

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 40-719

Name: Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL (10 mL multiple-dose vials) and
80 mg/mL (5 mL multiple-dose vials)

Sponsor: Sandoz Canada, Inc.

Approval Date: January 29, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-719

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-719

APPROVAL LETTER



ANDA 40-719

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 19, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL, packaged in 400 mg/10 mL multiple-dose vials, and 80 mg/mL, packaged in 400 mg/5 mL multiple-dose vials.

Reference is also made to your amendments dated August 3, September 15, October 4, and November 30, 2006; February 23, March 9, April 9, May 22, June 1, August 29, November 21, November 28, and December 10, 2007; September 3, September 17, and December 12, 2008; and January 13, 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 Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Depo-Medrol Injectable Suspension, 40 mg/mL and 80 mg/mL, respectively, of Pharmacia and Upjohn Company. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in the 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 40-719**".

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Robert L. West
1/29/2009 02:31:15 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-719

LABELING

(b) (4)

NDC 0781-3136-70

MethylPREDNISolone
Acetate Injectable
Suspension, USP

400 mg/10 mL

(40 mg/mL)

Rx only

10 mL

Multidose Vial

 **SANDOZ**

Contains Benzyl Alcohol as a Preservative.

For intramuscular, intrasynovial, and soft tissue injection only. NOT for IV use. See package insert for complete product information. Shake well immediately before using.

Each mL contains: Methylprednisolone acetate, 40 mg; polyethylene glycol 3350, 25.1 mg; polysorbate 80, 1.94 mg; monobasic sodium phosphate, 6.8 mg; dibasic sodium phosphate, 1.42 mg; benzyl alcohol, 9.16 mg added as preservative. Sodium chloride was added to adjust tonicity. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

05-3007M

Manufactured in Canada by Sandoz Canada Inc. for Sandoz Inc., Princeton, NJ 08540

1009069

Lot:
Exp:

(b) (4)

(b) (4)

NDC 0781 2127 75
MethylPREDNISolone
Acetate Injectable
Suspension, USP
400 mg/5 mL
(80 mg/mL) *Rx only*
5 mL Multidose Vial
 **SANDOZ**

For IM, Intraarticular and soft tissue
injection only
NOT for IV use
Contains Benzyl Alcohol as a
Preservative.
See package insert for complete
product information. Shake well
immediately before using.
05/2007M
Manufactured in Canada by
Sandoz Canada Inc. for
Sandoz Inc., Princeton, NJ 08540

1003065
Lot:
Exp.:

(b) (4)

(b) (4) Varnish

NDC 0781-3136-92

MethylPREDNISolone Acetate Injectable Suspension, USP

400 mg/10 mL (40 mg/mL)

Sterile NOT for IV use.
For intramuscular, intrasynovial and soft tissue injection only.
Contains Benzyl Alcohol as a Preservative.

Rx only 10 x 10 mL Multidose Vials



Rx only
10 x 10 mL Multidose Vials

NDC 0781-3136-92
**MethylPREDNISolone
Acetate Injectable
Suspension, USP**
400 mg/10 mL
(40 mg/mL)



N 0781-3136-92 7

LOT
EXP



See package insert for complete product information. Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature). Shake well immediately before using.
Sodium chloride was added to adjust tonicity. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.
05-2007M
Manufactured in Canada by Sandoz Canada Inc. for Sandoz Inc., Princeton, NJ 08540
Also: Polyethylene glycol 3350.....29.1 mg
Methylprednisolone acetate.....40 mg
Each mL contains:
Benzyl alcohol added.....9.16 mg
Dibasic sodium phosphate.....1.42 mg
Monobasic sodium phosphate.....6.8 mg
Polyborate 80.....1.94 mg
Sandoz Canada Inc. for Sandoz Inc., Princeton, NJ 08540 as preservative

NDC 0781-3136-92

MethylPREDNISolone Acetate Injectable Suspension, USP

400 mg/10 mL (40 mg/mL)

Sterile NOT for IV use.
For intramuscular, intrasynovial and soft tissue injection only.
Contains Benzyl Alcohol as a Preservative.

Rx only 10 x 10 mL Multidose Vials

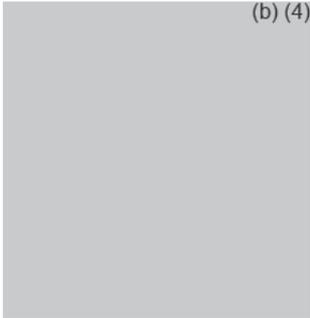


1005713

(b)
(4)

Carton

5 mL Carton
(b) (4)



1003064

MethylPREDNISolone
Acetate Injectable
Suspension, USP
400 mg/5 mL
(80 mg/mL)
SANDOZ
NDC 0781-3137-75

See package insert for complete product information. Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature). Shake well immediately before using.

Each mL contains:
Methylprednisolone acetate80 mg

Also
Polyethylene glycol 335028.2 mg
Polysorbate 801.88 mg
Monobasic sodium phosphate6.59 mg
Dibasic sodium phosphate1.37 mg
Benzyl alcohol8.88 mg added as preservative

Sodium chloride was added to adjust tonicity.

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

 **SANDOZ**

Manufactured in Canada by Sandoz Canada Inc. for Sandoz Inc., Princeton, NJ 08540

NDC 0781-3137-75
MethylPREDNISolone
Acetate Injectable
Suspension, USP

400 mg/5 mL
(80 mg/mL)

Sterile

For intramuscular, intrasynovial and soft tissue injection only.

NOT for IV use.

Contains Benzyl Alcohol as a Preservative.

Rx only

One 5 mL Multidose Vial

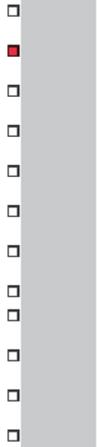
 **SANDOZ**


N 3 0781-3137-75 7

Manufactured in Canada by Sandoz Canada Inc. for Sandoz Inc., Princeton, NJ 08540

05-2007M

■ Varnish
■ (b) (4)



3064

(b) (4) Varnish

NDC 0781-3137-95

MethylPREDNISolone Acetate Injectable Suspension, USP

400 mg/5 mL (80 mg/mL)

Sterile NOT for IV use.
For intramuscular, intrasynovial and soft tissue injection only.
Contains Benzyl Alcohol as a Preservative.

Rx only 10 x 5 mL Multidose Vials

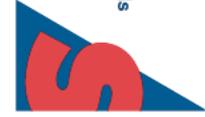


Rx only
10 x 5 mL Multidose Vials

NDC 0781-3137-95
MethylPREDNISolone Acetate Injectable Suspension, USP
400 mg/5 mL
(80 mg/mL)



3 0781-3137-95 5



LOT
EXP



See package insert for complete product information. Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature). Shake well immediately before using.
Each mL contains:
Methylprednisolone acetate80 mg
Also: Polyethylene glycol 3350.....28.2 mg
Polyborate 80.....1.88 mg
Monobasic sodium phosphate.....6.59 mg
Dibasic sodium phosphate1.37 mg
Benzyl alcohol added8.88 mg
as preservative

05-2007M
Manufactured in Canada by
Sandoz Canada Inc. for
Sandoz Inc. Princeton, NJ 08540

Sodium chloride was added to adjust tonicity.
When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

NDC 0781-3137-95

MethylPREDNISolone Acetate Injectable Suspension, USP

400 mg/5 mL (80 mg/mL)

Sterile NOT for IV use.
For intramuscular, intrasynovial and soft tissue injection only.
Contains Benzyl Alcohol as a Preservative.

Rx only 10 x 5 mL Multidose Vials



1003066

10 x 5 mL Carton



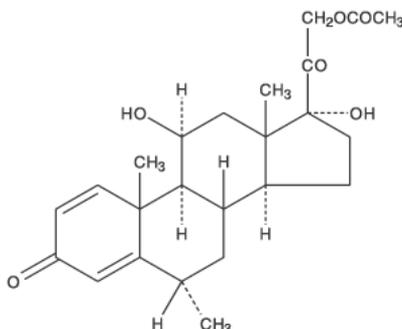
MethylPREDNISolone Acetate Injectable Suspension, USP

R_x only

Not For Intravenous Use

DESCRIPTION:

Methylprednisolone acetate sterile injectable suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water. The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6 α , 11 β)- and the molecular weight is 416.51. The structural formula is represented below.



Methylprednisolone acetate injectable suspension is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intraliesional injection. It is available in two strengths: 40 mg/mL; 80 mg/mL.

Each mL of these preparations contains:

Methylprednisolone acetate	40 mg	80 mg
Polyethylene glycol 3350	29.1 mg	28.2 mg
Polysorbate 80	1.94 mg	1.88 mg
Monobasic sodium phosphate	6.8 mg	6.50 mg
Dibasic sodium phosphate USP	1.42 mg	1.37 mg
Benzyl alcohol added as a preservative	9.16 mg	8.88 mg
Sodium Chloride was added to adjust tonicity.		
When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.		
The pH of the finished product remains within the USP specified range; i.e., 3.0 to 7.0.		

CLINICAL PHARMACOLOGY:

Naturally occurring glucocorticoids (hydrocortisone), which also have salt retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

INDICATIONS AND USAGE:

A. For Intramuscular Administration:

When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the intramuscular use of methylprednisolone acetate injectable suspension is indicated as follows:

1. Endocrine 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)

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)

Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful:

- Congenital adrenal hyperplasia
- Hypocalcemia associated with cancer
- Nonsuppurative thyroiditis

2. Rheumatic Disorders:

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

- Acute and subacute bursitis
- Epicondylitis
- Acute nonspecific tenosynovitis
- Acute gouty arthritis
- Psoriatic arthritis
- Ankylosing spondylitis

3. Collagen Diseases:

During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus
- Systemic dermatomyositis (polymyositis)
- Acute rheumatic carditis

4. Dermatologic Diseases:

• Pemphigus

• Severe erythema multiforme (Stevens-Johnson syndrome)

• Exfoliative dermatitis

• Bullous dermatitis herpetiformis

• Severe seborrheic dermatitis

• Severe psoriasis

• Mycosis fungoides

• Keratitis

• Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

- Bronchial asthma
- Contact dermatitis
- Atopic dermatitis
- Serum sickness
- Seasonal or perennial allergic rhinitis
- Drug hypersensitivity reactions
- Urticarial transfusion reactions

• Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)

6. Ophthalmic Diseases:

• Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

- Herpes zoster ophthalmicus
- Iritis, iridocyclitis
- Choroiditis
- Diffuse posterior uveitis and chorioiditis
- Optic neuritis
- Sympathetic ophthalmia
- Anterior segment inflammation
- Allergic conjunctivitis
- Allergic corneal marginal ulcers
- Keratitis

7. Gastrointestinal Diseases:

• To tide the patient over a critical period of the disease in:

- Ulcerative colitis (systemic therapy)
- Regional enteritis (systemic therapy)

8. Respiratory Diseases:

• Symptomatic sarcoidosis

• Berylliosis

• Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy

• Loeffler's syndrome not manageable by other means

• Aspiration pneumonitis

9. Hematologic Disorders:

• Acquired (autimmune) hemolytic anemia

• Secondary thrombocytopenia in adults

• Erythroblastopenia (RBC anemia)

• Congenital (erythroid) hypoplastic anemia

10. Neoplastic Diseases:

• For palliative management of:

• Leukemias and lymphomas in adults

• Acute leukemia of childhood

11. Edematous States:

• To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus

12. Nervous System:

• Acute exacerbations of multiple sclerosis

13. Miscellaneous:

• Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy

• Trichinosis with neurologic or myocardial involvement

B. For Intrasynovial or Soft Tissue Administration:

(See WARNINGS)

Methylprednisolone acetate injectable suspension is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

• Synovitis of osteoarthritis

• Rheumatoid arthritis

• Acute and subacute bursitis

• Acute gouty arthritis

• Epicondylitis

• Acute nonspecific tenosynovitis

• Post-traumatic osteoarthritis

C. For Intraliesional Administration:

Methylprednisolone acetate injectable suspension is indicated for intraliesional use in the following conditions:

• Keloids

• Localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis)

• Discoid lupus erythematosus

• Necrobiosis lipoidica diabetiformis

• Alopecia areata

Methylprednisolone acetate injectable suspension also may be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS:

Methylprednisolone acetate injectable suspension is contraindicated for intrathecal administration and is contraindicated for use in premature infants because the formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" in premature infants. Methylprednisolone acetate injectable suspension is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS:

Multidose use of methylprednisolone acetate injectable suspension, USP from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. The preservative in methylprednisolone acetate injectable suspension, USP will prevent growth of most pathogenic organisms, but certain ones (e.g., *Serratia marcescens*) may remain viable. Particular care, such as use of disposable sterile syringes and needles is necessary.

While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physicochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site. The degree to which this reaction occurs will vary with the amount of adrenal steroid injected. Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed.

In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the dermis of the lesion should be made whenever possible. The technique of intrasynovial and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

It is critical that, during administration of methylprednisolone acetate, appropriate technique be used and care taken to assure proper placement of drug.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Do not use intra-articularly, intrabursally or for intraliesional administration for local effect in the presence of acute infection.

Prolonged 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 fungi or viruses.

Usage in Pregnancy:

Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone 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 used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially in high doses, because of possible hazards of neurological complications and lack of antibody response.

The use of methylprednisolone acetate in 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 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.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

PRECAUTIONS:

General:

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.

When multidose vials are used, special care to prevent contamination of the contents is essential. There is some evidence that benzalkonium chloride is not an adequate antiseptic for sterilizing methylprednisolone acetate injectable suspension multidose vials. A povidone-iodine solution or similar product is recommended to cleanse the vial top prior to aspiration of contents. (See WARNINGS.)

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

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

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

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.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoproteinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. Caution must also be used in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis, when steroids are used as direct or adjunctive therapy.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

The following additional precautions apply for parenteral corticosteroids. Intrasynovial injection of a corticosteroid may produce systemic as well as local effects.

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.

Local injection of a steroid into a previously infected joint is to be avoided.

Corticosteroids should not be injected into unstable joints.

The slower rate of absorption by intramuscular administration should be recognized. 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 corticosteroids 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.)

(Continued)

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.

ADVERSE REACTIONS:**Fluid and electrolyte disturbances:**

Sodium retention
Fluid retention
Congestive heart failure in susceptible patients
Potassium loss
Hypokalemic alkalosis
Hypertension

Musculoskeletal:

Muscle weakness
Steroid myopathy
Loss of muscle mass
Osteoporosis
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones

Gastrointestinal:

Peptic ulcer with possible subsequent perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis

Dermatologic:

Impaired wound healing
Thin fragile skin
Petechie and ecchymoses
Facial erythema
Increased sweating
May suppress reactions to skin tests

Neurological:

Convulsions
Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment
Vertigo
Headache

Endocrine:

Menstrual irregularities
Development of Cushingoid state
Suppression of growth in children
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycemic agents in diabetes

Ophthalmic:

Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos

Metabolic:

Negative nitrogen balance due to protein catabolism
The following *additional* adverse reactions are related to parenteral corticosteroid therapy:

Anaphylactic reaction
Allergic or hypersensitivity reactions
Urticaria
Hyperpigmentation or hypopigmentation
Subcutaneous and cutaneous atrophy
Sterile abscess
Injection site infections following non-sterile administration (see **WARNINGS**)
Postinjection flare, following intrasynovial use
Charcot-like arthropathy

Adverse Reactions Reported with the Following Routes of Administration:**Intrahecal/Epidural:**

Arachnoiditis
Meningitis
Paraparesis/paraplegia
Sensory disturbances
Bowel/bladder dysfunction
Headache
Seizures

Intranasal:

Temporary/permanent visual impairment including blindness
Allergic reactions
Rhinitis

Ophthalmic:

Temporary/permanent visual impairment including blindness
Increased intraocular pressure
Ocular and periorcular inflammation including allergic reactions
Infection
Residue or slough at injection site

Miscellaneous Injection sites:

(scalp, tonsillar fauces, sphenopalatine ganglion)-blindness

DOSAGE AND ADMINISTRATION:

Because of possible physical incompatibilities, methylprednisolone acetate injectable suspension should not be diluted or mixed with other solutions.

A. Administration for Local Effect:

Therapy with methylprednisolone acetate injectable suspension does not obviate the need for the conventional measures usually employed.

Although this method of treatment will ameliorate symptoms, it is in no sense a cure and the hormone has no effect on the cause of the inflammation.

1. Rheumatoid and Osteoarthritis:

The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, injections may be repeated at intervals ranging from one to five or more weeks depending upon the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide:

Size of Joint	Examples	Range of Dosage
Large	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	10 to 40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

Procedure:

It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Proaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the joint space has been entered by the needle. *The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves.* With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of methylprednisolone acetate. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing.

Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal, and hip joints. Since difficulty is not infrequently encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile. Local therapy does not alter the underlying disease process, and whenever possible comprehensive therapy including physiotherapy and orthopedic correction should be employed.

Following intra-articular steroid therapy, care should be taken to avoid overuse of joints in which symptomatic benefit has been obtained. Negligence in this matter may permit an increase in joint deterioration that will more than offset the beneficial effects of the steroid.

Unstable joints should not be injected. Repeated intra-articular injection may in some cases result in instability of the joint. X-ray follow-up is suggested in selected cases to detect deterioration.

If a local anesthetic is used prior to injection of methylprednisolone acetate injectable suspension, the anesthetic package insert should be read carefully and all the precautions observed.

2. Bursitis:

The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 percent procaine hydrochloride solution. A 20 to 24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

3. Miscellaneous: Ganglion, Tendinitis, Epicondylitis:

In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken, following application of a suitable antiseptic to the overlying skin, to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst. In many cases, a single injection causes a marked decrease in the size of the cystic tumor and may effect disappearance. The usual sterile precautions should be observed, of course, with each injection.

The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4 to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

4. Injections for Local Effect in Dermatologic Conditions:

Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg of the suspension is injected into the lesion. It may be necessary to distribute doses ranging from 20 to 40 mg by repeated local injections in the case of large lesions. Care should be taken to avoid injection of sufficient material to cause blanching since this may be followed by a small slough. One to four injections are usually employed, the intervals between injections varying with the type of lesion being treated and the duration of improvement produced by the initial injection.

When multidosage vials are used, special care to prevent contamination of the contents is essential. (See **WARNINGS**.)

B. Administration for Systemic Effect:

The intramuscular dosage will vary with the condition being treated. When employed as a temporary substitute for oral therapy, a single injection during each 24-hour period of a dose of the suspension equal to the total daily oral dose of methylprednisolone tablets is usually sufficient. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a single intramuscular injection.

Dosage must be individualized according to the severity of the disease and response of the patient. For infants and children, the recommended dosage will have to be reduced, but dosage should be governed by the severity of the condition rather than by strict adherence to the ratio indicated by age or body weight.

Hormone therapy is an adjunct to, and not a replacement for, conventional therapy. Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. The severity, prognosis and expected duration of the disease and the reaction of the patient to medication are primary factors in determining dosage. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

In patients with the **adrenogenital syndrome**, a single intramuscular injection of 40 mg every two weeks may be adequate. For maintenance of patients with **rheumatoid arthritis**, the weekly intramuscular dose will vary from 40 to 120 mg. The usual dosage for patients with **dermatologic lesions** benefited by systemic corticoid therapy is 40 to 120 mg of methylprednisolone acetate administered intramuscularly at weekly intervals for one to four weeks. In acute severe dermatitis due to poison ivy, relief may result within 8 to 12 hours following intramuscular administration of a single dose of 80 to 120 mg. In chronic contact dermatitis repeated injections at 5 to 10 day intervals may be necessary. In seborrheic dermatitis, a weekly dose of 80 mg may be adequate to control the condition.

Following intramuscular administration of 80 to 120 mg to asthmatic patients, relief may result within 6 to 48 hours and persist for several days to two weeks. Similarly in patients with allergic rhinitis (hay fever) an intramuscular dose of 80 to 120 mg may be followed by relief of coryzal symptoms within six hours persisting for several days to three weeks.

If signs of stress are associated with the condition being treated, the dosage of the suspension should be increased. If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate is indicated.

Multiple Sclerosis:

In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

HOW SUPPLIED:

Methylprednisolone acetate injectable suspension is available in the following strengths and package sizes:

400 mg/10 mL (40 mg/mL)

NDC 0781-3136-70 multidose vials of 10 mL in boxes of 1
NDC 0781-3136-02 multidose vials of 10 mL in boxes of 10

400 mg/5 mL (80 mg/mL)

NDC 0781-3137-75 multidose vials of 5 mL in boxes of 1
NDC 0781-3137-95 multidose vials of 5 mL in boxes of 10
Store at 20° to 25°C (68° to 77°F) (see USP Controlled Room Temperature).

11-2007M

1003055

Manufactured in Canada by
Sandoz Canada Inc. for Sandoz Inc.
Princeton, NJ 08540

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-719

LABELING REVIEWS

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

ANDA Number: 40-719
Date of Submission: December 19, 2005 and March 8, 2006
Applicant's Name: Sandoz Canada Inc.
Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4)
10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER - [40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
 - A. Assure the text is at least 4 point type.
 - B. Please provide the complete NDC number. If the NDC number is not available at the time you submit your final printed labels, please delete "NDC 0781-XXXX-XX". You can add the NDC number to your labels when it is available.

2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
 - A. Refer to CONTAINER comment 1.B.
 - B. Please add the statement "Sterile"

3. PACKAGE INSERT (Refer to the attached mocked-up copy of your insert labeling for guidance.)
 - A. GENERAL COMMENT: We encourage you to update the section headings to be in accord with 21 CFR 201.56(d)(1)
 - B. TITLE: We encourage you to add the phrase "Rx only" to a location just under the TITLE of the package insert.
 - C. DESCRIPTION
 - i. Please add a statement that the product is sterile [refer to 21 CFR 201.57(a)(iv)].
 - ii. First paragraph, last sentence: delete the extra colon.
 - iii. Second paragraph, first sentence: "Methylprednisolone acetate injectable suspension is an..."
 - D. WARNINGS
 - i. **Multidose use of methylprednisolone acetate injectable suspension, USP from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. The preservative in methylprednisolone acetate injectable suspension, USP will prevent growth of most pathogenic organisms, but certain ones (e.g., Serratia marcescens) may remain viable. Particular care, such as use of disposable sterile syringes and needles is necessary.**
 - ii. **While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially in high doses, because of possible hazards of neurological complications and lack of antibody response.**
 - E. DOSAGE AND ADMINISTRATION: Please use the established name throughout this section.
 - F. HOW SUPPLIED: Refer to CONTAINER comment 1.B.

Please revise your labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

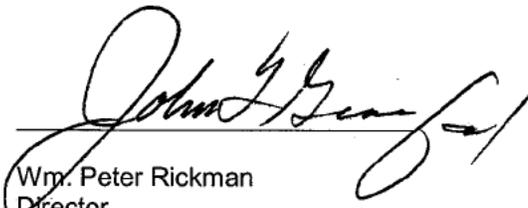
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

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://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

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



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

Attachment: Mocked-up copy of your insert labeling (A through F)

NOTE TO THE CHEMIST:

FOR THE RECORD:

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia NDA 11-757/S-064; approved November 14, 1990).

