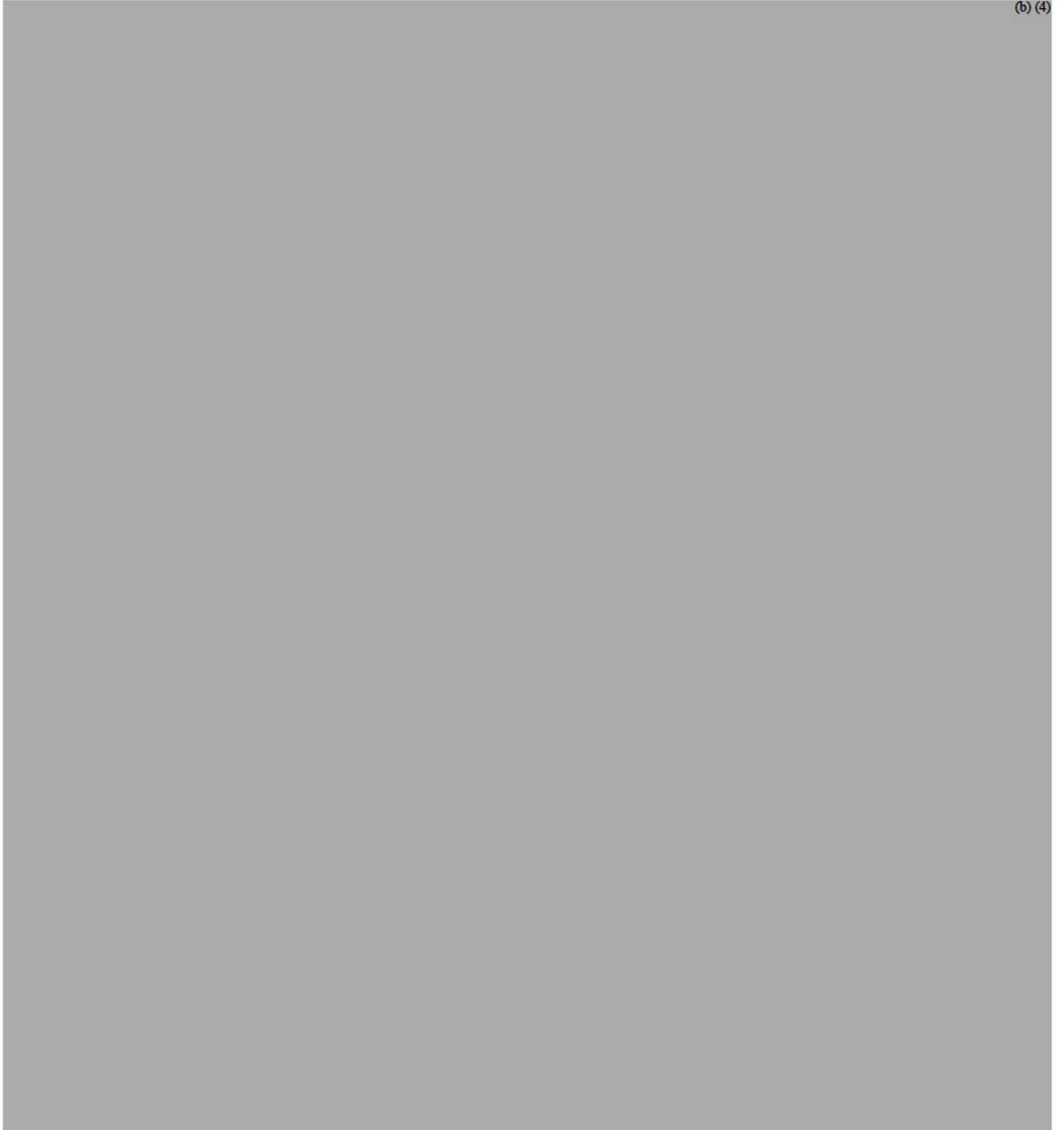
2. **FDA Comment:** Please revise

(b) (4)

**Sandoz Response:**

(b) (4)

(b) (4)



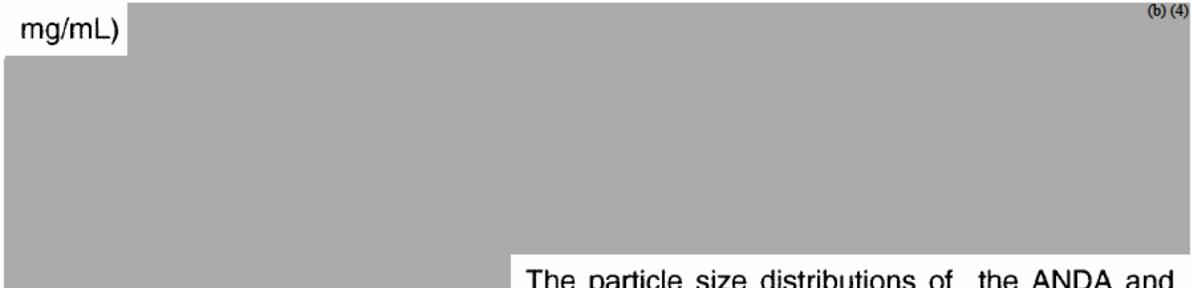
3. **FDA Comment:** Please provide clearly identified (b) (4) Particle Size results for the ANDA and RLD lots.