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 5/2/06)

2. Patent/ Exclusivities:
Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:
RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.
ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
- 80 mg/mL
- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
Dibasic sodium phosphate (b) (4)	1.42	1.37

Sodium Hydroxide NF (b) (4)	To adjust pH	To adjust pH
Hydrochloric Acid		(b) (4)

[Vol. B1.6, section 3.2.P.1, pg. 3]

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]
Vial: clear, (b) (4), type 1 glass vial
Stopper: rubber stopper and flip-off seal
7. Finished product appearance:
White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
[Vol. B1.7, section 3.2.P.5.1, pg. 4-12]
8. Bioequivalency: Pending as of 5/2/06
9. All manufacturing will be done by
Sandoz Canada Inc.
Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: May 2, 2006

Date of Submission: December 19, 2005 and March 8, 2006

Primary Reviewer: Ruby Wu

RW

Date: 5/2/06

Team Leader: John Grace

John Grace

Date:

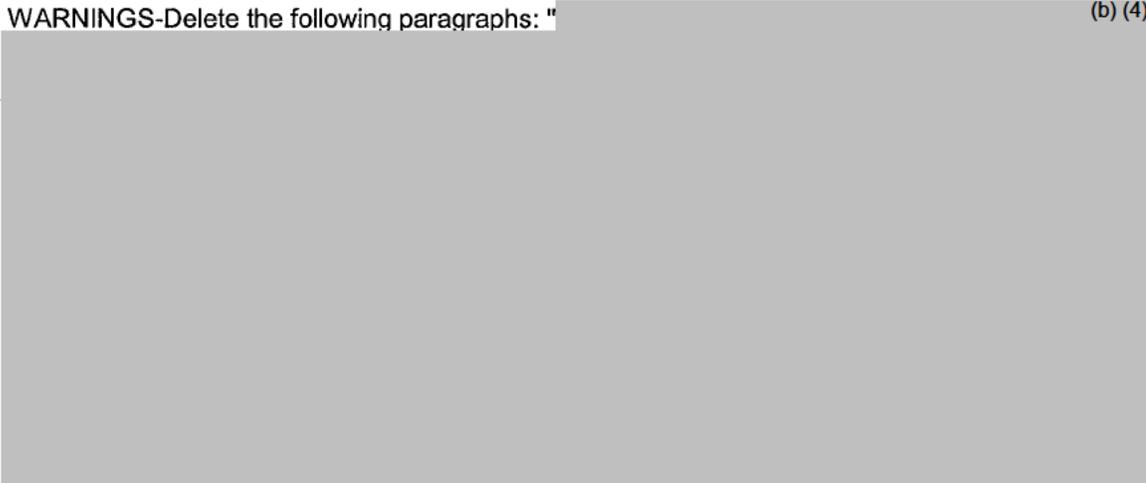
5-9-06

cc: ANDA: 40-719
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Review

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

ANDA Number: 40-719
Date of Submission: June 12, 2006 (amendment)
Applicant's Name: Sandoz Canada Inc.
Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4)
10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER - [40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the June 12, 2006 submission.
2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Satisfactory in final print as submitted in the June 12, 2006 submission.
3. PACKAGE INSERT
 - A. WARNINGS-Delete the following paragraphs: " (b) (4)

 - B. PRECAUTIONS, General Precautions- add the following as the seventh paragraph "Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia."

Please revise your insert labeling as described above and submit in final print electronically.

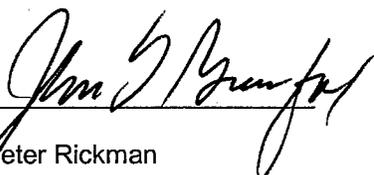
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

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://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

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



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

NOTE TO THE CHEMIST:

FOR THE RECORD:

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia NDA 11-757/S-064; approved November 14, 1990).

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 5/2/06)

2. Patent/ Exclusivities:

Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:

RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.

ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
- 80 mg/mL
- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
Dibasic sodium phosphate (b) (4)	1.42	1.37

Sodium Hydroxide NF (b) (4)	To adjust pH	To adjust pH
Hydrochloric Acid		(b) (4)

[Vol. B1.6, section 3.2.P.1, pg. 3]

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]
Vial: clear, (b) (4), type 1 glass vial
Stopper: rubber stopper and flip-off seal
7. Finished product appearance:
White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
[Vol. B1.7, section 3.2.P.5.1, pg. 4-12]
8. Bioequivalency: Pending as of 6/21/06
9. All manufacturing will be done by
Sandoz Canada Inc.
Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: June 21, 2006

Date of Submission: June 12, 2006

Primary Reviewer: Ruby Wu

Date: 6/21/06

Team Leader: John Grace

Date:

6.30.06

cc: ANDA: 40-719
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Review

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

ANDA Number: 40-719
Date of Submission: August 3, 2006 (amendment)
Applicant's Name: Sandoz Canada Inc.
Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4)
10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER - [40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Upon further review, we ask that you make the following revisions:
 - a. Revise labels to visually differentiate the established name from "Methyltestosterone" with the use of "Tall Man" letters, such as "MethylPREDNISolone". Refer to <http://www.fda.gov/cder/drug/mederrors/namediff.htm> for guidance.
 - b. Revise the expression of strength in the principal display panel so that the entire contents/mL is the primary expression of strength followed immediately by contents per mL. For example:
(b) (4)
(40 mg/mL)
2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL]; 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Refer to CONTAINER comments
3. PACKAGE INSERT
Refer to CONTAINER comments

Please revise your labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy. However, for ease of review, we recommend that you submit them electronically

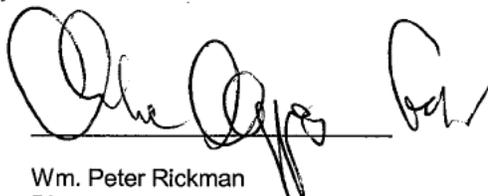
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

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



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

NOTE TO THE CHEMIST:

FOR THE RECORD:

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USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 8/14/06)

2. Patent/ Exclusivities:
Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:
RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.
ANDA: Same as RLD

4. Product Line:
RLD: 40 mg/mL
 - 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
 80 mg/mL
 - 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients:
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Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
Dibasic sodium phosphate (b) (4)	1.42	1.37
Sodium Hydroxide NF (b) (4)	To adjust pH	To adjust pH
Hydrochloric Acid		(b) (4)

[Vol. B1.6, section 3.2.P.1, pg. 3]

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]

Vial: clear, (b) (4) type 1 glass vial
Stopper: rubber stopper and flip-off seal

7. Finished product appearance:

White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
[Vol. B1.7, section 3.2.P.5.1, pg. 4-12]

8. Bioequivalency: 7/24/2006 - Bio dissolution prereview complete IC (repeat dissolution)/AS

9. All manufacturing will be done by
Sandoz Canada Inc.

Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: August 14, 2006

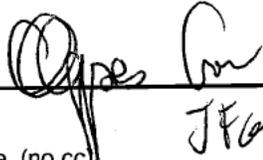
Date of Submission: August 3, 2006

Primary Reviewer: Ruby Wu



Date: 8/28/06

Team Leader: John Grace



Date:

8/29/06

cc:

ANDA: 40-719
DUP/DIVISION FILE
HFD-613/Rwu/JGrace (no cc)
V:\FIRMSNZ\SANDOZ\LTRS&REV\40719.na3.L.doc
Review

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

ANDA Number: 40-719

Date of Submission: October 4, 2006 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL ((b) (4)
10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL ((b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the October 4, 2006 submission.
2. CARTON- [40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
40 mg/mL ((b) (4) The NDC number on the top lid is incorrect. Please revise.
3. PACKAGE INSERT
HOW SUPPLIED: "...multi-dose vials of XX mL in..." [add a space]

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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.

NOTE TO THE CHEMIST:**FOR THE RECORD:**

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia NDA 11-757/S-064; approved November 14, 1990).

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 11/1/06)

2. Patent/ Exclusivities:

Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:

RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.

ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
- 80 mg/mL
- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
Dibasic sodium phosphate (b) (4)	1.42	1.37
Sodium Hydroxide NF (b) (4) Hydrochloric Acid	To adjust pH	To adjust pH
		(b) (4)

[Vol. B1.6, section 3.2.P.1, pg. 3]

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]
Vial: clear, (b) (4) type 1 glass vial
Stopper: rubber stopper and flip-off seal
7. Finished product appearance:
White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
[Vol. B1.7, section 3.2.P.5.1, pg. 4-12]
8. Bioequivalency: 7/24/2006 - Bio dissolution prereview complete IC (repeat dissolution)/AS
9. All manufacturing will be done by
Sandoz Canada Inc.
Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: November 1, 2006

Date of Submission: October 4, 2006

Primary Reviewer: Ruby Wu

Date:

Team Leader: John Grace

Date:

ANDA: 40-719
V:\FIRMSNZ\SANDOZ\LTRS&REV\40719.na4.L.doc
Review

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

/s/

Ruby Wu
11/1/2006 11:06:50 AM
MEDICAL OFFICER

John Grace
11/1/2006 02:20:51 PM
MEDICAL OFFICER

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

ANDA Number: 40-719

Date of Submission: November 30, 2006 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL ((b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL ((b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the October 4, 2006 submission.

2. CARTON- [40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
40 mg/mL ((b) (4) Satisfactory in final print as submitted in the November 30, 2006 amendment.

40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL): Satisfactory in final print as submitted in the October 4, 2006 submission.

3. PACKAGE INSERT
Satisfactory in draft. You are reminded that final printed labels submitted in electronic format must be actual size, color and clarity.

Please submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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.

NOTE TO THE CHEMIST:

FOR THE RECORD:

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia NDA 11-757/S-064; approved November 14, 1990).

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 11/1/06)

2. Patent/ Exclusivities:

Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:

RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.

ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
- 80 mg/mL
- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
Dibasic sodium phosphate (b) (4)	1.42	1.37
Sodium Hydroxide NF (b) (4) Hydrochloric Acid	To adjust pH	To adjust pH
		(b) (4)

[Vol. B1.6, section 3.2.P.1, pg. 3]

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]
Vial: clear, (b) (4) type 1 glass vial
Stopper: rubber stopper and flip-off seal
7. Finished product appearance:
White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
[Vol. B1.7, section 3.2.P.5.1, pg. 4-12]
8. Bioequivalency: 11/17/2006 - Bio dissolution prereview complete IC (repeat dissolution)/AS
9. All manufacturing will be done by
Sandoz Canada Inc.
Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: December 7, 2006

Date of Submission: November 30, 2006

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-719
V:\FIRMSNZ\SANDOZ\LTRS&REV\40719.na5.L.doc
Review

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

/s/

Ruby Wu
12/7/2006 02:31:19 PM
MEDICAL OFFICER

John Grace
12/7/2006 06:07:43 PM
MEDICAL OFFICER

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

ANDA Number: 40-719

Date of Submission: February 23, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the February 23, 2007 submission.
2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Satisfactory in final print as submitted in the February 23, 2007 submission.
3. PACKAGE INSERT
DESCRIPTION: Please update the pH range of the drug product to be in accord with the USP as well as your finished product specification.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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.

NOTE TO THE CHEMIST:

FOR THE RECORD:

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia NDA 11-757/S-064; approved November 14, 1990).

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 3/5/07)

2. Patent/ Exclusivities:

Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:

RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.

ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
- 80 mg/mL
- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
Dibasic sodium phosphate (b) (4)	1.42	1.37
Sodium Hydroxide NF (b) (4) Hydrochloric Acid	To adjust pH	To adjust pH
		(b) (4)

[Vol. B1.6, section 3.2.P.1, pg. 3]

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]
Vial: clear, (b) (4) type 1 glass vial
Stopper: rubber stopper and flip-off seal
7. Finished product appearance:
White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
[Vol. B1.7, section 3.2.P.5.1, pg. 4-12]
8. Bioequivalency: 11/17/2006 - Bio dissolution prereview complete IC (repeat dissolution)/AS
9. All manufacturing will be done by
Sandoz Canada Inc.
Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: March 5, 2007

Date of Submission: February 23, 2007

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-719
V:\FIRMSNZ\SANDOZ\LTRS&REV\40719.na6.L.doc
Review

Following this page, 11 pages withheld in full - (b)(4) draft labeling

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

/s/

Ruby Wu
3/5/2007 03:29:29 PM
MEDICAL OFFICER

John Grace
3/6/2007 11:50:00 AM
MEDICAL OFFICER

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

ANDA Number: 40-719

Date of Submission: April 9, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4)
10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Please update your “manufactured by” statement to be consistent with the insert labeling.
2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Please update your “manufactured by” statement to be consistent with the insert labeling.
3. PACKAGE INSERT
Satisfactory in final print as submitted in the April 9, 2007 e-amendment.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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.

NOTE TO THE CHEMIST:

-----Original Message-----

From: Wu, Ruby (Chi-Ann)
Sent: Friday, April 13, 2007 5:05 PM
To: Bykadi, Gururaj
Cc: Woodland Outlaw, Kathy P; Shen, Aijin
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Sandoz has revised their labeling for 40-719 and 40-794 to read "the pH of the finished product remains within the USP specified range; i.e., 3.0 to 7.0."

-----Original Message-----

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:40 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
There we go...
Let us have 3.0 to 7.0 as the pH limit both in ANDA manufacturing documentation and the label.
Paul: Thank you.

-----Original Message-----

From: Schwartz, Paul
Sent: Thursday, April 05, 2007 9:36 AM
To: Wu, Ruby (Chi-Ann); Bykadi, Gururaj
Subject: Re: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
USP limits are always acceptable limits (except for "any other" impurity) regardless of RLD limits. We can ask for additional tests but not tighter limits on existing tests.

----- Original Message -----

From: Wu, Ruby (Chi-Ann)
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Sent: Thu Apr 05 09:19:46 2007
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,
It's not that I "want to tighten the ANDA product pH". What is the general rule in chemistry? For a USP product, if the RLD has tighter specs then what is stated in the USP, do you allow the generic to follow the USP range or do you require that the product still meet the RLD spec? What were the FP pH spec for other generics on the market? If generics have the same formulation as the RLD, why can't the generic products meet the RLD specs?
Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:14 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
We have to see why the pH was revised in first place (from 3.5 to 7.0 to 3.0-7.0) in the USP just a few years ago (1999?).
Then I can cleverly answer the your comment.
If you want to tighten the ANDA product pH spec (3.5 to 7.0), I believe there won't be a generic product with 24 months expiry.

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 9:07 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,
If it is clear that the RLD's statement about the USP range is wrong, then we shouldn't use it. I just see the sentence stating what the USP range is.
However, just because the ANDA has the statement "within the USP specified range i.e. 3.0 to 7.0" doesn't mean that the finished product specification should be the same. I assume the ANDA FP COA needs to be consistent with the RLD FP COA. The question is, does the ANDA meet the RLD pH Range? I believe Larry said the USP specs are the MINIMUM requirement for a product to meet USP...but in this case, the RLD is tighter...so I assume the ANDA also needs to be tighter.

Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:02 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
You mean the ANDA label should not read same as the RLD label ?
(The pH of the finished product remains within the USP specified range ; i.e., 3.5 to 7.0. ".)
If so I do not see any problem

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 8:57 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,
I'm not sure where the disagreement is. I believe we can have the ANDA state USP specified range 3.0-7.0...we don't need to wait until RLD changes.
Since our product is USP, then ANDA can state 3.0-7.0.
Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 8:55 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
I do not agree with you.
"...USP specified range 3.5 to 7.0" on the label is an inaccurate statement.
The actual USP range is 3.0 - 7.0.
Either the word "USP" should be deleted or the number "3.5" should be corrected.
Raj

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 8:13 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,

Because the labeling states "USP specified range", I do not think it is inaccurate for ANDAs to state the range 3.0-7.0 in their insert labeling to reflect the USP recommended range. If the finished product spec for the ANDA will be 3.5 to 7.0 to be consistent with the RLD, I don't think having the statement "The pH of the finished product remains within the USP specified range ; i.e., 3.0 to 7.0." is inaccurate. You are just stating what the USP range is and that the product (3.5 to 7.0) is within the USP range (3.0 to 7.0).

However, the bigger problem appears to be the ANDA cannot meet the RLD specification of 3.5 to 7.0. If the ANDA needs to meet the RLD spec, even after the RLD corrects their labeling, the ANDA still does not pass the spec.
These are just my own thoughts...

Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 5:56 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul; Wu, Ruby (Chi-Ann); Ouder Kirk, Larry A; Schwartz, Paul; Raghavachari, Ramesh; Stradley, Sara; Jani, Parinda; Rana, Pratibha; Patel, Rashmikant M; Bhavnagri, Vispi P

Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH

Hi Ruby, the answer is "NO".

There is a problem with RLD labeling which reads:

" The pH of the finished product remains within the USP specified range ; i.e., 3.5 to 7.0. "

As you know this is not an accurate statement (USP pH spec is 3.0-7.0). Some one should take care of it. I do not know who that person is.
PLEASE HELP!

Raj

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, April 04, 2007 11:51 AM
To: Bykadi, Gururaj
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP
Hi Raj,
Has a decision been made on the finished product spec for pH for ANDAs?
Ruby

From: Bykadi, Gururaj
Sent: Friday, March 16, 2007 1:09 PM
To: Schwartz, Paul; Wu, Ruby (Chi-Ann)
Cc: Ouder Kirk, Larry A
Subject: FW: Sterile Methylprednisolone Acetate Suspension, USP
Dear All,
I looked at a couple of ANDA reviews (40-557/Sicor and 40-719/Sandoz). A pH spec of 3.0 to 7.0. for shelf life is provided in these reviews. I believe these ANDAs have the NDA pH spec (3.5 - 7.0) on their product label, however, this needs verification.
If a product is called as a USP monograph item, then, it should meet all the USP limits; otherwise it may be called as "misbranded" or "adulterated" drug. Moreover, this being a monograph item, the ANDA holders are already complying by updating their specs to USP, especially if they have observed pH issues with their product during stability.
This leads to the question, "Is the generic drug is same as the RLD?".
Perhaps, "NOT" ...in this case.
Because of the pH issue. A low pH such as 3.0 for the generic drug may be more tissue irritating than the RLD drug whose pH is above 3.5 during shelf life (or if some one in the medical dept has determined otherwise).
I really do not have the answer. But note that generic companies are quickly updating the spec to USP since it became official in the USP on 11/15/97.

Any Comments ?

Raj

FOR THE RECORD:

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia NDA 11-757/S-064; approved November 14, 1990).

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD

insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 4/13/07)

2. Patent/ Exclusivities:

Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:

RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.
ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
- 80 mg/mL
- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
Dibasic sodium phosphate (b) (4)	1.42	1.37
Sodium Hydroxide NF (b) (4) Hydrochloric Acid	To adjust pH	To adjust pH
		(b) (4)

[Vol. B1.6, section 3.2.P.1, pg. 3]

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]

Vial: clear, (b) (4) type 1 glass vial
Stopper: rubber stopper and flip-off seal

7. Finished product appearance:

White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
[Vol. B1.7, section 3.2.P.5.1, pg. 4-12]

8. Bioequivalency: 4/5/2007 - Bio IC (dissolution acknowledgement)/AS
4/5/2007 - Bioequivalence deficiency letter entered into DFS/AS

9. All manufacturing will be done by
Sandoz Canada Inc.
Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: April 13, 2007

Date of Submission: April 9, 2007 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-719
V:\FIRMSNZ\SANDOZ\LTRS&REV\40719.na7.L.doc
Review

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

/s/

Ruby Wu
4/13/2007 05:31:06 PM
MEDICAL OFFICER

John Grace
4/15/2007 11:13:03 AM
MEDICAL OFFICER

APPROVAL SUMMARY

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

ANDA Number: 40-719

Date of Submission: May 22, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL ((b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

APPROVAL SUMMARY:

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER –[40 mg/mL ((b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the May 22, 2007 e-amendment.
2. CARTON- [40 mg/mL ((b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Satisfactory in final print as submitted in the May 22, 2007 e-amendment.
3. PACKAGE INSERT
Satisfactory in final print as submitted in the April 9, 2007 e-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: Depo-Medro

NDA Number: 11-757

NDA Drug Name: Methylprednisolone Acetate Injectable Suspension USP

NDA Firm: Pharmacia

Date of Approval of NDA Insert and supplement: NDA 11-757/S-064 approved November 14, 1990

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 – NDA 11-757

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.	PII	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

NOTE TO THE CHEMIST:

-----Original Message-----

From: Wu, Ruby (Chi-Ann)
Sent: Friday, April 13, 2007 5:05 PM
To: Bykadi, Gururaj
Cc: Woodland Outlaw, Kathy P; Shen, Aijin
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Sandoz has revised their labeling for 40-719 and 40-794 to read "the pH of the finished product remains within the USP specified range; i.e., 3.0 to 7.0."

-----Original Message-----

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:40 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
There we go...
Let us have 3.0 to 7.0 as the pH limit both in ANDA manufacturing documentation and the label.
Paul: Thank you.

-----Original Message-----

From: Schwartz, Paul
Sent: Thursday, April 05, 2007 9:36 AM
To: Wu, Ruby (Chi-Ann); Bykadi, Gururaj
Subject: Re: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
USP limits are always acceptable limits (except for "any other" impurity) regardless of RLD limits. We can ask for additional tests but not tighter limits on existing tests.

----- Original Message -----

From: Wu, Ruby (Chi-Ann)
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Sent: Thu Apr 05 09:19:46 2007
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,
It's not that I "want to tighten the ANDA product pH". What is the general rule in chemistry? For a USP product, if the RLD has tighter specs then what is stated in the USP, do you allow the generic to follow the USP range or do you require that the product still meet the RLD spec? What were the FP pH spec for other generics on the market? If generics have the same formulation as the RLD, why can't the generic products meet the RLD specs?
Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:14 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
We have to see why the pH was revised in first place (from 3.5 to 7.0 to 3.0-7.0) in the USP just a few years ago (1999?).
Then I can cleverly answer the your comment.
If you want to tighten the ANDA product pH spec (3.5 to 7.0), I believe there won't be a generic product with 24 months expiry.

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 9:07 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,
If it is clear that the RLD's statement about the USP range is wrong, then we shouldn't use it. I just see the sentence stating what the USP range is.
However, just because the ANDA has the statement "within the USP specified range i.e. 3.0 to 7.0" doesn't mean that the finished product specification should be the same. I assume the ANDA FP COA needs to be consistent with the RLD FP COA. The question is, does the ANDA meet the RLD pH Range? I believe Larry said the USP specs are the MINIMUM requirement for a product to meet USP...but in this case, the RLD is tighter...so I assume the ANDA also needs to be tighter.

Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:02 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
You mean the ANDA label should not read same as the RLD label ?
(The pH of the finished product remains within the USP specified range ; i.e., 3.5 to 7.0. ".)
If so I do not see any problem

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 8:57 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,
I'm not sure where the disagreement is. I believe we can have the ANDA state USP specified range 3.0-7.0...we don't need to wait until RLD changes.
Since our product is USP, then ANDA can state 3.0-7.0.
Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 8:55 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
I do not agree with you.
"...USP specified range 3.5 to 7.0" on the label is an inaccurate statement.
The actual USP range is 3.0 - 7.0.
Either the word "USP" should be deleted or the number "3.5" should be corrected.
Raj

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 8:13 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,

Because the labeling states "USP specified range", I do not think it is inaccurate for ANDAs to state the range 3.0-7.0 in their insert labeling to reflect the USP recommended range. If the finished product spec for the ANDA will be 3.5 to 7.0 to be consistent with the RLD, I don't think having the statement "The pH of the finished product remains within the USP specified range ; i.e., 3.0 to 7.0." is inaccurate. You are just stating what the USP range is and that the product (3.5 to 7.0) is within the USP range (3.0 to 7.0).

However, the bigger problem appears to be the ANDA cannot meet the RLD specification of 3.5 to 7.0. If the ANDA needs to meet the RLD spec, even after the RLD corrects their labeling, the ANDA still does not pass the spec.
These are just my own thoughts...

Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 5:56 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul; Wu, Ruby (Chi-Ann); Ouder Kirk, Larry A; Schwartz, Paul; Raghavachari, Ramesh; Stradley, Sara; Jani, Parinda; Rana, Pratibha; Patel, Rashmikant M; Bhavnagri, Vispi P
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Hi Ruby, the answer is "NO".
There is a problem with RLD labeling which reads:
" The pH of the finished product remains within the USP specified range ; i.e., 3.5 to 7.0. ".
As you know this is not an accurate statement (USP pH spec is 3.0-7.0). Some one should take care of it. I do not know who that person is.
PLEASE HELP!
Raj

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, April 04, 2007 11:51 AM
To: Bykadi, Gururaj
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP
Hi Raj,
Has a decision been made on the finished product spec for pH for ANDAs?
Ruby

From: Bykadi, Gururaj
Sent: Friday, March 16, 2007 1:09 PM
To: Schwartz, Paul; Wu, Ruby (Chi-Ann)
Cc: Ouder Kirk, Larry A
Subject: FW: Sterile Methylprednisolone Acetate Suspension, USP
Dear All,
I looked at a couple of ANDA reviews (40-557/Sicor and 40-719/Sandoz). A pH spec of 3.0 to 7.0 for shelf life is provided in these reviews. I believe these ANDAs have the NDA pH spec (3.5 - 7.0) on their product label, however, this needs verification.
If a product is called as a USP monograph item, then, it should meet all the USP limits; otherwise it may be called as "misbranded" or "adulterated" drug. Moreover, this being a monograph item, the ANDA holders are already complying by updating their specs to USP, especially if they have observed pH issues with their product during stability.
This leads to the question, "Is the generic drug is same as the RLD?".
Perhaps, "NOT" ...in this case.
Because of the pH issue. A low pH such as 3.0 for the generic drug may be more tissue irritating than the RLD drug whose pH is above 3.5 during shelf life (or if some one in the medical dept has determined otherwise).
I really do not have the answer. But note that generic companies are quickly updating the spec to USP since it became official in the USP on 11/15/97.

Any Comments ?
Raj

FOR THE RECORD:

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia NDA 11-757/S-064; approved November 14, 1990).

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
pH: between 3.0 and 7.0. (checked 5/31/07)

2. Patent/ Exclusivities:

Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:

RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.

ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
 - 10 mL MD vials (individual and 25 x 10 mL MD vials)
- 80 mg/mL
- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

5. Inactive Ingredients: [Vol. B1.6, section 3.2.P.1, pg. 3]

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
D basic sodium phosphate (b) (4)	1.42	1.37
Sodium Hydroxide NF (b) (4)	To adjust pH	To adjust pH
Hydrochloric Acid		
		(b) (4)

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]

Vial: clear, (b) (4) type 1 glass vial

Stopper: rubber stopper and flip-off seal

7. Finished product appearance: [Vol. B1.7, section 3.2.P.5.1, pg. 4-12]

White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.

8. Bioequivalency: 4/5/2007 - Bio IC (dissolution acknowledgement)/AS

4/5/2007 - Bioequivalence deficiency letter entered into DFS/AS

9. All manufacturing will be done by

Sandoz Canada Inc. Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: May 31, 2007

Date of Submission: May 22, 2007 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-719

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Review

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

/s/

Ruby Wu
5/31/2007 12:13:15 PM
LABELING REVIEWER

John Grace
5/31/2007 10:14:08 PM
LABELING REVIEWER

APPROVAL SUMMARY

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

ANDA Number: 40-719

Date of Submission: November 21, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

APPROVAL SUMMARY:

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER –[40 mg/mL (10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the May 22, 2007 e-amendment.
2. CARTON- [40 mg/mL (1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Satisfactory in final print as submitted in the May 22, 2007 e-amendment.
3. PACKAGE INSERT
Satisfactory in final print as submitted in the November 21, 2007 e-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: Depo-Medro

NDA Number: 11-757

NDA Drug Name: Methylprednisolone Acetate Injectable Suspension USP

NDA Firm: Pharmacia

Date of Approval of NDA Insert and supplement: NDA 11-757/S-064 approved November 14, 1990

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 – NDA 11-757

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.	PII	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

NOTE TO THE CHEMIST:

From: Wu, Ruby (Chi-Ann)
Sent: Monday, December 10, 2007 10:37 AM
To: Woodland Outlaw, Kathy P; Bykadi, Gururaj
Subject: 40-719

Hi Kathy,

In the November 21, 2007 labeling amendment, the firm delete the (b) (4) packaging configuration. I assume this is in response to your chemistry deficiency

5. You have indicated that the results of the (b) (4). This is not acceptable. Please submit data to support the (b) (4)
(b) (4)

-----Original Message-----

From: Wu, Ruby (Chi-Ann)
Sent: Friday, April 13, 2007 5:05 PM
To: Bykadi, Gururaj
Cc: Woodland Outlaw, Kathy P; Shen, Aijin
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Sandoz has revised their labeling for 40-719 and 40-794 to read "the pH of the finished product remains within the USP specified range; i.e., 3.0 to 7.0."

-----Original Message-----

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:40 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
There we go...
Let us have 3.0 to 7.0 as the pH limit both in ANDA manufacturing documentation and the label.
Paul: Thank you.

-----Original Message-----

From: Schwartz, Paul
Sent: Thursday, April 05, 2007 9:36 AM
To: Wu, Ruby (Chi-Ann); Bykadi, Gururaj
Subject: Re: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
USP limits are always acceptable limits (except for "any other" impurity) regardless of RLD limits. We can ask for additional tests but not tighter limits on existing tests.

----- Original Message -----

From: Wu, Ruby (Chi-Ann)
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Sent: Thu Apr 05 09:19:46 2007
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,

It's not that I "want to tighten the ANDA product pH". What is the general rule in chemistry? For a USP product, if the RLD has tighter specs then what is stated in the USP, do you allow the generic to follow the USP range or do you require that the product still meet the RLD spec? What were the FP pH spec for other generics on the market? If generics have the same formulation as the RLD, why can't the generic products meet the RLD specs?

Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:14 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
We have to see why the pH was revised in first place (from 3.5 to 7.0 to 3.0-to 7.0) in the USP just a few years ago (1999?).
Then I can cleverly answer the your comment.
If you want to tighten the ANDA product pH spec (3.5 to 7.0), I believe there won't be a generic product with 24 months expiry.

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 9:07 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,

If it is clear that the RLD's statement about the USP range is wrong, then we shouldn't use it. I just see the sentence stating what the USP range is.

However, just because the ANDA has the statement "within the USP specified range i.e. 3.0 to 7.0" doesn't mean that the finished product specification should be the same. I assume the ANDA FP COA needs to be consistent with the RLD FP COA. The question is, does the ANDA meet the RLD pH Range? I believe Larry said the USP specs are the MINIMUM requirement for a product to meet USP...but in this case, the RLD is tighter...so I assume the ANDA also needs to be tighter.

Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 9:02 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
You mean the ANDA label should not read same as the RLD label ?
(The pH of the finished product remains within the USP specified range ; i.e., 3.5 to 7.0. ".)
If so I do not see any problem

From: Wu, Ruby (Chi-Ann)

Sent: Thursday, April 05, 2007 8:57 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,

I'm not sure where the disagreement is. I believe we can have the ANDA state USP specified range 3.0-7.0...we don't need to wait until RLD changes. Since our product is USP, then ANDA can state 3.0-7.0.
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From: Bykadi, Gururaj
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Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
I do not agree with you.
"...USP specified range 3.5 to 7.0" on the label is an inaccurate statement.
The actual USP range is 3.0 - 7.0.
Either the word "USP" should be deleted or the number "3.5" should be corrected.
Raj

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, April 05, 2007 8:13 AM
To: Bykadi, Gururaj
Cc: Schwartz, Paul
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Raj,

Because the labeling states "USP specified range", I do not think it is inaccurate for ANDAs to state the range 3.0-7.0 in their insert labeling to reflect the USP recommended range. If the finished product spec for the ANDA will be 3.5 to 7.0 to be consistent with the RLD, I don't think having the statement "The pH of the finished product remains within the USP specified range ; i.e., 3.0 to 7.0." is inaccurate. You are just stating what the USP range is and that the product (3.5 to 7.0) is within the USP range (3.0 to 7.0).

However, the bigger problem appears to be the ANDA cannot meet the RLD specification of 3.5 to 7.0. If the ANDA needs to meet the RLD spec, even after the RLD corrects their labeling, the ANDA still does not pass the spec.

These are just my own thoughts...
Ruby

From: Bykadi, Gururaj
Sent: Thursday, April 05, 2007 5:56 AM
To: Wu, Ruby (Chi-Ann)
Cc: Schwartz, Paul; Wu, Ruby (Chi-Ann); Ouderkirk, Larry A; Schwartz, Paul; Raghavachari, Ramesh; Stradley, Sara; Jani, Parinda; Rana, Pratibha; Patel, Rashmikant M; Bhavnagri, Vispi P
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP - USP pH vs. RLD pH
Hi Ruby, the answer is "NO".
There is a problem with RLD labeling which reads:
" The pH of the finished product remains within the USP specified range ; i.e., 3.5 to 7.0. ".
As you know this is not an accurate statement (USP pH spec is 3.0-7.0). Some one should take care of it. I do not know who that person is.
PLEASE HELP!
Raj

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, April 04, 2007 11:51 AM
To: Bykadi, Gururaj
Subject: RE: Sterile Methylprednisolone Acetate Suspension, USP
Hi Raj,
Has a decision been made on the finished product spec for pH for ANDAs?
Ruby

From: Bykadi, Gururaj
Sent: Friday, March 16, 2007 1:09 PM
To: Schwartz, Paul; Wu, Ruby (Chi-Ann)
Cc: Ouderkirk, Larry A
Subject: FW: Sterile Methylprednisolone Acetate Suspension, USP
Dear All,
I looked at a couple of ANDA reviews (40-557/Sicor and 40-719/Sandoz). A pH spec of 3.0 to 7.0. for shelf life is provided in these reviews. I believe these ANDAs have the NDA pH spec (3.5 - 7.0) on their product label, however, this needs verification.
If a product is called as a USP monograph item, then, it should meet all the USP limits; otherwise it may be called as "misbranded" or "adulterated" drug. Moreover, this being a monograph item, the ANDA holders are already complying by updating their specs to USP, especially if they have observed pH issues with their product during stability.
This leads to the question, "Is the generic drug is same as the RLD?".
Perhaps, "NOT" ...in this case.
Because of the pH issue. A low pH such as 3.0 for the generic drug may be more tissue irritating than the RLD drug whose pH is above 3.5 during shelf life (or if some one in the medical dept has determined otherwise).
I really do not have the answer. But note that generic companies are quickly updating the spec to USP since it became official in the USP on 11/15/97.

Any Comments ?
Raj

FOR THE RECORD:

1. Model Labeling: The review was based on the most recently approved RLD labeling, Depo-Medrol (by Pharmacia

NDA 11-757/S-064; approved November 14, 1990). There are SLR supplements pending!

There are 2 Depo-Medrol formulations in the marketplace. The old formulation contains myristyl-gamma-picolinium chloride. The new formulation contains benzyl alcohol (this formulation was approved on November 14, 1990 NDA 11-757/S-064). The ANDA applicant has chosen to model their generic product after Depo-Medrol's old formulation. Changes required in the November 14, 1990 RLD insert labeling to reflect the old formulation was described in detail in a "Depo-Medrol Labeling" memo signed-off on October 16, 1991.

USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass. pH: between 3.0 and 7.0. (checked 12/10/07)

2. Patent/ Exclusivities:

Patent Data – NDA 11-757

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.	PI	None

Exclusivity Data– NDA 11-757

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

[B1.5, section 1.2.2, pg. 2]

3. Storage/Dispensing Conditions:

RLD: Store at CRT 20°-25°C (68°-77°F). See USP. Shake well immediately before using.

ANDA: Same as RLD

4. Product Line:

RLD: 40 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)
- 10 mL MD vials (individual and 25 x 10 mL MD vials)

80 mg/mL

- 5 mL MD vials (individual and 25 x 5 mL MD vials)

ANDA: 40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)

Note: firm (b) (4) [11/21/07 amendment]

5. Inactive Ingredients: [Vol. B1.6, section 3.2.P.1, pg. 3]

The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components.

Ingredients	40 mg/mL each mL contains: (mg)	80 mg/mL each mL contains: (mg)
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.1	28.2
Benzyl Alcohol	9.16	8.88
Polysorbate 80	1.94	1.88
Sodium Chloride USP	To adjust tonicity	To adjust tonicity
Monobasic Sodium Phosphate, (b) (4)	6.80	6.59
D basic sodium phosphate (b) (4)	1.42	1.37
Sodium Hydroxide NF (b) (4)	To adjust pH	To adjust pH
Hydrochloric Acid		(b) (4)

6. Container/Closure [Vol. B1.6, section 3.2.P.1, pg. 2]

Vial: clear, (b) (4) type 1 glass vial

Stopper: rubber stopper and flip-off seal

7. Finished product appearance: [Vol. B1.7, section 3.2.P.5.1, pg. 4-12]

White suspension contained in a XX mL clear vial, with a 13 mm rubber stopper and a flip-off closure.

8. All manufacturing will be done by

Sandoz Canada Inc. Boucherville, Canada [B1.5, section 1.2.12.1, pg. 2]

Date of Review: December 10, 2007

Date of Submission: November 21, 2007 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-719

V:\FIRMSNZ\SANDOZ\LTRS&REV\40719.ap.2L.doc

Review

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

/s/

Ruby Wu
12/10/2007 11:48:26 AM
LABELING REVIEWER

John Grace
12/10/2007 12:25:23 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-719

CHEMISTRY REVIEWS

ANDA 40-719

Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL, 5 mL and 10 mL vials
80 mg/mL, 5 mL vials

Sandoz Canada Inc.

Kathy P. Woodland
Division of Chemistry I



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II. Summary of Chemistry Assessments.....	7
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B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	8
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Chemistry Review Data Sheet

1. ANDA 40-719
2. REVIEW #: 1
3. REVIEW DATE: August 31, 2006
4. REVIEWER: Kathy P. Woodland
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original submission

December 19, 2005

Refuse to receive

March 2, 2006

Amendment

March 8, 2006

Acceptable for Filing

March 9, 2006

Amendment (Labeling)

June 12, 2006 and Aug 3, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc. (Formerly Sabex 2002)
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Beth Brannon Sandoz Inc. 2555 W. Midway Blvd. Broomfield, CO 80038-0446
Telephone:	303-438-4237
Fax:	303-438-4600



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Methylprednisolone Acetate Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION:

- a. The basis for Sandoz's proposed ANDA Methylprednisolone Injectable Suspension USP is the approved, RLD, Depo-Medrol[®], manufactured by Pharmacia and Upjohn Company, NDA 11-757.
- b. According to the information published in the Orange Book, the RLD is not entitled to a period of marketing exclusivity under section 505(j)(4)(D).

10. PHARMACOL. CATEGORY: Steroidal Anti-inflammatory Agent

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40 mg/mL and 80 mg/mL

13. ROUTE OF ADMINISTRATION: IM, Intrasyvial, intraleasional

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

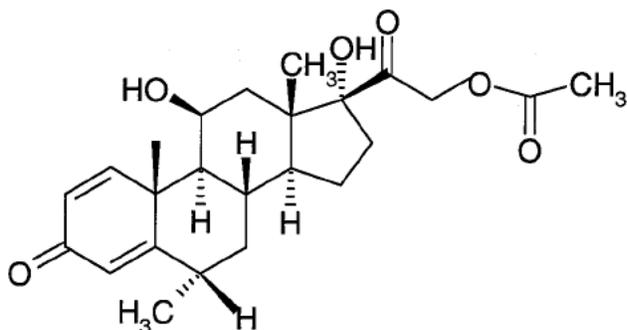
SPOTS product – Form Completed

Not a SPOTS product

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

Molecular Formula: $C_{24}H_{32}O_6$
Formula Weight: 416.51
Chemical Name: Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6 α ,11 β)-11b,17,21-Trihydroxy-6a-methylpregna-1,4-diene-3,20-dione 21-acetate.

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	B. Lim	1-18-2005
	III		4				
	III		4				
	III		4				
	III		4				

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER



CHEMISTRY REVIEW



Chemistry Review Data Sheet

REVIEWS			
Microbiology	Pending		
EES	Pending		
Methods Validation	Not Required		
Labeling	Deficient	8/30/2006	R.Wu
Bioequivalence*	Pending		As per Master Q
EA	N/A		
Radiopharmaceutical	N/A		

*Bio dissolution deficient 7/24/2006

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 40-719

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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)

Drug Substance: The drug substance Methylprednisolone Acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, alcohol, chloroform, and methanol. It is slightly soluble in ether and practically insoluble in water.

Drug Product: Methylprednisolone acetate injectable suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available in two strengths: 40 mg/mL and 80 mg/mL. The 40 mg/mL contains the following: 40 mg Methylprednisolone acetate, 29.1 mg Polyethylene glycol 3350, 1.94 mg Polysorbate 80, 6.8 mg Monobasic sodium phosphate, 1.42 mg Dibasic sodium phosphate USP, and 9.16 mg Benzyl alcohol, added as a preservative. The 80 mg/mL contains the following: 80 mg Methylprednisolone acetate, 28.2 mg Polyethylene glycol 3350, 1.88 mg Polysorbate 80, 6.59 mg Monobasic sodium phosphate, 1.37 mg Dibasic sodium phosphate USP, and 8.88 mg Benzyl alcohol, added as a preservative.

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

The MDD is 120 mg. The drug product is administered intramuscular, intrasynovial, soft tissue or intralesional injection. Methylprednisolone Acetate Injectable Suspension is available as follows:

40 mg/mL: (b) (4) 1x10 mL, 10x10 mL multidose vials

Executive Summary Section

80 mg/mL: 1x5 mL, 10x5 mL multidose vials
The product is stored at 20° to 25°C(68° to 77°F)

IT and QT for DS: 0.10 and 0.15% respectively
IT and QT for DP: 0.2% for both

C. Basis for Approvability or Not-Approval Recommendation

Minor Chemistry deficiencies

Following this page, 12 pages withheld in full - (b)(4)



(b) (4)



30. MICROBIOLOGY

Pending Review

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation is not required.

32. LABELING

Deficient, R.Wu, 8/30/2006

33. ESTABLISHMENT INSPECTION

Pending

34. BIOEQUIVALENCE: PENDING

Dissolution review: Deficient, 7/24/2006

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Sandoz is claiming a categorical exclusion.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-719 APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.  (b) (4)
Please explain.

2. Regarding the drug substance, we have the following comments:

- a.  (b) (4)
- b.
- c.
- d.
- e.

3. Please revise the  (b) (4)
 (b) (4)

4. Please indicate the  (b) (4)

5. Regarding the drug product release, we have the following comments:

- a. [REDACTED] (b) (4)
- b. [REDACTED]

6. Please provide the [REDACTED] (b) (4)
[REDACTED]
in Methylprednisolone Acetate Injectable Suspension.

7. Please provide the [REDACTED] (b) (4)
[REDACTED] in Methylprednisolone Acetate Injectable
Suspension.

8. Regarding the drug product stability, we have the following comments:

- a. [REDACTED] (b) (4)
- b. [REDACTED]
- c. [REDACTED]

9. [REDACTED] (b) (4)
[REDACTED] Please explain.

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

1. Bioequivalency deficiencies were communicated to you on July 24, 2006 and have not been responded. Please provide a response to the bioequivalency deficiencies.
2. Labeling deficiencies were communicated to you on August 30, 2006 and have not been responded. Please provide a response to the labeling deficiencies.
3. The microbiology information you have provided is under review. After the review is complete, any deficiencies found will be communicated to you under separate cover.

4. The USP methods for the drug substance and the drug product are the regulatory methods and they will prevail in the event of any dispute.
5. Please provide all available long-term stability data to update your studies.
6. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

Sincerely yours,

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

cc: ANDA 40-719
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/K.Woodland *K. Woodland 9/27/06*
HFD-620/R.Bykadi, Ph.D. *R. Bykadi 9-27-2006*
HFD-617/Benjamin Danso, Pharm.D. *B. Danso 9/27/06*

V:\Chemistry Division \Team 5\Final Version For DFS Folder\40719.rv1.doc
F/T by:

NOT APPROVABLE - MINOR

ANDA 40-719

Methylprednisolone Acetate Injectable Suspension, USP
40 mg/mL, 5 mL and 10 mL vials
80 mg/mL, 5 mL vials

Sandoz Canada Inc.

Kathy P. Woodland
Division of Chemistry I

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Chemistry Review Data Sheet

1. ANDA 40-719
2. REVIEW #: 2
3. REVIEW DATE: July 13, 2007
4. REVIEWER: Kathy P. Woodland
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Original submission	December 19, 2005
Refuse to receive	March 2, 2006
Amendment	March 8, 2006
Acceptable for Filing	March 9, 2006
Amendment (Labeling)	June 12, 2006 and Aug 3, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Amendment	January 30, 2007
-----------	------------------

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc. (Formerly Sabex 2002)
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Beth Brannon Sandoz Inc. 2555 W. Midway Blvd. Broomfield, CO 80038-0446
Telephone:	303-438-4237
Fax:	303-438-4600

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Methylprednisolone Acetate Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Sandoz's proposed ANDA Methylprednisolone Injectable Suspension USP is the approved, RLD, Depo-Medrol[®], manufactured by Pharmacia and Upjohn Company, NDA 11-757.

b. According to the information published in the Orange Book, the RLD is not entitled to a period of marketing exclusivity under section 505(j)(4)(D).

10. PHARMACOL. CATEGORY: Steroidal Anti-inflammatory Agent

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40 mg/mL and 80 mg/mL

13. ROUTE OF ADMINISTRATION: IM, Intrasynovial, intraleasional

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

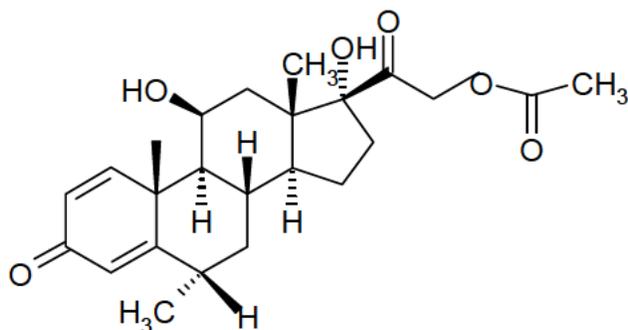
SPOTS product – Form Completed

Not a SPOTS product

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

Molecular Formula:	C ₂₄ H ₃₂ O ₆
Formula Weight:	416.51
Chemical Name:	Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6 α ,11 β)-11b,17,21-Trihydroxy-6a-methylpregna-1,4-diene-3,20-dione 21-acetate.