**Sandoz Response:** Sandoz Canada could not identify the (b) (4) Particle Size results referred to by the reviewers (all particle size data appeared adequately labelled). However, please find in ATTACHMENT -6- the (b) (4) Particle Size results for RLD lot 8C42471 (10 mg/mL) and Sandoz ANDA lots 1280605 (10 mg/mL) and 1370607-1 (40



mg/mL)

(b) (4)



The particle size distributions of the ANDA and RLD lots are comparable.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	ANDA 90-164
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Fax Amendment- Teleconference Request	cmc folder fax amendment.pdf (bookmarked) fax amendment.doc

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

Alison Sherwood, Manager  
Regulatory Affairs

Enclosures

cc. Daniel Abran (CL)



Alison Sherwood, Manager  
Regulatory Affairs

Sandoz Inc.  
2555 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4513  
Fax +1 303 438-4600  
Email:  
alison.sherwood@sandoz.com

**OVERNIGHT DELIVERY**

Gary Buehler, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**LABELING AMENDMENT**

MAY 28 2009

**RE: ANDA 90-164 Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL  
Labeling Amendment**

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting a labeling amendment to our unapproved Abbreviated New Drug Application 90-164 for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

The physician insert has been revised. (b) (4)

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

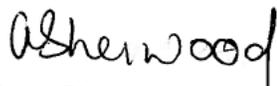
Document	ANDA 90-164
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
Labeling Folder	
8.5 x 11 pdf format text of Physician Insert	U1003019.pdf
Final Print of Physician Insert in pdf format (actual size and layout)	U1003019 Actual Size 5-2009.pdf
Side by side comparison with previous revision	U1003019Side by Side 7_08 v 5_09.pdf
Word version of text of Physician Insert	U1003019.doc
SPL Format	SPL Folder

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

**Sandoz Inc.**

A handwritten signature in black ink that reads "ASherwood". The signature is written in a cursive style with a large initial 'A'.

Alison Sherwood, Manager  
Regulatory Affairs

Enclosures

AS/sld

OGD APPROVAL ROUTING SUMMARY

ANDA # 90-164 Applicant Sandoz Canada Inc  
Drug Triamcinolone Acetonide Injectable Suspension USP Strength(s) 40 mg/mL

APPROVAL  TENTATIVE APPROVAL  SUPPLEMENTAL APPROVAL (NEW STRENGTH)  OTHER

REVIEWER: DRAFT Package FINAL Package

1. Martin Shimer Date 8 April 2009 Date 5/27/09  
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes  No  Determ. of Involvement? Yes  No   
(required if sub after 6/1/92) Pediatric Exclusivity System

RLD = Kenalog-40 NDA#14-901

Patent/Exclusivity Certification: Yes  No  Date Checked N/A

If Para. IV Certification- did applicant Nothing Submitted

Notify patent holder/NDA holder Yes  No  Written request issued

Was applicant sued w/in 45 days: Yes  No  Study Submitted

Has case been settled: Yes  No  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: ANDA submitted on 12/3/2007, BOS=NDA 14-901 Kenalog-40 Injectable Suspension, PI Cert provided. ANDA ack for filing on 12/3/2007 (LO dated 3/4/2008). Firm requested expedited review in MC received by the Agency on 2/27/2008. This ANDA is eligible for Full Approval as there are no unexpired patents or exclusivities which protect the RLD.

2. Project Manager, Esther Chuh Team 2 Review Support Branch Date 4/7/2009 Date \_\_\_\_\_  
Initials EC Initials \_\_\_\_\_

Original Rec'd date 12/3/2007 EER Status Pending  Acceptable  OAI

Date Acceptable for Filing 12/3/2007 Date of EER Status 2/5/2009

Patent Certification (type) I Date of Office Bio Review 12/23/2008

Date Patent/Exclus. expires n/a Date of Labeling Approv. Sum 7/23/2008

Citizens' Petition/Legal Case Yes  No  Date of Sterility Assur. App. 10/21/2008

(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes  No

First Generic Yes  No  MV Commitment Rcd. from Firm Yes  No

Priority Approval Yes  No  Modified-release dosage form: Yes  No

(If yes, prepare Draft Press Release, Email it to Cecelia Parise) Interim Dissol. Specs in AP Ltr: Yes

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:

3. **Labeling Endorsement**

Reviewer:

Date

Name/Initials Ruby Wu

Labeling Team Leader:

Date

Name/Initials John Grace

Comments:

Thanks!