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Inadequate	A.Shen	5/7/2007
	III		4				
	III		4				
	III		4				
	III		4				

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

REVIEWS			
Microbiology	Pending		
EES	Acceptable	11/13/2006	Per Master Q
Methods Validation	Not Required		
Labeling	Acceptable	6/4/2007	Per Master Q
Bioequivalence	Deficient*	6/26/2007	Per Master Q
EA	N/A		
Radiopharmaceutical	N/A		

* Bio dissolution IC per MC

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:

Minor Amendment

The Chemistry Review for ANDA 40-719

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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)

Drug Substance: The drug substance Methylprednisolone Acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, alcohol, chloroform, and methanol. It is slightly soluble in ether and practically insoluble in water.

Drug Product: Methylprednisolone acetate injectable suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available in two strengths: 40 mg/mL and 80 mg/mL. The 40 mg/mL contains the following: 40 mg Methylprednisolone acetate, 29.1 mg Polyethylene glycol 3350, 1.94 mg Polysorbate 80, 6.8 mg Monobasic sodium phosphate, 1.42 mg Dibasic sodium phosphate USP, and 9.16 mg Benzyl alcohol, added as a preservative. The 80 mg/mL contains the following: 80 mg Methylprednisolone acetate, 28.2 mg Polyethylene glycol 3350, 1.88 mg Polysorbate 80, 6.59 mg Monobasic sodium phosphate, 1.37 mg Dibasic sodium phosphate USP, and 8.88 mg Benzyl alcohol, added as a preservative.

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

The MDD is 160 mg. The drug product is administered intramuscular, intrasynovial, soft tissue or intralesional injection. Methylprednisolone Acetate Injectable Suspension is available as follows:

40 mg/mL: (b) (4) 1x10 mL, 10x10 mL multidose vials

Executive Summary Section

80 mg/mL: 1x5 mL, 10x5 mL multidose vials
The product is stored at 20° to 25°C(68° to 77°F)

IT and QT for DS: 0.10 and 0.15% respectively
IT and QT for DP: 0.20% for both

C. Basis for Approvability or Not-Approval Recommendation

Minor Chemistry deficiencies
Bioequivalence deficient

Following this page, 11 pages withheld in full - (b)(4)

Chemistry Assessment Section

Deficiency #6c You have provided a justification for [REDACTED] (b) (4)

[REDACTED]

Conclusion Not Acceptable.

New Deficiency You have indicated that the results of the [REDACTED] (b) (4)
[REDACTED] (b) (4). This is not acceptable. Please submit data to support the [REDACTED] (b) (4)
[REDACTED] (b) (4)

Notes: The intended [REDACTED] (b) (4)

[REDACTED]

30. MICROBIOLOGY

Pending Review

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation is not required.

32. LABELING

Acceptable, R.Wu, 6/4/2007

33. ESTABLISHMENT INSPECTION

Acceptable 11/13/07

34. BIOEQUIVALENCE:

Deficient, 6/26/2007

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Sandoz is claiming a categorical exclusion.

In addition to responding to the deficiencies presented, the applicant noted and

Chemistry Assessment Section

acknowledged the following comments in their response:

1. Bioequivalency deficiencies were communicated to you on July 24, 2006 and have not been responded. Please provide a response to the bioequivalency deficiencies.
 - A response to the deficiencies has been addressed separately on September 15, 2006.
2. Labeling deficiencies were communicated to you on August 30, 2006 and have not been responded. Please provide a response to the labeling deficiencies.
 - A response to the deficiencies has been addressed separately on August 30, 2006.
3. The microbiology information you have provided is under review. After the review is complete, any deficiencies found will be communicated to you under separate cover.
 - Noted and acknowledged
4. The USP methods for the drug substance and the drug product are the regulatory methods and they will prevail in the event of any dispute.
 - Noted and acknowledged
5. Please provide all available long-term stability data to update your studies.
 - Updated data was submitted.
6. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.
 - Noted and acknowledged

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-719 APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF (b) (4) is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the Agency.
2. (b) (4)
Please clarify.
3. Your proposed (b) (4)
(b) (4)
4. Please set specifications for (b) (4)
(b) (4) is not acceptable.
5. You have indicated that the results of the (b) (4)
(b) (4). This is not acceptable. Please submit data to support the (b) (4)
(b) (4)

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

1. Bioequivalency deficiencies were communicated to you on June 26, 2007 and have not been responded. Please provide a response to the bioequivalency deficiencies.

2. Please provide all available long-term stability data to update your studies.

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 40-719
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/K.Woodland
HFD-620/R.Bykadi, Ph.D./ July 27, 2997/ August 17, 2007
HFD-617/Benjamin Danso, Pharm.D./8-17-07

V:\CHEMISTRY DIVISION I\TEAM 5\FINAL VERSION FOR DFS\40719.RV2.DOC

NOT APPROVABLE - MINOR

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

/s/

Kathy P. Woodland
8/21/2007 08:31:41 AM
CHEMIST

Benjamin Danso
9/11/2007 08:36:15 AM
CSO

Gururaj Bykadi
9/11/2007 11:15:04 AM
CHEMIST

ANDA 40-719

**Methylprednisolone Acetate Injectable Suspension, USP
40 mg/mL (10 mL multiple-dose vials) and
80 mg/mL (5 mL multiple-dose vials)**

Sandoz Canada Inc.

**Kathy P. Woodland
Division of Chemistry I**

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Chemistry Review Data Sheet

1. ANDA 40-719
2. REVIEW #: 3a
3. REVIEW DATE: May 30, 2008
July 22, 2008
4. REVIEWER: Kathy P. Woodland
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	12/19/2005
Refuse to receive	3/2/2006
Amendment (AC)	3/8/2006
Acceptable for Filing	3/9/2006
Amendments (AF))	6/12; 10/4, 10/30,2006; 2/23; 4/9; 5/22; 11/21/2007
Amendments (AB)	9/15/2006; 3/9; 6/1; 11/28/2007
Amendment (AM)	1/30/2007
Amendment (AA/Microbiology)	12/10/2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	November 5, 2007
Amendment	May 9, 2008
Telephone deficiency	July 2 and July 15, 2008

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Sandoz Canada Inc. (Formerly Sabex 2002)
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Beth Brannon Sandoz Inc. 2555 W. Midway Blvd. Broomfield, CO 80038-0446
Telephone:	303-438-4237
Fax:	303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Methylprednisolone Acetate Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Sandoz's proposed ANDA Methylprednisolone Injectable Suspension USP is the approved, RLD, Depo-Medrol[®], manufactured by Pharmacia and Upjohn Company, NDA 11-757.

b. According to the information published in the Orange Book, the RLD is not entitled to a period of marketing exclusivity under section 505(j)(4)(D).

10. PHARMACOL. CATEGORY: Steroidal Anti-inflammatory Agent

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40 mg/mL and 80 mg/mL

13. ROUTE OF ADMINISTRATION: IM, Intrasynovial, intraleasional

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

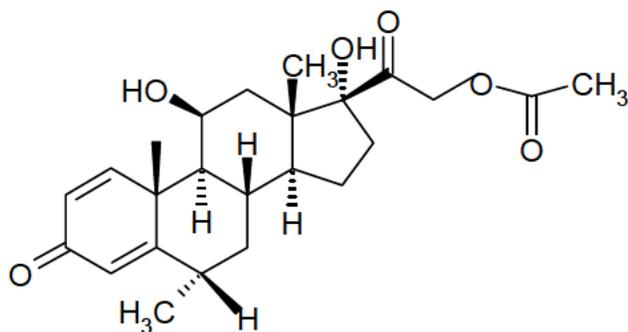
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Molecular Formula:	C ₂₄ H ₃₂ O ₆
Formula Weight:	416.51
Chemical Name:	Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6 α ,11 β)- 11b,17,21-Trihydroxy-6a-methylpregna-1,4-diene-3,20-dione 21-acetate.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	A.Shen	4/21/2008
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Deficient	6/24/2008	Per Master Q
EES	Acceptable	11/13/2006	Per Master Q
Methods Validation	Not Required		
Labeling	Acceptable	12/10/2007	Per Master Q
Bioequivalence	Acceptable	1/8/2008	Per Master Q/AS
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:

Minor Amendment

The Chemistry Review for ANDA 40-719

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable. CMC deficient, MICRO DEFICIENT

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance: The drug substance Methylprednisolone Acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, alcohol, chloroform, and methanol. It is slightly soluble in ether and practically insoluble in water.

Drug Product: Methylprednisolone acetate injectable suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available in two strengths: 40 mg/mL and 80 mg/mL. The 40 mg/mL contains the following: 40 mg Methylprednisolone acetate, 29.1 mg Polyethylene glycol 3350, 1.94 mg Polysorbate 80, 6.8 mg Monobasic sodium phosphate, 1.42 mg Dibasic sodium phosphate USP, and 9.16 mg Benzyl alcohol, added as a preservative. The 80 mg/mL contains the following: 80 mg Methylprednisolone acetate, 28.2 mg Polyethylene glycol 3350, 1.88 mg Polysorbate 80, 6.59 mg Monobasic sodium phosphate, 1.37 mg Dibasic sodium phosphate USP, and 8.88 mg Benzyl alcohol, added as a preservative.

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

The MDD is 160 mg. The drug product is administered intramuscular, intrasynovial, soft tissue or intralesional injection. Methylprednisolone Acetate Injectable Suspension is available as follows:
40 mg/mL: 1x10 mL, 10x10 mL multidose vials

Executive Summary Section

80 mg/mL: 1x5 mL, 10x5 mL multidose vials
The product is stored at 20° to 25°C(68° to 77°F)

IT and QT for DS: 0.10 and 0.15% respectively
IT and QT for DP: 0.20% for both

C. Basis for Approvability or Not-Approval Recommendation

MICRO DEFICIENT, CMC DEFICIENT

Following this page, 11 pages withheld in full - (b)(4)

Acceptable, R.Wu, 12/10/2007

33. ESTABLISHMENT INSPECTION

Acceptable 11/13/06

34. BIOEQUIVALENCE:

Acceptable 1/2/2008, DFS

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Sandoz is claiming a categorical exclusion.

In addition to responding to the deficiencies presented, the applicant noted and acknowledged the following comments in their response:

1. Bioequivalency deficiencies were communicated to you on June 26, 2007 and have not been responded. Please provide a response to the bioequivalency deficiencies.
 - A response to the deficiencies has been addressed separately on August 29, 2007.
2. Please provide all available long-term stability data to update your studies.
 - Updated data was submitted.

36. Chemistry Comments to be Provided to the Applicant:

ANDA: 40-719

APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP
40 mg/mL and 80 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. USP <467> became effective July 1, 2008. Please refer to the OGD website at <http://www.fda.gov/cder/ogd/ResidualSolvents.pdf> for important information about this change.

Please submit the following:

- A statement in the Drug Product specification, "Meets USP <467> requirements for residual solvents" along with the method used to establish permitted daily exposure for residual solvents (Options 1 or 2).
- A statement from the excipient/drug substance manufacturer for following two scenarios:
 - (1) If solvents are used in the manufacturing process:
 - ❖ Names of the residual solvents and specifications. Certificates of Analysis (your COAs and the manufactures' COAs)
 - ❖ A statement from the manufacturer stating that no other solvents are used in the manufacturing process.
 - (2) If solvents are NOT used in the manufacturing process:
 - ❖ A statement from the manufacturer that no solvents are used in the manufacturing process.
- Submit copies of the revised drug substance/excipient specifications.
- Submit a commitment to re-assess your compliance with USP<467> if you change ingredient suppliers in the post approval period including implementing revised controls, if appropriate.

2. Microbiology deficiencies were communicated to you on or about June 24, 2008 and have not been responded. Please provide a response to the Microbiology deficiencies.

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 40-719
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/K.Woodland/7/22/2008
HFD-620/R.Bykadi, Ph.D./ July 28, 2008
HFD-617/Benjamin Danso, Pharm.D./84/2008

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/s/

Kathy P. Woodland
8/19/2008 08:48:34 AM
CHEMIST

Benjamin Danso
8/22/2008 07:39:46 AM
CSO

Gururaj Bykadi
8/25/2008 05:41:21 AM
CHEMIST

ANDA 40-719

**Methylprednisolone Acetate Injectable Suspension, USP
40 mg/mL (10 mL multiple-dose vials) and
80 mg/mL (5 mL multiple-dose vials)**

Sandoz Canada Inc.

**Kathy P. Woodland
Division of Chemistry I**

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B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	8

Chemistry Review Data Sheet

1. ANDA 40-719
2. REVIEW #: 4
3. REVIEW DATE: November 19, 2008
Revised December 17, 2008
4. REVIEWER: Kathy P. Woodland
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	12/19/2005
Refuse to receive	3/2/2006
Amendment (AC)	3/8/2006
Acceptable for Filing	3/9/2006
Amendments (AF))	6/12; 10/4, 10/30,2006; 2/23; 4/9; 5/22; 11/21/2007
Amendments (AB)	9/15/2006; 3/9; 6/1; 11/28/2007
Amendment (AM)	1/30/2007
Amendment (AA/Microbiology)	12/10/2007
Amendment	November 5, 2007
Amendment	May 9, 2008
Telephone deficiency	July 2 and July 15, 2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Telephone Amendment	September 17, 2008
Telephone Amendment	December 17, 2008
Telephone Amendment	January 13, 2009

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Sandoz Canada Inc. (Formerly Sabex 2002)
Address:	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
Representative:	Beth Brannon Sandoz Inc. 2555 W. Midway Blvd. Broomfield, CO 80038-0446
Telephone:	303-438-4237
Fax:	303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Methylprednisolone Acetate Injectable Suspension USP

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Sandoz's proposed ANDA Methylprednisolone Injectable Suspension USP is the approved, RLD, Depo-Medrol[®], manufactured by Pharmacia and Upjohn Company, NDA 11-757.

b. According to the information published in the Orange Book, the RLD is not entitled to a period of marketing exclusivity under section 505(j)(4)(D).

10. PHARMACOL. CATEGORY: Steroidal Anti-inflammatory Agent

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40 mg/mL and 80 mg/mL

13. ROUTE OF ADMINISTRATION: IM, Intrasynovial, intraleasional

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

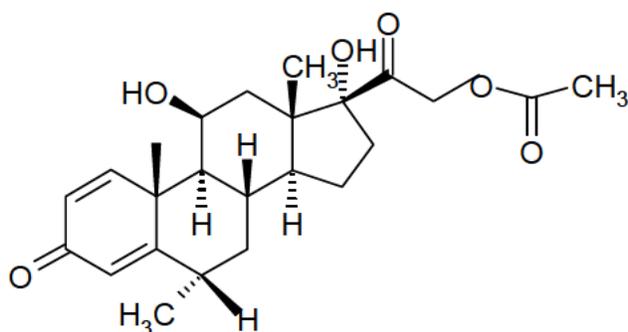
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Molecular Formula: $C_{24}H_{32}O_6$
 Formula Weight: 416.51
 Chemical Name: Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6 α ,11 β)-
 11b,17,21-Trihydroxy-6 α -methylpregna-1,4-diene-3,20-dione 21-acetate.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	A.Shen	4/21/2008
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	9/14/2008	Per Master Q
EES	Acceptable	11/13/2006	Per Master Q
Methods Validation	Not Required		
Labeling	Acceptable	12/10/2007	Per Master Q
Bioequivalence	Acceptable	1/8/2008	Per Master Q/AS
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:

Minor Amendment

The Chemistry Review for ANDA 40-719

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance: The drug substance Methylprednisolone Acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, alcohol, chloroform, and methanol. It is slightly soluble in ether and practically insoluble in water.

Drug Product: Methylprednisolone acetate injectable suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available in two strengths: 40 mg/mL and 80 mg/mL. The 40 mg/mL contains the following: 40 mg Methylprednisolone acetate, 29.1 mg Polyethylene glycol 3350, 1.94 mg Polysorbate 80, 6.8 mg Monobasic sodium phosphate, 1.42 mg Dibasic sodium phosphate USP, and 9.16 mg Benzyl alcohol, added as a preservative. The 80 mg/mL contains the following: 80 mg Methylprednisolone acetate, 28.2 mg Polyethylene glycol 3350, 1.88 mg Polysorbate 80, 6.59 mg Monobasic sodium phosphate, 1.37 mg Dibasic sodium phosphate USP, and 8.88 mg Benzyl alcohol, added as a preservative.

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

The MDD is 160 mg. The drug product is administered intramuscular, intrasynovial, soft tissue or intralesional injection. Methylprednisolone Acetate Injectable Suspension is available as follows:
40 mg/mL: 1x10 mL, 10x10 mL multidose vials

Executive Summary Section

80 mg/mL: 1x5 mL, 10x5 mL multidose vials
The product is stored at 20° to 25°C(68° to 77°F)

IT and QT for DS: 0.10 and 0.15% respectively
IT and QT for DP: 0.20% for both

C. Basis for Approvability or Not-Approval Recommendation

APPROVABLE

Following this page, 11 pages withheld in full - (b)(4)

Deficiency #5 You have indicated that the results of the [REDACTED] (b) (4)
[REDACTED] This is not acceptable. Please submit data to support the [REDACTED] (b) (4)

Response [REDACTED] (b) (4)

Conclusion Satisfactory

Notes Rv#2: The intended [REDACTED] (b) (4)

Deficiency Please submit complete [REDACTED] (b) (4)

Response At the time of the ANDA submission, [REDACTED] (b) (4)

Conclusion Satisfactory. All results were within the proposed specifications.

30. MICROBIOLOGY

Acceptable 9/17/2008, per MQ

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation is not required.

32. LABELING

Acceptable, R.Wu, 12/10/2007

33. ESTABLISHMENT INSPECTION

Acceptable 11/13/06

34. BIOEQUIVALENCE:

Acceptable 1/2/2008, DFS

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Sandoz is claiming a categorical exclusion.

In addition to responding to the deficiencies presented, the applicant noted and

acknowledged the following comments in their response:

1. Bioequivalency deficiencies were communicated to you on June 26, 2007 and have not been responded. Please provide a response to the bioequivalency deficiencies.
 - A response to the deficiencies has been addressed separately on August 29, 2007.
2. Please provide all available long-term stability data to update your studies.
 - Updated data was submitted.

cc: ANDA 40-719
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/K.Woodland/12-1-2008/12-16-2008/1-13-2009
HFD-620/R.Bykadi, Ph.D./
HFD-617/Benjamin Danso, Pharm.D./1-9-09

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(ORIGINAL)\40719.RV4AP.DOC

APPROVABLE

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

/s/

Kathy P. Woodland
1/27/2009 10:11:46 AM
CHEMIST

Gururaj Bykadi
1/27/2009 10:30:25 AM
CHEMIST

Benjamin Danso
1/27/2009 01:39:16 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-719

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	40-719
Drug Product Name	Methylprednisolone Acetate Injectable Suspension USP
Strength	40 mg/mL & 80 mg/mL
Applicant Name	Sandoz Canada
Submission Date(s)	September 15, 2006 (Current Submission)
Amendment Date	
First Generic	No
Reviewer	Hoainhon Nguyen
Clinical Site	Biovail Contract Research, Toronto Canada
Analytical Site	(b) (4)

EXECUTIVE SUMMARY

This is a review of amendments of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method (based on the approved ANDA 40-557). The firm had conducted dissolution testing using the FDA-recommended method as requested. However, the firm did not obtain any meaningful data using the FDA-recommended method. The firm has also developed its own method using USP apparatus IV (flow-through-cell), and challenged the FDA-recommended method as inappropriate for the dosage form since the drug is practically insoluble in water. The FDA method uses water as the dissolution medium whereas the firm's proposed method uses 0.55% Sodium Docedyl Sulfate (SDS).

Although the dissolution data based on the firm's proposed method appear to be discriminating and promising, no data for the RLD product were submitted. In addition, the firm has not provided adequate method development data to show that: 1) the conventional USP apparatus II (paddle) is not suitable, 2) dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration, and 3) the filter size (0.45 µm nylon filter) used for sample preparation is justified for the drug product.

The firm is requested to provide additional method development data above to assist the DBE in determining that its proposed method is indeed the most appropriate method for the drug product.

The dissolution testing is, therefore, **incomplete**.

The DBE will review the fasted and fed BE studies at a later date.

Table 1. Submission Content Checklist

Information		YES	NO	N/A	
Did the firm use the FDA-recommended dissolution method		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Did the firm use the USP dissolution method		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Did the firm use 12 units of both test and reference in dissolution testing		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Did the firm provide complete dissolution data (all raw data, range, mean, % CV)		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Did the firm conduct dissolution testing with its own proposed method		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is FDA method in the public dissolution database (on the web)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Plasma concentrations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Fed BE study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Other study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Are all eight electronic summary biotables present		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Are electronic summary biotables in pdf format		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

NOTE: The current FDA-recommended method is as follows (ANDA 40-557):

USP Apparatus: II (paddle) @ 50 rpm
 Dissolution Medium: water
 Volume of Dissolution Medium: 900 mL

Discussion of Current Issues and Deficiency Comments:

In the current dissolution amendment, the firm has submitted dissolution data based on the above FDA-recommended method, as requested. However, the dissolution data were not meaningful, as shown below:

Testing Conditions: (Recommended by DBE)

USP Apparatus: II (paddle)
RPM: 50
Medium: Water
Volume: 900 mL
Sample Filter: 0.2 µm Nylon membrane

(NOTE: The sample filter used for the FDA method was different from that used for the firm’s method (0.45 µm Nylon membrane).

Sampling Time (min)	Test Product, Strength 40 mg/mL Lot No. 1090401			Reference Product, Strength 40 mg/mL		
	Mean	%CV	Range	Mean	%CV	Range
15	0			Not submitted		
20	0					
30	0					
45	0					
60	0					
120	0					
240	1.6					

Sampling Time (min)	Test Product, Strength 80 mg/mL Lot No. 1810312			Reference Product, Strength 80 mg/mL Lot No. 59JMX		
	Mean	%CV	Range	Mean	%CV	Range
15	0			0		
20	0			0		
30	1.4			0		
45	0			0		
60	0			0		
120	0			0		
240	0			0		

The firm has also developed its own method and submitted the following results:

Testing Conditions: (Proposed by Firm)

USP Apparatus: IV (flow-through-cell) – open system

Flow rate: 8 mL/min

Medium: 0.55% Sodium Docedyl Sulfate (SDS)

Temperature: 37°C

Sampling Time (min)	Test Product, Strength 40 mg/mL Lot No. 1090401			Reference Product, Strength 40 mg/mL		
	Mean	%CV	Range	Mean	%CV	Range
5	8.7	4.7	(b) (4)	Not submitted		
30	60.0	7.4				
90	87.7	2.8				

Sampling Time (min)	Test Product, Strength 80 mg/mL Lot No. 1810312			Reference Product, Strength 80 mg/mL		
	Mean	%CV	Range	Mean	%CV	Range
5	10.4	14.2	(b) (4)	Not submitted		
30	58.4	13.9				
90	97.0	2.3				

F2 between Test strengths: 62.6

The firm challenged the FDA-recommended method: After 240 minutes, the dissolution percentages based on the FDA method are very low and negligible. The firm believed that the small percentages that are obtained may be due to undissolved particles in the dissolution samples which were then dissolved when diluted in diluting solvent prior to injection into the HPLC system. The firm concluded that water was not a suitable dissolution medium for dissolution testing of this dosage form. In addition, the firm argued that the USP apparatus II (paddle) at the specified rotation speed (50 rpm) didn't provide adequate mixing to disperse the drug product in the medium and to get a homogeneous mixture for sampling. *"The sink conditions are violated which are not relevant for small volume parenterals injected intramuscularly."* The firm stated that its method is more suitable since the UPS apparatus IV helps avoid aggregation problems and potential violation of sink conditions.

Further comparison between the current FDA-recommended method and the firm's proposed method can be summarized as follows:

	ANDA 40-557 (approved) Sicor	ANDA 40-719 Sandoz
Dissolution Method	900 mL of water @ 37°C USP apparatus II (paddle) at 50 rpm (Sample: 30 µLx80 mg/mL (2.4 mg) Or 60 µLx40 mg/mL (2.4 mg) in 900 mL)	0.55% SDS as dissolution medium @ 37°C USP apparatus IV (flow-through-cell) open system@ 8 mL/min *Apparatus cell filters: 1.2 µm, 25 mm diameter Whatman GF/C Glass Microfire
Dissolution Assay Method & Sample Preparation	HPLC/UV @ 244 nm Dissolution samples, collected directly from the dissolution vessels, were filtered prior to injection onto HPLC (using 0.2 µm Millex-GV filters; with the first 1 mL of filtrate discarded)	HPLC/UV @ 246 nm Dissolution samples, collected directly from the dissolution apparatus' fraction collector, were filtered prior to injection onto HPLC (using 0.45 µm Nylon filter membrane)
Particle Size Distribution Specification (Finished Product)	(b) (4)	(b) (4)
Particle Size Specification (Finished Product)		No specification under this category.

Although both methylprednisolone acetate and methylprednisolone are practically insoluble in water, it also should be noted that currently there is a UPS dissolution method for methylprednisolone tablets as follows:

USP Apparatus: II (paddle)

RPM: 50

Medium: Water

Volume: 900 mL

Specification: NLT 70%(Q) in 30 minutes

Sample: 4 mg tablet/900 mL

The firm's proposed dissolution method and data provided in the current amendment were discussed at the Bio Management meeting of 10/24/2006. (See the meeting minutes on v:\division\bio\Management Mtg\24Oct06.doc) Based on the data submitted by the firm in the current amendment, the DBE has the following observations:

1. The dissolution data based on the firm's proposed method appear to be promising and more discriminating compared with the current FDA-recommended method (as seen in the dissolution data submitted for ANDA 40-557 below). However, no data for the RLD product were submitted for comparison with the test product.

DISSOLUTION DATA – ANDA 40-557

Testing Conditions: (Recommended by DBE)

USP Apparatus: II (paddle)

RPM: 50

Medium: Water

Volume: 900 mL

Sampling Time (min)	Test Product, Strength 40 mg/mL Lot No. X02K617			Reference Product, Strength 40 mg/mL Lot No. 70KMW		
	Mean	%CV	Range	Mean	%CV	Range
15	84.8	1.3	(b) (4)	85.5	5.4	(b) (4)
30	88.1	2.6		86.4	3.9	
45	89.9	2.2		87.7	4.5	
60	88.3	4.2		87.5	4.3	
120	88.5	3.0		88.2	4.2	
240	89.2	3.5		89.4	5.8	

Sampling Time (min)	Test Product, Strength 80 mg/mL Lot No. X02C603			Reference Product, Strength 80 mg/mL Lot No. 17HSU		
	Mean	%CV	Range	Mean	%CV	Range
15	72.4	8.5	(b) (4)	71.5	5.1	(b) (4)
30	78.3	6.0		80.3	3.2	
45	80.0	6.8		83.9	3.9	
60	81.4	6.3		83.5	2.4	
120	82.6	7.5		85.3	2.1	
240	84.1	7.7		84.3	2.8	

F2 between the test and reference products: 80.03

2. In addition, the firm has not shown that it has conducted an exhaustive experiment with the conventional USP apparatus II (paddle) for the drug product. No method development data comparing USP apparatus II and IV (flow-through-cell) were submitted. The firm stated that “*the USP Apparatus II (Paddle) and rotational speed (50 rpm), recommended by FDA, didn’t provide adequate mixing to disperse the drug product in the Medium and to get a homogeneous mixture for sampling.*” The firm should submit data based on USP apparatus II (paddle), using the same medium chosen for USP apparatus IV (flow-through-cell), i.e., 0.55% SDS, to support the above statement.

3. The firm should also provide method development data showing that dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration.

4. Since solubility of the drug in dissolution medium is the primary focus of the method development, and filtration of dissolution samples is used to separate the soluble from insoluble particles, the firm should justify the selection of filter size (0.45 µm nylon filter) used for the sample preparation. It was also noted that the firm used 0.45 µm nylon filter for the firm’s method, but used 0.2 µm nylon filter for the FDA-recommended method. The firm should explain the reason for selecting different filters for the two methods, and provide additional dissolution data based on the firm’s dissolution method but with 0.2 µm nylon filter used in sample preparation.

The dissolution data of the RLD product, the comparative data between USP apparatuses, the medium optimization data and the filtration optimization data are essential in assisting the DBE to determine whether the firm’s proposed method is indeed the most appropriate method for the drug product. The firm should provide these additional method development data.

The dissolution testing is **incomplete**.

RECOMMENDATIONS:

The dissolution testing conducted by Sandoz for the test product using the FDA-recommended method is **incomplete** for the reasons cited in the Comments above.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 40-719

APPLICANT: Sandoz

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP, 40 mg/mL & 80 mg/mL

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver request will be conducted later. The following deficiencies have been identified in the dissolution testing:

1. The dissolution data based on the your proposed method appear to be discriminating and promising. However, no data for the RLD product, Depo-Medrol[®] (methylprednisolone acetate aqueous suspension), were submitted for comparison with the test product.
2. In addition, you have not shown that an exhaustive experiment with the conventional USP apparatus II (paddle) has been conducted for the drug product. No method development data comparing USP apparatus II (paddle) and IV (flow-through-cell) were submitted. You stated that "*the USP Apparatus II (Paddle) and rotational speed (50 rpm), recommended by FDA, didn't provide adequate mixing to disperse the drug product in the Medium and to get a homogeneous mixture for sampling.*" Please submit dissolution data based on USP apparatus II (paddle), using the same medium chosen for USP apparatus IV (flow-through-cell), i.e., 0.55% SDS, to support the above statement.
3. Please also provide method development data showing that dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration.
4. Since solubility of the drug in dissolution medium is the primary focus of the method development, and filtration of dissolution samples is used to separate the soluble from insoluble particles, please justify the selection of filter size (0.45 μ m nylon filter) used for the sample preparation. It was also noted that you used 0.45 μ m nylon filter for your proposed method, but used 0.2 μ m nylon filter for the FDA-recommended method in sample preparation. Please explain the reason for selecting

different filters for the two methods, and provide additional dissolution data based on your proposed dissolution method but with 0.2 µm nylon filter used in sample preparation.

The dissolution data of the RLD product, the comparative dissolution data based on both USP apparatus, the dissolution medium optimization data and the filtration optimization data are essential in assisting the DBE to determine whether your proposed method is indeed the most appropriate method for the drug product. Please provide these additional method development data.

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

DISSOLUTION - INCOMPLETE

Submission date: 09-15-06

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and the waiver request are pending review]

1. DISSOLUTION AMENDMENT

Strength: 40 mg/mL & 80 mg/mL

Outcome: IC

Outcome Decisions: IC – Incomplete

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

/s/

Hoainhon T. Nguyen
11/14/2006 02:22:06 PM
BIOPHARMACEUTICS

Moheb H. Makary
11/14/2006 02:24:32 PM
BIOPHARMACEUTICS

Barbara Davit
11/15/2006 11:20:26 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-719
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP (Multiple Dose Vials)
Strength	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz Canada Inc.
Applicant Address	145 Jules Leger Street, Boucherville (QC) Canada, J4B 7K8
Point of Contact	<u>U.S. Authorized Agent</u> Beth Brannan Sandoz Inc., 2555 W. Midway Blvd., P.O. Box 446, Broomfield, CO 80038-0446
Telephone Number	303-438-4237
Fax Number	303-438-4600
Clinical Site	<u>Fasting BE Study No. 3034 ((b) (4) Study No. 50529)</u> Biovail Contract Research 460 Comstock Road, Toronto, ON, M1L 4S4 Canada 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada
Analytical Site	<u>Fasting BE Study No. 3034 ((b) (4) Study No. 50529)</u> (b) (4)
Submission Date	March 08, 2006 - Refuse to File (Original Submission date: December 19, 2005)
Amendment Date	September 15, 2006 (Dissolution Amendment)
Reviewer	April C. Braddy, Ph.D.
First Generic	No

Review of a Bioequivalence Study and a Waiver Request

I. Executive Summary

In this application, the firm, Sandoz Inc. submitted a bioequivalence (BE) study under fasted conditions, comparing its test product, Methylprednisolone Acetate Injectable Suspension, USP, 80 mg/mL (Multiple Dose Vials) to the reference-listed drug (RLD) product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, by Pharmacia & Upjohn (NDA #: 11-757).

The fasting BE study No. 3034 was designed as a single-dose, **two-group**, crossover study in healthy, non-smoking, adult male and female subjects. Treatment Group No. 01 consisted of seventy-seven (77) subjects and Treatment Group No. 02 consisted of nine (9) subjects. The subjects received a 1 mL dose from a 5 mL multi-dose formulation (Treatment dose = 80 mg ~ 1 x 80 mg/mL). There was no significant group-by-treatment effect ($p > 0.1$). Therefore, the data from all subjects completing the fasting BE study ($N = 75$) were combined into one (1) group. Statistical analyses of the plasma concentration

DESI

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Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

data for methylprednisolone demonstrated bioequivalence in the fasting BE study. However, the fasting BE study is incomplete due to bioanalytical deficiencies.

For the fasting BE study No. 3034, methylprednisolone results, (point estimate, 90% CI) are: LAUC_T of 0.97, 93.81-99.35%, LAUC_∞ of 0.93, 88.78-97.69%, and LC_{max} of 1.02, 89.83-116.13%.

The Division of Bioequivalence (DBE) previously reviewed the *in vitro* dissolution testing and the BE reviewer determined that the dissolution testing and data was incomplete. The firm proposed its own dissolution method due to insignificant data obtained for its test product using the FDA-recommended method. The BE dissolution reviewer has requested that the firm provide additional method development data to assist the DBE in determining the appropriateness and acceptability of the firm's method for its test product.

In this application the firm also requested a waiver from *in vivo* BE study requirements for its lower strength, 40 mg/mL methylprednisolone acetate injectable suspension USP (Multiple Dose Vials). However, the waiver can not be granted at this time due to bioanalytical deficiencies and incomplete dissolution testing.

This application is **incomplete** with [deficiencies](#).

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Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

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 40 mg/mL and 80 mg/mL (Multiple Dose Vials)
 Review of a Bioequivalence Study and a Waiver Request Reviewer: April C. Braddy, Ph.D.

III. Submission Summary

A. Drug Product Information

Test Product	Methylprednisolone Acetate Injectable Suspension, USP (Multiple Dose Vials)
Reference Product	Depo-Medrol [®] (methylprednisolone acetate) Injectable Suspension
RLD Manufacturer	Pharmacia & Upjohn Company
NDA No.	11-757
RLD Approval Date	Approved Prior to January 01, 1982
Indication	Depo-Medrol [®] is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is indicated for the treatment of endocrine disorders, rheumatic disorders, collagen diseases, dermatologic disease, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states, nervous system (acute exacerbations of multiple sclerosis), and for miscellaneous conditions (Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy and trichinosis with neurologic or myocardial involvement).

B. PK/PD Information¹

Bioavailability	<i>As of November 1990, the formulation for DEPO-MEDROL Sterile Aqueous Suspension was revised. In a bioavailability study with thirty subjects, the new formulation was found to be more bioavailable. There was an increase in the rate and extent of absorption.</i>
------------------------	---

¹ 1. Online-Physicians' Desk Reference Electronic Library™. (2007). <http://www.thomsonhc.com>. Thomson Micromedex: Keyword Search: Depo-Medrol. Last accessed: 01/16/2007.
 2. Online-Clinical Pharmacology (2007). <http://cpip.gsm.com>. World-Class Drug Information: Monographs: Depo-Medrol: Last updated: 07/20/2006: Last accessed: 01/16/2007.
 3. Online-USP DI® Info. for Health Care Professionals – 27th Ed. (2007). Copyright© 2007 Thompson MICROMEDEX.
<http://online.statref.com/Document/Document.aspx?FxID=6&DocID=3560&QueryID=26455&SessionId=88B4A9LYFHILENEW> Keyword Search: methylprednisolone acetate injectable suspension. Last accessed: 01/16/2007.

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ANDA #: 40-719 Methylprednisolone Acetate Injectable Suspension USP Sandoz
 40 mg/mL and 80 mg/mL (Multiple Dose Vials)
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		<u>Previous Formulation</u>	<u>Current Formulation</u>
	AUC 0-240 hrs (ng × hr/mL)	1053 (47.3) * [133-2297] **	1286 (39.2) [208-2225]
	C _{MAX} (ng/mL)	8.98 (65.9) [0-28.5]	11.8 (44.1) [3.37-23.4]
	t _{1/2} (hr)	139 [46-990]	139 [58-866]
	* Coefficient of variation (%)		
	** Range of values		
	<i>Table is taken from Ref. 1</i>		
Food Effect	The labeling for Depo-Medrol [®] (methylprednisolone acetate) Injectable Suspension does not mention food.		
Tmax	The onset and duration of action of methylprednisolone suspensions are dependent on whether the drug is administered by intra-articular or IM injection, and on the extent of the local blood supply. Absorption of methylprednisolone from an intra-articular injection site can be very slow, continuing over about 7 days.		
Metabolism	Methylprednisolone is metabolized by the liver to inactive metabolites.		
Excretion	The inactive metabolites and a small portion of unchanged drug are excreted in the urine.		
Half-life	The biological half-life of methylprednisolone is 18 to 36 hours		
Relevant OGD or DBE History	Methylprednisolone Acetate Injectable Suspension is a DESI drug . It has a therapeutic equivalence code of “AB” in the Electronic Orange Book (current through December 2006).		
	Also, according to the Electronic Orange Book two (2) generic products for Methylprednisolone Acetate Injectable Suspension, USP are currently approved. The ANDAs and approval dates are as follows:		
	ANDA #	Firm	Dose/Vials
	40-557	Gensia Sicor	Single- Dose
	40-620	Gensia Sicor	Multiple Dose
	1. The DBE recommends the following studies to establish bioequivalence of methylprednisolone		

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Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

acetate suspension USP as per Control # [06-0452](#),
(b) (4), 03/27/2006):

- a. An *in-vivo* bioequivalence study comparing your single-dose Sterile Methylprednisolone Acetate Suspension, 80 mg/mL, to Pharmacia Upjohn's single-dose Sterile Methylprednisolone Acetate Suspension, 80 mg/mL.
 - b. An *in-vivo* bioequivalence study comparing your multiple-dose Sterile Methylprednisolone Acetate Suspension, 80 mg/mL, to Pharmacia Upjohn's multiple dose Sterile Methylprednisolone Acetate Suspension, 80 mg/mL.
2. Please measure methylprednisolone in plasma.
 3. Methylprednisolone Acetate Injection Suspension, 20 mg/mL and 40 mg/mL, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 80 mg/mL strength, (2) acceptable dissolution testing of the 20 mg/mL, 40 mg/mL, and 80 mg/mL strengths and (3) proportional similarity in the formulations of the 20 mg/mL, 40 mg/mL, and 80 mg/mL strengths.
 4. Please develop a dissolution method. In addition, please conduct comparative dissolution testing on 12 dosage units (from 12 different vials) of the test and reference products using the following FDA method:

Apparatus: USP apparatus II (paddle)
Speed: 50 rpm
Medium: Water
Volume: 900 mL
Sampling Times: 1 and 4 hours

To date, the DBE has reviewed several controlled documents and protocols.

Controlled documents:

DESI

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Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

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	# 93-044	(b) (4)	06/07/1993
	# 01-569	Sabex	11/20/2001
	# 02-298	Gensia Sicor	05/29/2002
	# 06-0452	(b) (4)	03/27/2006
	Protocols:		
	# 00-049	Gensia Sicor	11/30/2000
	# 02-064	Gensia Sicor	12/12/2002
	# 04-058	(b) (4)	12/15/2004
Agency Guidance	2003 Guidance Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (issued Mar 2003)		
Dosage and Administration	<p>Because of possible physical incompatibilities, DEPO-MEDROL Sterile Aqueous Suspension should not be diluted or mixed with other solutions.</p> <p>Dosage is dependent upon the disease or disorder being treated and the site of action (local or systemic).</p>		
Drug Specific Issues (if any)	<p style="text-align: center;">WARNING</p> <p>This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.</p> <p>Multidose use of DEPO-MEDROL Sterile Aqueous Suspension from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. Particular care, such as use of disposable sterile syringes and needles is necessary.</p> <p>While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physiochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site. The degree to which this reaction occurs will vary with the amount of adrenal steroid injected. Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed.</p> <p>In order to minimize the incidence of dermal and</p>		

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40 mg/mL and 80 mg/mL (Multiple Dose Vials)

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	<p>subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intrasynovial and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.</p> <p>It is critical that, during administration of DEPO-MEDROL, appropriate technique be used and care taken to assure proper placement of drug.</p>
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40 mg/mL and 80 mg/mL (Multiple Dose Vials)

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C. Contents of Submission

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

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Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

D. Pre-Study Bioanalytical Method Validation¹

Fast 50529 (3034)	DATA
Bioanalytical method validation report location	Appendices 4.2 of bioanalytical report
Analyte	Methylprednisolone *
Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of methylprednisolone and the internal standard from human plasma by solid phase extraction. Samples are kept frozen at -80°C prior to analysis and 0.500 mL of plasma was used for analysis.
Limit of quantitation (ng/mL)	0.25
Average recovery of drug range (%)	91.63 to 94.77
Average recovery of IS (%)	97.13
Standard curve concentrations range (ng/mL)	0.25 to 24.72
QC concentration (ng/mL)	QC1: 0.74 QC2: 7.44 QC3: 18.60
QC Intraday precision range (%)	1.06 to 7.51
QC Intraday accuracy range (%)	93.33 to 108.33
QC Interday precision range (%)	3.57 to 5.70
QC Interday accuracy range (%)	103.44 to 104.90
Bench-top stability (hrs)	24 hours at room temperature
Stock stability (days)	Analyte: 350 days at -20°C and 574 days at -80°C IS: 77 days at -20 °C
Processed stability (hrs)	98 hours at room temperature
Freeze-thaw stability (cycles)	4 at -20°C 4 at -80°C
Long-term storage stability (days)	5 days at -20°C and 5 days at -80°C
Dilution integrity	QC3 diluted 2 fold: CV (%) 2.47 % Nominal (%) 98.24 % DQC diluted 20 fold: CV (%) 4.08 % Nominal (%) 96.00 %
Selectivity	Human plasma samples (EDTA K ₂ or K ₃ as anti-coagulant) from 10 different individual human blank sources were tested for interfering peaks at the retention time of methylprednisolone and the internal standard. None of the sources showed significant interference at the retention time of methylprednisolone or the internal standard.

* Analytical method SOP. (Appendix 4.1 of bioanalytical report)

¹: The table is provided by the firm.

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 40 mg/mL and 80 mg/mL (Multiple Dose Vials)
 Review of a Bioequivalence Study and a Waiver Request Reviewer: April C. Braddy, Ph.D.

Table D-2. Additional Table for Pre-Study Bioanalytical Method Validation¹:

SOPs submitted	Yes		
20% Chromatograms included (Y/N)	Y	Serially Selected?	Y
Is Bioanalytical method acceptable?	No		

¹: Additional Table is provided by reviewer.

Reviewer's Comments: The bioanalytical method is incomplete. The long-term stability data provided by the firm of methylprednisolone in human plasma for 5 days in unacceptable. The long-term stability data should cover the timeframe from the first blood sample collection until the last plasma sample is analyzed (February 19, 2005 to November 30, 2005 – 285 days). The firm stated in its bioanalytical report, “*Additional long-term stability of methylprednisolone in human plasma NaF/potassium oxalate plasma under storage conditions at a nominal temperature of -80°C will be evaluated in the near future.*” At the time of this review, the firm had not amended its submission to provide adequate long-term stability data.

E. In Vivo Study

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study			
Study No.	3034		
Study Design	A randomized, open-label, single-dose, two-way crossover study		
No. of subjects enrolled	86		
No. of subjects completing	75		
No. of subjects analyzed	75		
Subjects (Healthy or Patients?)	Normal, healthy, non-smoking		
Sex(es) included (how many?)	Male:	52	Female: 34
Test product	Methylprednisolone Acetate Injectable Suspension, USP (Multiple Dose Vials)		
Reference product	Depo-Medrol [®] (methylprednisolone acetate) Injectable Suspension		
Strength tested	80 mg/mL (Multiple Dose Vials)		
Dose	1 mL from a 5 mL multi-dose formulation (Treatment dose = 80 mg ~ 1 x 80 mg/mL)		

DESI

ANDA #: 40-719 Methylprednisolone Acetate Injectable Suspension USP Sandoz
 40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Review of a Bioequivalence Study and a Waiver Request Reviewer: April C. Braddy, Ph.D.

Table E1-1. Summary of Statistical Analysis, Point Estimates and 90% Confidence Intervals for Methylprednisolone in the Fasting Bioequivalence Study

Summary of Statistical Analysis, Fasting Bioequivalence Study Additional Information Located in Appendix, Table A1-7 and Table A1-8		
METHYLPREDNISOLONE		
Parameter	Point Estimate	90% Confidence Interval
LAUC _T	0.97	93.81-99.35 %
LAUC _∞	0.93	88.78-97.69 %
LC _{max}	1.02	89.93-116.13 %

Reviewer's Comments:

- Eighty-six (86) normal, healthy, non-smoking male and female subjects were enrolled in the fasting BE study. The subjects were divided into two (2) groups. Treatment Group No. 01 consisted of seventy-seven (77) subjects (Nos. 01 to 29, 31-48, 50-77, 79, and 80) and Treatment Group No. 02 consisted of nine (9) subjects (Nos. 30, 49, 78, and 81-86)
- Eleven (11) subjects (Nos. 10, 13, 15, 20, 36, 39, 46, 48, 50, 66, and 69) from Treatment Group No. 01 were withdrawn and/or dropped out of the study by the principal investigator. Subject Nos. 13, 15, 20, 39, 46, 50, and 69 withdrew for personal reasons during the washout period between Period I and II dosing. Subject Nos. 10, 36, and 66 were dismissed from the study by the principal investigator during the washout period between Period I and II dosing and subject No. 48 was dismissed in Period II. According to the firm's protocol none of these subjects were replaced in this study.
- The eighty-six (86) subjects enrolled in the study were members of the community at large, varying in race and sex. Over 46% of the subjects enrolled in the study were Caucasians (40), the other 54% consisted of Asians (18, ~21%), Blacks, (17, ~20%), and Hispanics (11, ~13%). Forty-percent (40%) of the subjects were female and the other 60% were male. A table consisting of the demographic profiles for the subjects dosed in this study is in Appendix A, [Table A1-1](#).
- The firm calculated the pharmacokinetic (PK) parameters using the data from the seventy-five (75) subjects completing the fasting study. Initially, the firm used the group-by-treatment effect in its statistical model. Based on their analysis, the firm concluded it was not significant.
- The reviewer calculated the PK parameters using the group-by-treatment effect in the statistical model. The reviewer agreed with the firm's results. There was no statistically significant group by treatment effect ($p > 0.1$) in this study.