---

**From:** Lee, Koung U

**Sent:** Monday, June 01, 2009 9:28 AM

**To:** Eng, Simon; Wu, Ruby (Chi-Ann)

**Subject:** RE: 90164\_Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL packaged in 1 mL Vials

Simon,

I concur also.

Koung

---

**From:** Eng, Simon

**Sent:** Monday, June 01, 2009 7:20 AM

**To:** Wu, Ruby (Chi-Ann)

**Cc:** Lee, Koung U

**Subject:** 90164\_Triamcinolone Acetonide Injectable Suspension USP, 40 mg/mL packaged in 1 mL Vials

Ruby,

Please sign off, I am covering for Esther.

Thanks

4. **David Read (PP IVs Only)** Pre-MMA Language included  Date 5/27/09  
OGD Regulatory Counsel, Post-MMA Language Included  Initials rlw/for  
Comments: N/A. There are no patents currently listed in the "Orange Book" for  
this drug product.

5. **Div. Dir./Deputy Dir.**  
Chemistry Div. I

Date 4/14/09  
Initials PS

Comments: CMC acceptable.

6. **Frank Holcombe** First Generics Only Date 5/26/09  
 Assoc. Dir. For Chemistry Initials RR Comments: (First generic drug  
 review)  
**CMC acceptable. For Frank,**
7. Vacant Date \_\_\_\_\_ Deputy Dir., DLPS  
 Initials \_\_\_\_\_  
 RLD = Kenalog-40 Injection 40 mg/mL  
 Apothecon Inc. NDA 14-901
8. **Peter Rickman** Date 5/27/09  
 Director, DLPS Initials rlw/for  
 Para.IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No   
 (fasting) on the 40 mg/mL strength found acceptable. Comments: Bioequivalence study  
 In-vitro dissolution testing also found acceptable. Bio study sites have  
 acceptable DSI inspection histories. Office-level bio endorsed 6/23/08 and  
 12/23/08.  
 Final-printed labeling found acceptable for approval 7/23/08, as endorsed 4/14/09,  
 above.  
 Microbiology/Sterility Assurance found acceptable (Micro Review #3) 10/21/08.  
 CMC found acceptable for approval (Chemistry Review #4).
- OR**
8. **Robert L. West** Date 5/27/09  
 Deputy Director, OGD Initials RLWest  
 Para.IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No   
 Press Release Acceptable   
 Comments: Acceptable EES dated 2/5/09 (Verified 5/27/09). No "OAI" Alerts noted.  
 There are no patents or exclusivity listed in the current "Orange Book" for this  
 drug product.  
 This is the "sister" ANDA to Sandoz's ANDA 90-166 for the 10 mg/mL strength.  
 This ANDA is recommended for approval.
9. **Gary Buehler** Date 5/27/09  
 Director, OGD Initials rlw/for

Comments:

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

10. Project Manager, Esther Chuh Team 2

Date 6/1/09

Review Support Branch \_\_\_\_\_ Date PETS checked for first generic drug (just prior to notification to firm) Initials se

Applicant notification:

205pm Time notified of approval by phone  
210pm Time approval letter faxed

FDA Notification:

6/1/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.  
6/1/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

**EES Data for: 090164**

**\*\*\* Compliance Recommendations \*\*\***

App No	Doc Seq No	Date	OC Recommendation
090164	000	2/5/2009	ACCEPTABLE

**\*\*\* EER Table \*\*\***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
		(b) (4)	OC RECOMMENDATION	2/5/2009	AC	2/5/2009	None
			OC RECOMMENDATION	8/29/2008	AC	8/29/2008	None
9615155	SANDOZ CANADA	SVS	OC	5/30/2008	AC	5/30/2008	None

<a href="#">Volume Locator</a>											
N  <a href="#">Volume Locator</a>	000	AM	2/19/2009	2/20/2009	OP	2/20/2009				<a href="#">4090370</a>	
N  <a href="#">Volume Locator</a>	000	AM	5/12/2009	5/13/2009	OP	5/13/2009				<a href="#">4134555</a>	<i>Comis Document Table Data</i>

ORANGE BOOK PRINT OFF :

Patent and Exclusivity Search Results from query on Appl No 014901 Product 001 in the OB\_Rx list.

### 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.**

[View a list of all patent use codes](#)

[View a list of all exclusivity codes](#)

[Return to Electronic Orange Book Home Page](#)

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through April, 2009

Patent and Generic Drug Product Data Last Updated: May 26, 2009

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

-----  
Simon Eng  
6/1/2009 02:06:10 PM