ANDA #: 40-719

DESI
Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

Table E1-2. Reanalysis of Methylprednisolone Plasma Samples in the Fasting Bioequivalence Study²

Study No.50529 (3034)								
A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP (Multidose Formulation) Versus Depo-Medrol [®] 80 mg/mL Injectable Suspension (Multidose Formulation) in normal Healthy Non-Smoking Male and Female Subjects								
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 ¹	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	52	72	1.22	1.68	51	69	1.19	1.61
Poor chromatography	3	3	0.07	0.07	3	3	0.07	0.07
Unacceptable internal standard response	9	10	0.21	0.23	9	10	0.21	0.23
Equipment failure	24	29	0.56	0.68	24	29	0.56	0.68
The internal standard response is $\leq 5\%$ of the mean internal standard responses	2	1	0.05	0.02	2	1	0.05	0.02
Sample concentration above upper limit of quantification	11	23	0.26	0.54	11	23	0.26	0.54
Sample reanalyzed to obtain confirming value	2	5	0.05	0.12	1	2	0.02	0.05
Sample stability exceeding validation data	1	1	0.02	0.02	1	1	0.02	0.02
Total	52	72	1.22	1.68	51	69	1.19	1.61

¹ If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

^T Methylprednisolone Acetate, 80 mg/mL Injectable Suspension from a 5 mL multidose formulation, (Sabex Inc.), Lot: 1810312

^R Methylprednisolone Acetate (Depo-Medrol[®]), 80 mg/mL Injectable Suspension from a 5 mL multidose formulation, (Sabex Inc.), Lot: 59JMX

²: The table is provided by the firm.

Reviewer's Comments: One-hundred and twenty-four (124) methylprednisolone plasma samples were reassayed for analytical reasons. The firm did not report any samples as being reassayed for pharmacokinetic (PK) reasons. The recalculated values for one-hundred and twenty (120) methylprednisolone plasma samples were used in PK and statistical analyses. The firm reported that seven (7) methylprednisolone plasma samples were reassayed for the analytical reason coded (G), sample reanalyzed to obtain confirming value. However, in the analytical report, Table 3: Repeat Analysis Results for Methylprednisolone in Human Plasma (Study LBI), the reviewer could only identify four (4) samples that were reassayed for the reasons coded as: **9** (Code D, G, G), **10** (Code D, G) and **12** (Code G, G). The reviewer would like to ask the firm to please clarify which of the samples were indeed reassayed due to reason G.

Reviewer's Comments: The 90% confidence intervals are within the acceptable range of 80% - 125% for log transformed AUC_T , AUC_∞ and C_{max} for methylprednisolone. However, the fasting BE study is incomplete due to bioanalytical deficiencies.

F. Formulation

Location in appendix	Appendix, Section B, Table B-1
Are inactive ingredients within IIG limits?	Yes
If yes, list ingredients outside of limits	--
If a tablet, is the product scored?	N/AP
If yes, which strengths are scored?	--
Is scoring of RLD the same as test?	--
Is the formulation acceptable?	Yes
If not acceptable, why?	--

Reviewer's Comments: The formulations for the Sandoz's Methylprednisolone Acetate Injectable Suspension, USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) are acceptable. The inactive ingredients are within the FDA-recommended IIG limits. The formulations for Sandoz's test product are the same as the RLD product.

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	0.5% Sodium Docedyl Sulfate (SDS)
USP Apparatus type	IV (flow-through cell) – open system
Flow rate	8 mL/min
Firm's proposed specifications	--
FDA-recommended specifications	--
F2 metric calculated?	Yes
If no, reason why F2 not calculated	--
Is method acceptable?	No
If not then why?	In a deficiency letter to the firm, the DBE requested that the firm provide additional method development data to assist the DBE in determining that its proposed method is indeed the most appropriate for the drug product.

Reviewer's Comments: The comparative *in vitro* dissolution testing method and data provided by the firm for its test products is incomplete. The firm did conduct dissolution testing using the FDA-recommended method (based on the ANDA #: 40-557, [V:\FIRMSNZ\SICOR\LTRS&REV\40557a1104.doc](#)); however, the firm did not obtain

meaningful results (as shown in the initial dissolution review in DFS – amendment dated September 21, 2006 and Appendix, Section C, [Table C-2](#)). Based on these results, the firm conducted dissolution testing using its proposed method. The BE dissolution reviewer stated in their review that the firm did not provide ‘adequate method development data to show that: 1) the conventional USP apparatus II (paddle) is not suitable, 2) dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration, and 3) the filter size (0.45 µm nylon filter) used for sample preparation is justified for the drug product.’ Therefore, in a deficiency letter to the firm, the DBE requested the firm provide additional method development data to assist the DBE in determining that its proposed method is indeed the most appropriate for the drug product.

H. Waiver Request(s)

Strengths for which waivers are requested	40 mg/mL
Regulation cited	21 CFR § 320.22 (b) (1)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	<i>In vitro</i> dissolution testing is incomplete and the application contains bioanalytical deficiencies.

I. Deficiency Comments

1. The firm should provide adequate long-term stability for methylprednisolone in human plasma. The long-term stability data submitted by the firm only covered 5 days which is unacceptable. The long-term stability data should cover the timeframe from the first blood sample collection until the last plasma sample is analyzed (February 19, 2005 to November 30, 2005 – 285 days). The firm stated in its bioanalytical report, “*Additional long-term stability of methylprednisolone in human plasma NaF/potassium oxalate plasma under storage conditions at a nominal temperature of -80°C will be evaluated in the near future.*” At the time of this review, the firm had not amended its submission to provide adequate long-term stability data.
2. The firm should clearly identify the seven (7) methylprednisolone plasma samples that were reassayed for the analytical reason coded (G), sample reanalyzed to obtain confirming value. In the analytical report, Table 3: Repeat Analysis Results for Methylprednisolone in Human Plasma (Study LBI) the reviewer could only identify four (4) plasma samples as being reassayed for the reasons coded as: **9** (Code D, G, G), **10** (Code D, G) and **12** (Code G, G). The table below contains the information for the four (4) samples identified.

Subject No.	Period	Time, hr	Reason
35	1	8.5	9
35	1	12	10
63	2	PRE	12
71	2	PRE	12

3. The firm should provide the potency data for the reference-listed drug product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, Lot No. 59JMX.
4. The *in vitro* dissolution testing conducted by the firm on its Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) is incomplete. The firm was informed via a deficiency letter dated November 20, 2006, that they should provide additional method development data to assist the DBE in determining that its proposed method is indeed the most appropriate for the drug product.

J. Recommendations

1. The single-dose *in vivo* fasting bioequivalence (BE) study No. 3034 conducted by Sandoz Canada Inc. comparing its test product, Methylprednisolone Acetate Injectable Suspension USP, 80 mg/mL (Multiple Dose Vials), Lot No. 1810312, to the reference-listed drug (RLD) product, Depo-Medrol® (methylprednisolone acetate) Injectable Suspension, 80 mg/mL, Lot No. 59JMX by Pharmacia & Upjohn, is incomplete for the reasons given in the [deficiency comment Nos. 01 to 03](#).
2. The *in vitro* dissolution testing conducted by Sandoz Canada Inc. on its Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) is incomplete due to [deficiency comment No. 04](#).
3. The formulation for Sandoz Canada Inc., Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (Multiple Dose Vials) is similar to the Methylprednisolone Acetate Injectable Suspension USP, 80 mg/mL (Multiple Dose Vials), which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 40 mg/mL can not be granted at this time due to [deficiency comment Nos. 01 to 04](#).

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

IV. Appendix**A. Individual Study Reviews**

1. Single-dose Fasting Bioequivalence Study

a. Study Design

Study Information				
Study Number	3034			
Study Title	A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP (Multidose Formulation) Versus Depo-Medrol® 80 mg/mL Injectable Suspension (Multidose Formulation) in Normal Healthy Non-Smoking Male and Female Subjects			
Clinical Site	Biovail Contract Research 460 Comstock Road, Toronto, ON, M11 4S4 Canada 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada			
Principal Investigator	Paul Y. Tam, M.D., F.R.C.P, F.A.C.P.			
Study/Dosing Dates	Study Period	Dosing		
			Period I	Period 2
	Start Date: February 18, 2005	Group I	February 19, 2005	May 28, 2005
	End Date: August 30, 2005	Group II	March 10, 2005	June 16, 2005
Analytical Site	(b) (4)			
Analytical Director	(b) (6) B.Sc.			
Analysis Dates	September 26, 2005 to November 30, 2005			
Storage Period	285 days (February 19, 2005 to November 30, 2005)			

Treatment ID	A	B
Test or Reference	Test	
Product Name	Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP (Multidose Formulation)	Depo-Medrol [®] 80 mg/mL Injectable Suspension (Multidose Formulation)
Manufacturer	Sabex [®] Inc., Canada	Pharmacia & Upjohn Company
Batch/Lot No.	1810312	59JMX
Manufacture Date	Not provided	N/AP
Expiration Date	01/2006	01/2006
Strength	80 mg/mL	80 mg/mL
Dosage Form	Injectable Suspension	Injectable Suspension
Batch Size	(b) (4)	N/AP
Production Batch Size	(b) (4) (5 mL vials)	N/AP
Potency*	90.0-110.0%	Not provided
Content Uniformity**	85.0 -115.0% RSD: < 6.0%	Not provided
Formulation	Located in Table B-1	Located in Table B-2
Dose Administered	1 mL from a 5 mL multi- dose formulation (Treatment dose = 80 mg ~ 1 x 80 mg/mL)	1 mL from a 5 mL multi- dose formulation (Treatment dose = 80 mg ~ 1 x 80 mg/mL)
Route of Administration	Intramuscular injection	

*on a total of 10 vials

**Beginning, middle and end of lot

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	14-weeks (98 days)
Randomization Scheme	<p>Treatment Group No. 01</p> <p><u>Sequence AB</u> Subject Nos. 01, 02, 03, 04, 07, 11, 13, 14, 15, 16, 20, 21, 22, 27, 31, 33, 34, 37, 38, 39, 41, 44, 46, 51, 54, 55, 56, 58, 63, 64, 67, 68, 69, 73, 74, 75, 79, and 80</p> <p><u>Sequence BA</u> Subject Nos. 05, 06, 08, 09, 10, 12, 17, 18, 19, 23, 24, 25, 26, 28, 29, 32, 35, 36, 40, 42, 43, 45, 47, 48, 50, 52, 53, 57, 59, 60, 61, 62, 65, 66, 70, 71, 72, 76, and 77</p> <p>Treatment Group No. 02</p> <p><u>Sequence AB</u> Subject Nos. 49, 82, 83, 84, and 85</p> <p><u>Sequence BA</u> Subject Nos. 30, 78, 81, and 86</p>
Blood Sampling Times	0.0 (pre-dose), 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 10, 12, 16, 24, 48, 72, 120, 168, 216, 240, 360, 480, 720, 960, 1200, 1440, and 1680 hours (post-dose)
Blood Volume Collected/Sample	During each period, 29 blood samples were collected. Each blood sample was 6 mL.
Blood Sample Processing/Storage	The blood samples were stored in an ice bath before centrifugation and were centrifuged as soon as possible under refrigerated conditions (at 4 °C) at 3500 rpm for 7 minutes. The collected plasma from each blood sample collection tube was aliquotted into pre-cooled labeled polypropylene tubes. A minimum of 1.5 mL of plasma was transferred into the first polypropylene tube, and all remaining plasma, if any, was transferred into the first tube. The samples were kept in an ice bath, flash frozen in an upright position in a dry ice-acetone bath and stored at -70 °C ± 10 °C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	Located in Table A1-1
Length of Fasting	The subjects fasted overnight for at least 10 hours.
Length of Confinement	Subjects in both groups were admitted to the clinic the day before dosing, and remained until 24 hour post-

ANDA #: 40-719

Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

	dose blood draw of each period.
Safety Monitoring	Adverse events were monitored and documented throughout the confinement and washout portions of each study.

Is the design of the fasting bioequivalence study acceptable? No

Reviewer's Comments: The firm did not provide the potency data for the RLD product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, Lot No. 59JMX by Pharmacia & Upjohn.

b. Clinical Results

*Study Demographics***Table A1-1. Demographics of Subjects Completing the Fasting Bioequivalence Study No. 3034**.³**

Biovail Study # 3034		
A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP (Multidose Formulation) versus Depo-Medrol® 80 mg/mL Injectable Suspension in Normal, Healthy, Non-Smoking Male and Female Subjects		
	Treatment Groups (Includes All Dosed Subjects)	
	Test Product¹ n = 82	Reference Product² n = 80
Age (years)		
Mean ± SD	36 ± 10	37 ± 10
Range	(18-67)	(20-67)
Groups		
<18	0	0
18 – 40	56	52
41 – 64	24	26
65 – 75	2	2
> 75	0	0
Sex		
Male	52	48
Female	30	32
Race		
Asian	17	17
Black	17	14
Caucasian	38	39
Hispanic	10	10
Other	0	0
Other Factors		
Height (cm)		
Mean ± SD	170 ± 9	170 ± 10
Range	(143-187)	(143-187)
Weight (kg)		
Mean ± SD	74 ± 11	74 ± 11
Range	(45-95)	(45-95)
BMI (kg/m ²)		
Mean ± SD	25.6 ± 2.7	25.6 ± 2.6
Range	(19.8-29.7)	(19.8-29.8)

¹ Test: Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP (Multidose Formulation) (Lot #: 1810312)² Reference: Depo-Medrol® 80 mg/mL Injectable Suspension (Lot #: 59JMX)

**Completed by Biovail Contract Research

³ The table is provided by the firm.

*Study Dropout Information***Table A1-2. Subjects Discontinued from the Fasting Bioequivalence Study No. 3034**

Subject Number	10
Reason/Adverse Event	Unexpected adverse event Positive β -CG levels (Treatment B: Reference Product)
Period	Before Period II dosing
Release Date	May 28, 2005
Replacement	None
Subject Number	13
Reason/Adverse Event	Voluntarily withdrew for personal reasons
Period	During the washout period
Release Date	May 27, 2005
Replacement	None
Subject Number	15
Reason/Adverse Event	Voluntarily withdrew for personal reasons
Period	During the washout period
Release Date	May 27, 2005
Replacement	None
Subject Number	20
Reason/Adverse Event	Voluntarily withdrew for personal reasons
Period	During the washout period
Release Date	May 27, 2005
Replacement	None
Subject Number	36
Reason/Adverse Event	Due to adverse events and administrative reasons Headache, fever and congestion (Treatment B: Reference Product). The subject took concomitant medication for the treatment of adverse event.
Period	I
Release Date	May 21, 2005
Replacement	None
Subject Number	39
Reason/Adverse Event	Voluntarily withdrew for personal reasons
Period	Before dosing in Period II
Release Date	May 28, 2005
Replacement	None
Subject Number	46
Reason/Adverse Event	Voluntarily withdrew for personal reasons
Period	During the washout period
Release Date	May 27, 2005
Replacement	None

**Con't, Table A1-2. Subjects Discontinued from the Fasting Bioequivalence Study
No. 3034**

Subject Number	48
Reason/Adverse Event	Administrative reasons (spilled medication during dosing)
Period	II (During confinement)
Release Date	May 28, 2005
Replacement	None
Subject Number	50
Reason/Adverse Event	Voluntarily withdrew for personal reasons
Period	During the washout period
Release Date	May 27, 2005
Replacement	None
Subject Number	66
Reason/Adverse Event	Due to adverse events Headache, sinus congestion, and a red patch on the abdomen (Treatment B: Reference Product)
Period	During the washout period
Release Date	May 11, 2005
Replacement	None
Subject Number	69
Reason/Adverse Event	Voluntarily withdrew for personal reasons
Period	During the washout period
Release Date	May 27, 2005
Replacement	None

*Adverse Events***Was there a difference in side effects for the test versus the reference? No****Table A1-3. Reported Incidence of Adverse Events in the Fasting Bioequivalence Study No. 3034³**

Body System Adverse Event	Reported Incidence by Treatment Group	
	FASTED Bioequivalence Study Biovail Study # 3034	
	Test ¹	Reference ²
Gastrointestinal disorders [GD]		
Nausea	2	0
Vomiting	1	0
Dry Mouth	1	0
General disorders and administrative site conditions [GDASC]		
Pyrexia	0	2
Local Swelling	1	0
Oedema Peripheral	1	0
Cold Sweat	0	1
Investigations [INV]		
Eosinophil Count Increased	1	1
Blood Glucose Decreased	2	0
Blood Lactate Dehydrogenase Increased	1	0
Urine Ketone Body Present	0	2
Blood Glucose Increased	1	0
Blood Urine Present	1	0
Protein Urine Present	2	0
Blood Urea Increased	0	1
White Blood Cells Urine Positive	0	2
Blood Alkaline Phosphatase Decreased	0	1
Platelet Count Decreased	0	1
Alanine Aminotransferase Increased	1	0
Pregnancy Test Positive	0	1
Musculoskeletal and connective tissue disorders [MCTD]		
Back Pain	0	1
Arthralgia	1	1
Joint Swelling	0	1
Myalgia	1	0
Nervous system disorders [NSD]		
Headache	1	6
Dizziness	1	1
Respiratory, thoracic and mediastinal disorders [RTMD]		
Sinus Congestion	0	2
Skin and subcutaneous tissue disorders [SSTD]		
Rash	0	3
Total number of adverse events	19	27

¹ Test: Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP (Multidose Formulation) (Lot #: 1810312)² Reference: Depo-Medrol[®] 80 mg/mL Injectable Suspension (Lot #: 59JMX)

**Completed by Biovail Contract Research

³ The table is provided by the firm.

Reviewer's Comments: During the fasting BE study, thirty-one (31) subjects (Nos. 03, 06, 08, 10, 18, 20, 21, 23-26, 30-33, 36, 37, 46, 48, 52, 54, 58, 59, 62, 64, 66, 68, 76, 78, 81, and 85) reported experiencing a total of forty-six (46) adverse events. All of the adverse events experienced by these subjects were either mild (40) or moderate severity (6). Only five (5) of the adverse events (dizziness (No. 18), soreness in right deltoid (No. 21), and headache (Nos. 25, 30, and 54) were reported as being related to either study drug. As stated earlier, subject Nos. 10, 36, and 66 were withdrawn from the study due to the adverse events experienced after receiving a single dose of Treatment B: Reference Product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, 1 x 80 mg/mL). The adverse events experienced by these subjects were reported as being unrelated to the study drug.

Protocol Deviations

Additional Information is located in Volume 2, Section 16.2.6, pp. 180-94

Was there a difference in protocol deviations for the test versus the reference? No

Reviewer's Comments:

1. The protocol deviations reported by the firm consisted of Subject No. 36 taking concomitant medication (herbal patch) for treatment of an adverse event. Along, with the firm not conducting the post-study examination for Subject No. 15.
2. The firm also reported missed blood sample collections for subjects at various time points. The blood samples were not collected either because there was difficulty drawing the blood or the subjects did not return at the scheduled time. Also, less than 1.5 mL of plasma for aliquot 1 was collected from Subject 81 at the 960.0 hr time point during Period II.
3. In addition, the firm reported numerous blood sampling time deviations which were all insignificant. At least one blood sampling time for each subject deviated from its scheduled time. The sampling time deviation ranged from 1 hour early to 8 hours and 18 minutes late. The extremely early and late sampling time deviations occurred at the scheduled time points of 48-hours post-dose or later.

Reviewer's Comments: The adverse events and protocol deviations reported by the firm do not have an impact on the outcome or the integrity of the fasting BE study.

c. Bioanalytical Results

Table A1-4. Assay Quality Control – Within Study

Accuracy and Precision Summary: Quality Control Sample Analysis								
QC Conc. (ng/mL)	0.74		7.44			18.60		
Interday Accuracy (%)	104.05		103.23			103.17		
Interday Precision (%CV)	9.09		4.56			3.49		
Accuracy and Precision Summary: Calibration Curve								
Cal. Standards Conc. (ng/mL)	0.25	0.49	2.47	4.94	9.89	14.83	19.78	24.72
Interday Accuracy (%)	100.00	100.00	101.21	100.61	99.09	99.33	98.99	101.33
Interday Precision (%CV)	8.00	6.12	4.00	3.82	3.47	3.33	2.76	4.07
Linearity Range (range of R² values) :						0.9984		

Is the study assay quality controls acceptable: Yes

Table A1-5. Chromatograms Provided in the Bioanalytical Report of during the Fasting Bioequivalence Study No. 3034

Any interfering peaks in chromatograms?	Not significant
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially
Chromatograms provided for Subject Nos.	01, 02, 03, 04, 05, 06, 07, 08, 09, 11, 12, 14, 16, 17, 18, and 19

Are the chromatograms acceptable? Yes

Table A1-6. Standard Operation Procedures used for Analysis of Methylprednisolone Plasma Samples in the Fasting Bioequivalence Study No. 3034

Firm Provided SOPs		Yes
SOP No.	Effective Date of SOP	SOP Title
(b) (4)8908_02	October 17, 2005	Determination of Methylprednisolone in Human NaF/Potassium Oxalate Plasma over a Concentration Range of 0.25 to 25 ng/mL using High-Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection
(b) (4)153.07	December 11, 2002	Preparation, Identification and Acceptance Criteria of Stock Solutions, Calibration Standards, Quality Control Samples and Reference Solutions
(b) (4)156_09	September 23, 2005	Sample Reassays and Reporting of Final Concentrations
(b) (4)157.04	April 28, 2003	Application of Chromatographic Methods to Routine Drug Analysis
(b) (4)167_05	June 30, 2005	Chromatographic Acceptance Criteria and Verification of Chromatograms
Were the SOPs appropriate?		Yes
Number of Samples Re-assayed		124
Number of Pharmacokinetic Repeats		0
Were the reassays consistent with objective criteria in SOP?		Yes
Impact of Repeat-assays on the study outcome		None

Reviewer's Comments: (on analytical study)

1. The firm did provide acceptable standard operating procedures for determining methylprednisolone concentrations in human plasma samples.
2. As stated earlier, the firm did not provide adequate long-term stability for methylprednisolone in human plasma. The long-term stability data submitted by the firm only covered 5 days which is unacceptable. The long-term stability data should cover the timeframe from the first blood sample collection until the last plasma sample is analyzed (February 19, 2005 to November 30, 2005 – 285 days).
3. Also, the firm should clearly identify the seven (7) methylprednisolone plasma samples that were reassayed for the analytical reason coded (G), sample reanalyzed to obtain confirming value. In the analytical report, Table 3: Repeat Analysis Results for Methylprednisolone in Human Plasma (Study LBI) the reviewer could only identify four (4) plasma samples as being reassayed for that particular reason.

4. One-hundred and twenty-four (124) methylprednisolone plasma samples were reassayed for analytical reasons and one-hundred and twenty (120) of the recalculated values were used in pharmacokinetic (PK) and statistical analyses.
5. The firm did not report any samples as being reassayed for PK reasons.
6. The interday accuracy and precision values for the quality control samples and calibration curve standards during the fasting BE study are acceptable.
7. The firm provided *serial* chromatograms for 20% of the subjects enrolled in the fasting BE study. Chromatograms were provided for subject Nos. 01 to 09, 11, 12, 14, and 16-19.

Conclusion: The bioanalytical method is incomplete.

d. Pharmacokinetic and Statistical Results

Table A1-7. Arithmetic Mean of Pharmacokinetic Parameters (SAS Output)

Mean plasma methylprednisolone concentrations are presented in [Table A1-10](#) and [Figure A1-1](#)

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC _T (ng * hr/mL)	3115.53	25.22	3222.05	25.32	0.97
AUC _I (ng * hr/mL)	3395.25	26.40	3777.42	57.55	0.90
C _{MAX} (ng/mL)	14.37	239.97	13.67	175.79	1.05
T _{MAX} (h)	28.04	258.72	46.84	236.17	0.60
KE (h ⁻¹)	0.00	48.98	0.00	55.43	1.02
THALF (h)	276.40	54.79	295.86	60.26	0.93

Table A1-8. Geometric Mean and 90% Confidence Intervals (SAS Output)

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERC12	UPPERC12
LAUC _T	3026.89	3135.30	0.97	93.81	99.35
LAUC _I	3287.26	3529.85	0.93	88.78	97.69
LC _{MAX}	10.27	10.06	1.02	89.83	116.13

Table A1-9. Additional Study Information: Total SD and within-subject error (root MSE): (SAS Output)

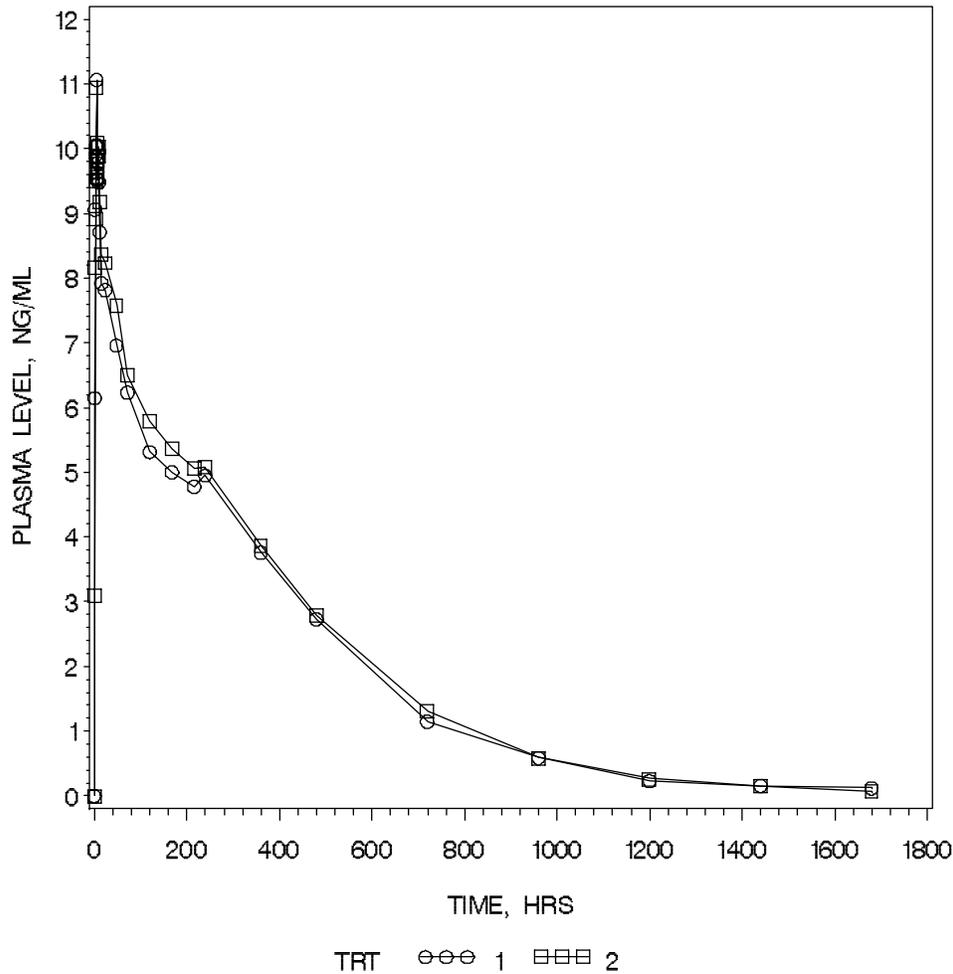
Root mean square error, LAUC _T	0.106
Root mean square error, LAUC _∞	0.170
Root mean square error, LC _{max}	0.472
Mean ratio AUC _T /AUC _∞	Test = 0.92 Reference: = 0.91
Range of values, ratio AUC _T /AUC _∞	Test = 0.67 – 0.99 Reference: = 0.28 – 0.99

Table A1-10. Mean Plasma Methylprednisolone Concentrations for Sandoz's Methylprednisolone Acetate Injectable Suspension, USP, 80 mg/mL (Multiple Dose Vials) and Pharmacia's Depo-Medrol® (methylprednisolone acetate) Injectable Suspension – Single-Dose Fasting BE Study (N = 75)

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0.00	.	0.00	.	.
1	6.15	439.29	3.10	46.91	1.98
2	9.06	386.05	8.17	296.67	1.11
3	9.89	289.12	8.92	237.54	1.11
4	10.04	220.79	9.50	162.96	1.06
5	11.06	167.99	10.94	129.46	1.01
6	10.06	112.03	10.10	93.79	1.00
6.5	9.63	93.81	9.57	84.48	1.01
7	9.54	70.36	9.81	74.28	0.97
7.5	9.69	66.52	9.86	65.78	0.98
8	9.78	59.33	9.81	59.47	1.00
8.5	9.52	53.40	10.03	58.81	0.95
10	9.47	38.65	9.89	54.60	0.96
12	8.71	36.89	9.17	51.30	0.95
16	7.92	38.66	8.36	50.02	0.95
24	7.82	36.83	8.24	45.57	0.95
48	6.96	35.11	7.59	44.07	0.92
72	6.23	37.88	6.50	43.08	0.96
120	5.31	31.80	5.79	42.29	0.92
168	5.00	36.29	5.37	38.73	0.93
216	4.78	38.06	5.07	44.03	0.94
240	4.95	46.80	5.08	45.90	0.97
360	3.76	40.54	3.86	59.85	0.97
480	2.73	53.33	2.80	61.65	0.98
720	1.15	69.41	1.30	59.70	0.88
960	0.59	97.54	0.59	98.00	1.00
1200	0.23	166.95	0.26	155.03	0.88
1440	0.16	206.18	0.16	186.96	1.02
1680	0.12	286.39	0.07	297.91	1.69

Figure A1-1. Mean Plasma Methylprednisolone Concentrations for Sandoz's Methylprednisolone Acetate Injectable Suspension, USP, 80 mg/mL (Multiple Dose Vials) and Pharmacia's Depo-Medrol® (methylprednisolone acetate) Injectable Suspension – Single-Dose Fasting BE Study (N = 75)

PLASMA METHYLPREDNISOLONE LEVELS
METHYLPREDNISOLONE ACETATE INJECTABLE SUSPENSION USP (MULTIDOSE FORMULATION), 80 MG/ML
UNDER FASTED CONDITIONS
DOSE= 1 X 80 MG/ML



1= TEST(SANDOZ) 2= REF(PHARMACIA AND UPJOHN)

Reviewer's Comments: (on pharmacokinetic analysis)

1. The firm assayed the plasma methylprednisolone concentrations. The firm provided the plasma profiles for methylprednisolone.
2. Initially, the firm used the group-by-treatment effect in its statistical model. Based on their analysis, the firm concluded it was not significant. Therefore, the firm calculated the pharmacokinetic (PK) parameters ($AUC_{0-\infty}$, AUC_T , C_{max} , T_{max} , $T_{1/2}$, and K_{el}) for methylprednisolone using the data from the seventy-five (75) subjects that completed the fasting study. Statistical analysis was performed on the PK parameters for methylprednisolone using the GLM procedure of SAS with a 90% confidence interval.
3. The firm reported that they did not calculate the elimination rate constant for subject Nos. 25, 61, 68, 73, and 76 because the statistical firm, (b) (4), was not able to properly estimate K_{el} as per its SOP. The firm did not include these subjects in analyses involving $AUC_{0-\infty}$, $AUC_{t/\infty}$, $T_{1/2}$, and K_{el} .
4. The reviewer also calculated the PK parameters using the group-by-treatment effect in the statistical model. Based on the reviewer's statistical analysis of the data, there was no significant group by treatment effect ($p > 0.1$). Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval.
5. The reviewer used the data from the seventy-five (75) normal, healthy, non-smoking, male and female subjects that completed the fasting bioequivalence (BE) study to conduct BE statistical evaluations.

Conclusion: The single-dose fasting bioequivalence study is incomplete.

ANDA #: 40-719

Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

B. Formulation Data**Table B-1. Formulation for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) manufactured by Sabex[®] Inc. for Sandoz Canada Inc.¹**

Ingredients	Amount per unit		Amount (%)	
	40 mg / mL	80 mg / mL	40 mg / mL	80 mg / mL
Methylprednisolone Acetate	40.0 mg	80.0 mg		(b) (4)
Polyethylene Glycol 3350	29.1 mg	28.2 mg		
Polysorbate 80	1.94 mg	1.88 mg		
Monobasic Sodium Phosphate (b) (4)	6.8 mg (b) (4)	6.59 mg (b) (4)		
Dibasic Sodium Phosphate (b) (4)	1.42 mg (b) (4)	1.37 mg (b) (4)		
Benzyl Alcohol	9.16 mg	8.88 mg		
Sodium Chloride	(b) (4)	(b) (4)		
Hydrochloric Acid	To adjust pH	To adjust pH	--	--
Sodium Hydroxide	To adjust pH	To adjust pH	--	--
				(b) (4)
Total	1 mL	1 mL	100%	100%

¹ The table is provided by the firm.

Table B-2. Formulation for Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, 40 mg/mL and 80 mg/mL by Pharmacia & Upjohn^{1,2}

Ingredients	Depo-Medrol [®] (methylprednisolone acetate) Injectable Suspension by Pharmacia & Upjohn	
	Amount Per Unit	
	40 mg/mL	80 mg/mL
Active Ingredient		
Methylprednisolone Acetate	40.0 mg	80.0 mg
Inactive Ingredients		
Polyethylene Glycol 3350	29.1 mg	28.2 mg
Polysorbate 80	1.94 mg	1.88 mg
Monobasic Sodium Phosphate (b) (4)	6.8 mg	6.59 mg
Dibasic Sodium Phosphate (b) (4)	1.42 mg	1.37 mg
Benzyl Alcohol	9.16 mg	8.88 mg
Sodium Chloride	To adjust tonicity	To adjust tonicity
Hydrochloric Acid	To adjust pH	To adjust pH
Sodium Hydroxide	To adjust pH	To adjust pH
		(b) (4)
Total	1 mL	1 mL

¹ The table is provided by the reviewer.

Reviewer's Comments: The formulations for Sandoz's test product, Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) are identical to the formulations for the RLD product, Depo-Medrol[®] (methylprednisolone

² 1. COMIS. Last accessed: January 17, 2007.

ANDA #: 40-719

Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

acetate) Injectable Suspension, 40 mg/mL and 80 mg/mL. The test and RLD products contain the same active and inactive ingredients in the same concentration.

C. In Vitro Dissolution Testing

The dissolution review is located in DFS.

Comparative *In Vitro* Dissolution Testing

Table C-1. A description of the FDA-Recommended Dissolution Method and the Firm's Proposed Dissolution Method

	FDA-Recommended Method	Firm's Proposed Method
Source of Method	FDA	Firm
Medium	Water	05% Sodium Docedyl Sulfate (SDS)
Volume (mL)	900	--
Temperature (°C)	37°C ± 0.5°C	37°C ± 0.5°C
Apparatus	II (Paddle)	IV (flow-through cell) – open system
Rotational Speed (rpm)	50 rpm	--
Sampling Times (min)	15, 20, 30, 45, 60, 120, and 240	5, 30, and 90
Specification	--	Not specified
Dosage Units	12	12

Table C-2. In Vitro Dissolution Testing Profile for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) using the FDA-recommended method¹

Sampling Time (min)	Test Product, Strength 40 mg/mL Lot No. 1090401			Reference Product, Strength 40 mg/mL		
	Mean	%CV	Range	Mean	%CV	Range
15	0			Not submitted		
20	0					
30	0					
45	0					
60	0					
120	0					
240	1.6					

Sampling Time (min)	Test Product, Strength 80 mg/mL Lot No. 1810312			Reference Product, Strength 80 mg/mL Lot No. 59JMX		
	Mean	%CV	Range	Mean	%CV	Range
15	0			0		
20	0			0		
30	1.4			0		
45	0			0		
60	0			0		
120	0			0		
240	0			0		

¹ The table is taken from the initial dissolution review located in DFS.

Table C-3. In Vitro Dissolution Testing Profile for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) using the Firm's Proposed Dissolution Method¹

Sampling Time (min)	Test Product, Strength 40 mg/mL Lot No. 1090401			Reference Product, Strength 40 mg/mL		
	Mean	%CV	Range	Mean	%CV	Range
5	8.7	4.7	(b) (4)	Not submitted		
30	60.0	7.4				
90	87.7	2.8				

Sampling Time (min)	Test Product, Strength 80 mg/mL Lot No. 1810312			Reference Product, Strength 80 mg/mL		
	Mean	%CV	Range	Mean	%CV	Range
5	10.4	14.2	(b) (4)	Not submitted		
30	58.4	13.9				
90	97.0	2.3				

ANDA #: 40-719

Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

D. Consult Reviews

None.

ANDA #: 40-719

Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

E. Attachments

None.

Following this page, 47 pages withheld in full - (b)(4) SAS data

ANDA #: 40-719

Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

Sandoz

Review of a Bioequivalence Study and a Waiver Request

Reviewer: April C. Braddy, Ph.D.

G. Additional Attachments

None.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 40-719

APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP,
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please provide sufficient long-term stability for methylprednisolone in human plasma. The long-term stability data should cover the timeframe from the first blood sample collection until the last plasma sample is analyzed (February 19, 2005 to November 30, 2005, i.e., 285 days). You stated in your bioanalytical report, "*Additional long-term stability of methylprednisolone in human plasma NaF/potassium oxalate plasma under storage conditions at a nominal temperature of -80°C will be evaluated in the near future.*"
2. Please clearly identify the seven (7) methylprednisolone plasma samples that were reassayed for the analytical reason coded (G), sample reanalyzed to obtain confirming value. In the analytical report, Table 3: Repeat Analysis Results for Methylprednisolone in Human Plasma (Study LBI) we could only identify four (4) plasma samples as being reassayed for the reasons coded as: **9** (Code D, G, G), **10** (Code D, G) and **12** (Code G, G) The table below contains the information for the four (4) samples identified.

Subject No.	Period	Time, hr	Reason
35	1	8.5	9
35	1	12	10
63	2	PRE	12
71	2	PRE	12

3. Please provide the potency data for the reference-listed drug product, Depo-Medrol® (methylprednisolone acetate) Injectable Suspension, Lot No. 59JMX by Pharmacia & Upjohn.
4. As per the deficiency letter faxed on November 20, 2006, please provide all of the requested additional method development data, for your *in vitro* dissolution method as outlined below:
 - a. The dissolution data based on your proposed method appear to be discriminating and promising. However, no data for the RLD product, Depo-Medrol® (methylprednisolone acetate aqueous suspension), were submitted for comparison with the test product.
 - b. In addition, you have not shown that an exhaustive experiment with the conventional USP apparatus II (paddle)

has been conducted for the drug product. No method development data comparing USP apparatus II (paddle) and IV (flow-through-cell) were submitted. You stated that "*the USP Apparatus II (Paddle) and rotational speed (50 rpm), recommended by FDA, didn't provide adequate mixing to disperse the drug product in the Medium and to get a homogeneous mixture for sampling.*" Please submit dissolution data based on USP apparatus II (paddle), using the same medium chosen for USP apparatus IV (flow-through cell), i.e., 0.55% SDS, to support the above statement.

- c. Please also provide method development data showing that dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration.
- d. Since solubility of the drug in dissolution medium is the primary focus of the method development, and filtration of dissolution samples is used to separate the soluble from insoluble particles, please justify the selection of filter size (0.45 μm nylon filter) used for the sample preparation. It was also noted that you used 0.45 μm nylon filter for your proposed method, but used 0.2 μm nylon filter for the FDA-recommended method in sample preparation. Please explain the reason for selecting different filters for the two methods, and provide additional dissolution data based on your proposed dissolution method but with 0.2 μm nylon filter used in sample preparation.

The dissolution data of the RLD product, the comparative dissolution data based on both USP apparatus, the dissolution medium optimization data and the filtration optimization data are essential in assisting the DBE to determine whether your proposed method is indeed the most appropriate method for the drug product.

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

CC: 40-719

BIOEQUIVALENCY – Incomplete

Submission date: March 08, 2006

(Refuse to File, Original submission date: December 19, 2005)

1. **FASTING STUDY (STF)**

Strength: 80 mg/mL

Outcome: IC

Clinical Site: Biovail Contract Research

460 Comstock Road, Toronto, ON, M11 4S4 Canada

689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada

Analytical Site:

(b) (4)

A large grey rectangular redaction box covers the majority of the text following the 'Analytical Site:' label. The only visible text within this redacted area is '(b) (4)'.

2. **WAIVER INJECTABLE (WAI)**

Strength: 40 mg/mL

Outcome: IC

Outcome Decisions: IC - Incomplete

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

/s/

April Braddy
1/22/2007 02:53:38 PM
BIOPHARMACEUTICS

Moheb H. Makary
1/22/2007 02:55:48 PM
BIOPHARMACEUTICS

Dale Conner
1/22/2007 03:24:32 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-719
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP (Multiple Dose Vials)
Strength(s)	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz Canada Inc.
Address	145 Jules Leger Street, Boucherville (QC) Canada, J4B 7K8
Applicant's Point of Contact	<u>U.S. Authorized Agent</u> Ms. Beth Brannan Sandoz Inc., 2555 W. Midway Blvd., P.O. Box 446, Broomfield, CO 80038-0446
Contact's Telephone Number	303-438-4237
Contact's Fax Number	303-438-4600
Original Submission Date(s)	March 08, 2006 - Refuse to File (Original Submission date: December 19, 2005)
Submission Date(s) of Amendment(s) Under Review	March 09, 2007
Reviewer	April C. Braddy, Ph.D.

Review of an Amendment

Executive Summary

The firm, Sandoz Canada, Inc., submitted an amendment on March 09, 2007 in response to the deficiency letters received on November 20, 2006 and January 23, 2007 from the Division of Bioequivalence (DBE). The deficiency letters are for the firm's proposed drug product, Methylprednisolone Acetate Injectable Suspension, USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials). The firm's application had a few bioanalytical deficiencies and incomplete dissolution testing. The firm's responses to the bioanalytical deficiencies are acceptable, but the *in vitro* dissolution testing is still incomplete. The additional method development data submitted by the firm provided supportive evidence that its proposed dissolution method using USP Apparatus IV (Flow-through-cell) and water containing 0.55% SDS as the medium is the most appropriate for its test product. However, the firm does not propose any specifications for its Methyl Methylprednisolone Acetate Injectable Suspension, USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials). Therefore, based on the submitted data, the DBE recommends the following specifications:

	40 mg/mL:	80 mg/mL
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

The firm should acknowledge and accept the DBE-recommended dissolution specifications for its test product using its proposed dissolution method.

The application is **incomplete**.

Background

On March 08, 2006, the firm's application for Methylprednisolone Acetate Injectable Suspension, USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) was accepted for filing. In its application, the firm submitted a single-dose, *in vivo* bioequivalence (BE) study under fasting conditions comparing its test product, Methylprednisolone Acetate Injectable Suspension, USP, 80 mg/mL, Lot No. 1810312 to the reference-listed drug (RLD) product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, 80 mg/mL, Lot No. 59JMX, by Pharmacia & Upjohn (NDA #11-757). Seventy-five (75) healthy, adult male and female subjects completed the fasting BE study No. 3034 and their data was used in BE statistical evaluations. The firm also requested a waiver of *in vivo* bioequivalence study requirements for its lower strength, 40 mg/mL Methylprednisolone Acetate Injectable Suspension, USP. The BE reviewer determined the fasting BE study was incomplete due to the following reasons: (1) the firm did not provide adequate long-term stability data of methylprednisolone in human plasma, (2) the firm did not clearly identify methylprednisolone plasma samples that were reanalyzed for the analytical reason coded (G), sample reanalyzed to obtain confirming value, and (3) the firm did not provide the potency (assay) data for the RLD product, Lot No. 59JMX.¹

In addition, the BE dissolution reviewer had previously determined that the firm's comparative *in vitro* dissolution was incomplete.² The firm conducted dissolution testing using the FDA-recommended dissolution method (based on the ANDA #40-557)³. It should be noted that the FDA-recommended method is not available in the public or internal database. Based on the results obtained with the FDA-recommended method, the firm developed and conducted dissolution testing using its own proposed method, see [Table 1](#). The BE dissolution reviewer determined the firm did not provide 'adequate method development data to show that: (1) the conventional USP apparatus II (paddle) is not suitable, (2) dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration, and (3) the filter size (0.45 µm nylon filter) used for sample preparation is justified for the drug product.' Therefore, in a deficiency letter dated November 20, 2006, the Division of Bioequivalence (DBE) requested the firm provide additional method development data to assist the DBE in determining that its proposed method is indeed the most appropriate for the drug product.

¹ Division of System Files v 2.0. ANDA #40-719. Bioequivalence Review. N 040719 N 000 19-Dec-2005.

² Division of System Files v 2.0. ANDA #40-719. Bioequivalence Dissolution Review. N 040719 N 000 19-Dec-2005.

³ ANDA #40-557. Bioequivalence Review. Submission date: November 10, 2004
<V:\FIRMSNZ\SICOR\LTRS&REV\40557a1104.doc>.

Table 1. The FDA-Recommended Method and Sandoz's Proposed Dissolution Method for Methylprednisolone Acetate Injectable Suspension, USP

	FDA-Recommended Method	Firm's Proposed Method
Source of Method	FDA	Firm
Medium	Water	0.55% Sodium Dodecyl Sulfate (SDS)
Volume (mL)	900	--
Temperature (°C)	37°C ± 0.5°C	37°C ± 0.5°C
Apparatus	II (Paddle)	IV (flow-through cell) – open system
Rotational Speed (rpm)	50 rpm	--
Sampling Times (min)	15, 20, 30, 45, 60, 120, and 240	5, 30, and 90
Specifications	For the 40mg strength: 1 hr: (b) (4)% 4 hrs: NLT (b) (4)% For the 80 mg strength: 1 hr: (b) (4)% 4 hrs: NLT (b) (4)%	Not specified
Dosage Units	12	12

DBE Deficiency Comment No. 01

1. *Please provide sufficient long-term stability for methylprednisolone in human plasma. The long-term stability data should cover the timeframe from the first blood sample collection until the last plasma sample is analyzed (February 19, 2005 to November 30, 2005, i.e., 285 days). You stated in your bioanalytical report, "Additional long-term stability of methylprednisolone in human plasma NaF/potassium oxalate plasma under storage conditions at a nominal temperature of -80°C will be evaluated in the near future."*

Firm's Response: Please note that the long-term stability of methylprednisolone in human NAF/potassium oxalate plasma at -80°C was done for 491 days. This period covers the period from the first blood draw to last sample analysis. By the same occasion, the stability of the internal standard in solution was done to cover the period of analysis of study samples. The internal standard was found to be stable for 492 days at -80°C.

The final report has been amended to include these stability data. Please refer to the **FINAL REPORT AMENDMENT I & FINAL STUDY REPORT (AMENDED DOCUMENTS)** documents enclosed in **ATTACHMENT 2**.

Reviewer's Comment: The firm's response to deficiency comment No. 01 is acceptable. The long-term stability data of methylprednisolone is sufficient. It covers the timeframe from the first blood sample collection until the last plasma sample analysis in the fasting BE Study No. 3034 (285 days, February 19, 2005 to November 30, 2005).

DBE Deficiency Comment No. 02

2. *Please clearly identify the seven (7) methylprednisolone plasma samples that were reassayed for the analytical reason coded (G), sample reanalyzed to obtain confirming value. In the analytical report, Table 3: Repeat Analysis Results for Methylprednisolone in Human Plasma (Study LBI) we could only identify four (4) plasma samples as being reassayed for the reasons coded as: 9 (Code D, G, G), 10 (Code D, G) and 12 (Code G, G) The table below contains the information for the four (4) samples identified.*

<i>Subject No.</i>	<i>Period</i>	<i>Time, hr</i>	<i>Reason</i>
35	1	8.5	9
35	1	12	10
63	2	PRE	12
71	2	PRE	12

Firm's Response: Table 4 (Summary of Study Sample Reassays) gives the number of repeats done for each code. In this table, the number of repeats done for code G is 7. These repeats were done for four study samples since three study samples were reanalyzed twice for code G (resulting in 7 codes G) as presented below⁴:

Subject No.	Period	Time, hr	Reason	Number of repeats for code G
35	1	8.5	9	2
35	1	12	10	1
63	2	PRE	12	2
71	2	PRE	12	2

Reviewer's Comment: The firm's response to deficiency comment No. 02 is acceptable. The firm clarified the methylprednisolone plasma samples reanalyzed for the analytical reason (coded G), samples reanalyzed to obtain confirming value, see the table provided above. The recalculated values for the plasma samples of subject No. 35 were used in pharmacokinetic (PK) and statistical analyses. The recalculated values for the

⁴ Replicate of the firm's table provided in the current amendment, March 09, 2007 on pp. 4.

plasma samples of Subject No. 63 and 71 were reported as 0.0, since the repeat values obtained for these samples concentrations were still below the limit of quantitation. The analytical reason (coded G) provided by the firm for reanalysis of the methylprednisolone plasma samples is acceptable and in accordance with the bioanalytical facility's standard operating procedures (SOPs).

DBE Deficiency Comment No. 03

3. *Please provide the potency data for the reference-listed drug product, Depo-Medrol® (methylprednisolone acetate) Injectable Suspension, Lot No. 59JMX by Pharmacia & Upjohn.*

Firm's Response: Please find enclosed in Attachment 2, the certificate of analysis for the RLD product, Depo-Medrol® (methylprednisolone) Injectable Suspension, Lot No. 59JMX by Pharmacia & Upjohn.

A result for the potency was 81.4 mg/mL corresponding to 101.75% of the nominal.

Reviewer's Comment: The firm's response to deficiency comment No. 03 is acceptable. The firm provided the potency (101.75%) for the RLD product, Depo-Medrol® (methylprednisolone) Injectable Suspension, 80 mg/mL, Lot No. 59JMX by Pharmacia & Upjohn.

DBE Deficiency Comment No. 04

4. *As per the deficiency letter faxed on November 20, 2006, please provide all of the requested additional method development data, for your in vitro dissolution method as outlined below:*
 - a. *The dissolution data based on your proposed method appear to be discriminating and promising. However, no data for the RLD product, Depo-Medrol® (methylprednisolone acetate aqueous suspension), were submitted for comparison with the test product.*
 - b. *In addition, you have not shown that an exhaustive experiment with the conventional USP apparatus II (paddle) has been conducted for the drug product. No method development data comparing USP apparatus II (paddle) and IV (flow-through-cell) were submitted. You stated that "the USP Apparatus II (Paddle) and rotational speed (50 rpm), recommended by FDA, didn't provide adequate mixing to disperse the drug product in the Medium and to get a homogeneous mixture for sampling." Please submit dissolution data based on USP apparatus II (paddle), using the same medium chosen for USP apparatus IV (flow-through cell), i.e., 0.55% SDS, to support the above statement.*
 - c. *Please also provide method development data showing that dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration.*

- d. *Since solubility of the drug in dissolution medium is the primary focus of the method development, and filtration of dissolution samples is used to separate the soluble from insoluble particles, please justify the selection of filter size (0.45 μm nylon filter) used for the sample preparation. It was also noted that you used 0.45 μm nylon filter for your proposed method, but used 0.2 μm nylon filter for the FDA-recommended method in sample preparation. Please explain the reason for selecting different filters for the two methods, and provide additional dissolution data based on your proposed dissolution method but with 0.2 μm nylon filter used in sample preparation.*

The dissolution data of the RLD product, the comparative dissolution data based on both USP apparatus, the dissolution medium optimization data and the filtration optimization data are essential in assisting the DBE to determine whether your proposed method is indeed the most appropriate method for the drug product.

Firm's responses:

- a. Please find enclosed in **ATTACHMENT 3**, the report ADSR-06-43, the dissolution development method studies for the RLD product, Depo-Medrol[®] and Sandoz Product of Methylprednisolone Acetate Injectable Suspension, USP for both strengths.

Summaries of raw data are presented in appendices at the end of the report.

- b. In-vitro dissolution testing was performed for Methylprednisolone Acetate Injectable Suspension, USP 40 mg/mL & 80 mg/mL for both Sandoz product and the RLD product, Depo-Medrol[®]. USP apparatus II (paddle) was used for the study using the same medium chosen for USP apparatus IV (flow-through-cell), i.e., 0.55% SDS.

The results demonstrate clearly that no dissolution profile was obtained in all cases since the dissolution occurred too fast (below 5 minutes). Thus, it was concluded that the USP Apparatus II (Paddle) with a rotational speed of 50 rpm whether using water or 0.55% as media is not appropriate to establish the dissolution profile of Methylprednisolone Acetate Injectable Suspension, USP. Please refer to report **ADSR-07-02(02)** enclosed in **ATTACHMENT 4** for details of the study.

Summaries of raw data are presented in appendices at the end of the report.

- c. Optimization of the dissolution profiles was performed during the method development.

Dodecyl Sodium Sulfate (SDS) was selected among three different surfactants based on the cumulative dissolution percentage after ninety (90) minutes of Methylprednisolone Acetate Injectable Suspension, USP.

Four (4) different concentrations were studied ranging from 0.3% up to 0.55%. The concentration of 0.55% was found to be the optimal medium concentration based on the profiles of the release rate and the overall of reproducibility (RSD).

Please refer to **section 3.3: Selection and concentration study of dissolution medium** of the report **ADSR-06-50** enclosed in **ATTACHMENT 5**, for further details for the dissolution profiles method development.

- d. During the dissolution profiles method development for USP apparatus IV (flow-through-cell), the effect of pore size filters was studied.

The results show no significant difference between 0.2µm and 0.45µm Nylon filters was observed for the in-vitro dissolution testing. However, the reproducibility of the 0.45 µm Nylon filter was better.

Please refer to **section 3.4.2: Selection of filter for dissolution samples** in the report **ADSR-06-50** enclosed in **ATTACHMENT 5**.

During the in-vitro dissolution testing study for Methylprednisolone Acetate Injectable Suspension using USP apparatus II (Paddle), the impact of the use of 0.2 µm and 0.45 µm filters was evaluated as well. Data show that the pore sizes of filter does not affect the dissolution results when using 0.55% SDS as a dissolution medium.

Please refer to **section 5.2: 0.55% as dissolution medium** in the report **ADSR-07-02(02)** enclosed in **ATTACHMENT 4**.

Reviewer's Comments:

1. The firm's responses to deficiency comment No. 04 is acceptable.
 - a. The firm provided the dissolution data for both strengths of the RLD product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, 40 mg/mL (Lot No. 37MPJ), and 80 mg/mL (Lot No. 59JMX) using its proposed dissolution method. The dissolution testing data for the RLD product confirmed that the firm's proposed method is discriminating. The report is located in **ATTACHMENT 3** of the amendment. The raw data is also located in the [Additional Attachments](#) section of this review.

The F2 value of the lower strength, 40 mg/mL Methylprednisolone Acetate Injectable Suspension compared to the test/biostrength meets the acceptance criteria of $50 \leq F_2 \leq 100$ (50.67). The F2 value for the lower strength test and RLD product, 40 mg/mL also meets the acceptance criteria of $50 \leq F_2 \leq 100$ (62.06), but the F2 value for the higher strength test and RLD product, 80 mg/mL does not meet the acceptance criteria of $50 \leq F_2 \leq 100$ (39.12). Based on the data, the formulation of the firm's lower strength, 40 mg/mL is similar to the firm's higher strength, 80 mg/mL Methylprednisolone Acetate Injectable Suspension.

F2 metric, biostudy strength compared to other strength(s)			
Biostudy Strength	Waiver Strength	F2 metric for test	F2 metric for RLD
80 mg/mL (Lot No. 10810312)	40 mg/mL (Lot No. 1090401)	50.67	39.12

- b. The firm provided data showing that they have put extensive effort into the development of a dissolution method using the conventional USP Apparatus II (paddle). The firm provided evidence supporting that when using the FDA-recommended with the dissolution media, water, no dissolution profile was obtained for methylprednisolone acetate, see [Table 2](#). The firm also provided evidence showing when they modified the FDA-recommended dissolution by changing the dissolution media to 0.55% SDS, the release rate of methylprednisolone acetate was rapid (over 90% dissolved in 5 minutes). The data is provided in [Table 3](#). The data submitted supports the firm's claim that the current USP Apparatus II (Paddle) was "*not relevant*" for its Methylprednisolone Acetate Injectable Suspension (Multiple Dose Vials).
- c. The data also showed that the dissolution profiles were optimized with the selected dissolution medium, Dodecyl Sodium Sulfate (SDS) as well as the selection of the concentration. The firm conducted dissolution testing using the same conditions for the following three (3) different surfactants at the same concentration of 0.55%: (1) anionic surfactant, SDS, (2) cationic surfactant, Cetyltrimethylammonium bromide (CTAB), and (3) Nonionic, Polysorbate 80 (Tween 80). The most optimal dissolution profile of Methylprednisolone Acetate Injection Suspension USP, 80 mg/mL, Lot No. 1810312 was obtained using the surfactant, SDS. Over 90% of methylprednisolone acetate in the injection suspension was dissolved in 90 minutes with 0.55% SDS. Whereas, only 30% and 70% of methylprednisolone acetate was dissolved after 90 minutes for Tween and CTAB, respectively. The data and illustrations are provided below in [Table 4 and Figures 1 and 2](#).

Next the firm studied the effects of the SDS concentration on the dissolution and release rate of methylprednisolone acetate in Methylprednisolone Acetate Injection Suspension USP, 80 mg/mL, Lot No. 1810312. The four (4) different concentrations used were 0.3%, 0.4%, 0.5%, and 0.55%. After the allotted time of 90 minutes passed, it appeared that as the concentration of SDS increased the cumulative dissolution of methylprednisolone acetate increased. The sample time points were 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 minutes. The firm reported that the results for the 0.5% and 0.55% SDS were comparable; however, the reproducibility of the 0.55% SDS was much better than 0.5% SDS. The data and illustrations are provided below in [Table 5 and Figures 3 and 4](#).

- d. The firm provided additional dissolution testing data using its proposed dissolution method with 0.2 μm and 0.45 μm nylon filters being used in

sample preparation see [Table 6](#). Based on the data submitted by the firm pore size does not have an effect on the dissolution results. The firm determined that based on the reproducibility (%RSD) of the 0.45 μm nylon filter was better than the 0.2 μm . The reviewer agrees with the firm's assessment.

Table 2. Data using water as medium for dissolution testing with apparatus II (Paddle)⁵

Sampling Time Point (minutes)	Dissolution percentage for Sandoz Canada products		Dissolution percentage for Pharmacia Depo-Medrol product
	40 mg/mL lot 1090401	80 mg/mL lot 1810312	80 mg/mL lot 59JMX
15	0	0	0
20	0	0	0
30	0	1.4	0
45	0	0	0
60	0	0	0
120	0	0	0
240	1.6	0	0

⁵ Tables 2 and 3 are located in Attachment 4, Report No. ADSR-07-02(02). Study of an In-vitro dissolution method for the apparatus USP II (Paddle), pp. 6-9 (121-24).

Table 3. Data using 0.55% SDS as dissolution medium for dissolution testing with apparatus USP 2 (Paddle)⁵

Sampling Time Point (min)	Dissolution percentage for Sandoz Canada products				Dissolution percentage for Pharmacia Depo-Medrol products					
	40 mg/mL lot 1090401		80 mg/mL lot 1810312		40 mg/mL lot 62PTA		80 mg/mL lot 59JMX		80 mg/mL lot 36PPR	
	0.2 µm Nylon filter (%)	0.45µm Nylon filter (%)	0.2 µm Nylon filter (%)	0.45µm Nylon filter (%)	0.2 µm Nylon filter (%)	0.45µm Nylon filter (%)	0.2 µm Nylon filter (%)	0.45µm Nylon filter (%)	0.2 µm Nylon filter (%)	0.45µm Nylon filter (%)
5	(b) (4)									
10										
15										
20										
30										
40										
45										
50										
60										
70										
80										
90										
120										
240										
Average (%)	93.5	94.0	95.6	96.1	97.9	98.6	98.2	99.3	96.9	97.3
RSD (%)	0.4	0.6	0.7	0.6	0.7	0.5	1.0	1.0	0.6	0.4

Table 4. Dissolution Study of three (3) classification of surfactants⁶

Time (minutes)	0.55% Tween 80 (Nonionic surfactant)		0.55% CTAB (Cationic surfactant)		0.55% SDS (Anionic surfactant)	
	Cumulative Dissolution (%)	RSD (%)	Cumulative Dissolution (%)	RSD (%)	Cumulative Dissolution (%)	RSD (%)
5	(b) (4)	5.8	(b) (4)	40.3	(b) (4)	4.2
10	(b) (4)	4.4	(b) (4)	39.4	(b) (4)	5.4
15	(b) (4)	4.2	(b) (4)	36.7	(b) (4)	6.9
20	(b) (4)	5.8	(b) (4)	33.7	(b) (4)	6.7
30	(b) (4)	10.0	(b) (4)	28.0	(b) (4)	3.4
40	(b) (4)	13.2	(b) (4)	23.5	(b) (4)	3.8
50	(b) (4)	15.3	(b) (4)	20.6	(b) (4)	4.5
60	(b) (4)	16.4	(b) (4)	17.4	(b) (4)	4.9
70	(b) (4)	16.5	(b) (4)	15.0	(b) (4)	5.2
80	(b) (4)	16.2	(b) (4)	12.3	(b) (4)	5.4
90	(b) (4)	14.7	(b) (4)	10.5	(b) (4)	5.6

⁶ Table 4 and Figures 1 and 2 are located in Attachment 5, Report No. ADSR-06-50: Development of an In-vitro dissolution method for the apparatus USP 4 (Flow-Through-Cell), pp. 6-8 (138-40).

Figure 1

In-vitro dissolution profiles of three (3) different classifications of surfactants.⁶

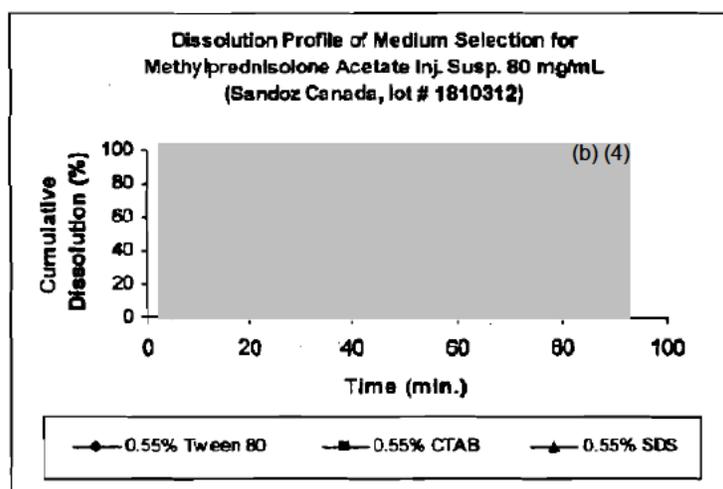


Figure 2

In-vitro dissolution release rates of three (3) different classifications of surfactants.⁶

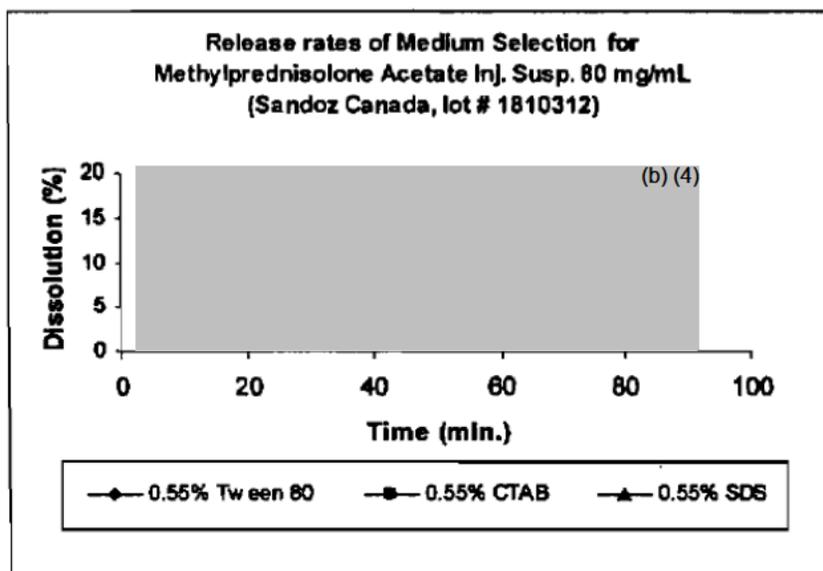
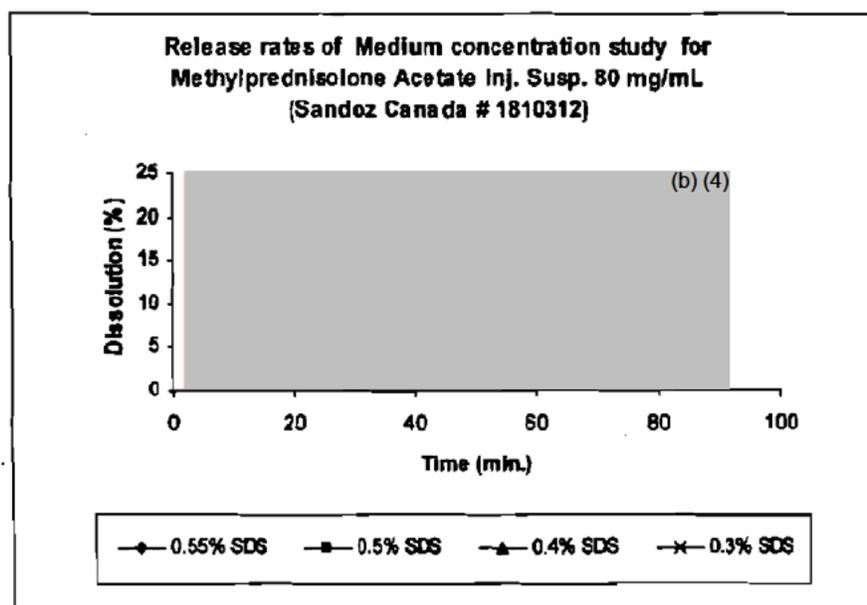


Table 5. Dissolution Study of four (4) different concentrations of SDS⁷

Time (min.)	0.3% SDS		0.4% SDS		0.5% SDS		0.55% SDS	
	Cumulative Dissolution (%)	RSD (%)	Cumulative Dissolution (%)	RSD (%)	Cumulative Dissolution (%)	RSD (%)	Cumulative Dissolution (%)	RSD (%)
5	(b) (4)	0.0	(b) (4)	2.3	(b) (4)	15.1	(b) (4)	4.2
10		0.9		3.8		10.5		5.4
15		1.7		5.3		10.8		6.9
20		1.7		5.1		10.0		6.7
30		3.8		1.5		2.5		3.4
40		4.3		2.3		1.1		3.8
50		3.4		0.9		1.3		4.5
60		2.5		0.5		1.2		4.9
70		1.8		0.5		1.1		5.2
80		1.2		0.6		1.1		5.4
90		0.5		0.8		1.1		5.6

Figure 3

In-vitro dissolution profiles of four (4) different concentrations of SDS.⁷



⁷ Table 5 and Figures 3 and 4 are located in Attachment 5, Report No. ADSR-06-50: Development of an In-vitro dissolution method for the apparatus USP 4 (Flow-Through-Cell), pp. 9-10 (141-2).

Figure 4

In-vitro dissolution release rates of four (4) different concentrations of SDS.⁷

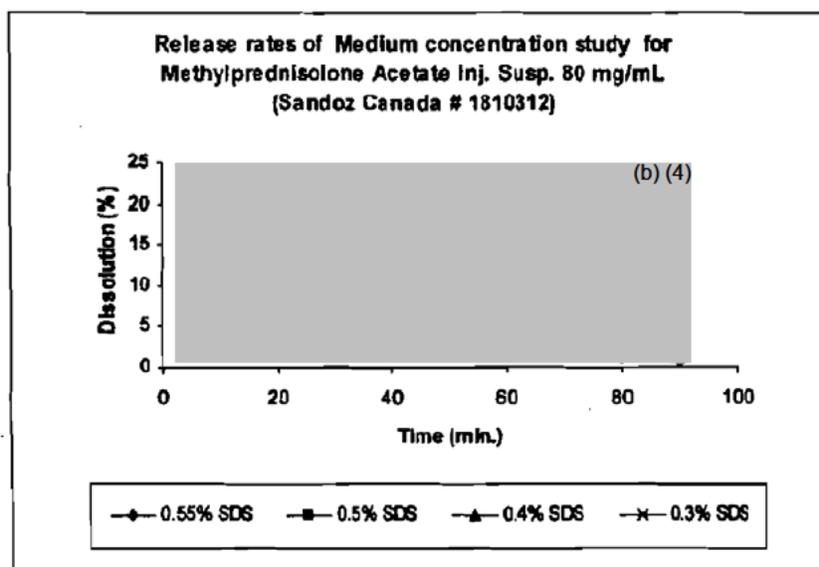


Table 6. Study of pore sizes of Nylon Filter for dissolution sample solutions⁸

Time (min.)	Lot 1810312 for 80 mg/mL				Lot 1090401 for 40 mg/mL			
	Acrodisc 0.2 µm Nylon filter		Acrodisc 0.45 µm Nylon filter		Acrodisc 0.2 µm Nylon filter		Acrodisc 0.45 µm Nylon filter	
	Cumulative dissolution (%)	RSD (%)	Cumulative dissolution (%)	RSD (%)	Cumulative dissolution (%)	RSD (%)	Cumulative dissolution (%)	RSD (%)
5	(b) (4)	15.3	(b) (4)	4.2	(b) (4)	2.0	(b) (4)	1.7
10		14.3		5.4		2.3		1.5
15		14.0		6.9		3.6		1.9
20		13.3		6.7		5.5		2.3
30		12.5		3.4		6.8		3.0
40		8.3		3.8		5.5		3.3
50		5.3		4.5		5.1		3.4
60		3.6		4.9		4.8		3.1
70		2.7		5.2		4.5		3.1
80		2.1		5.4		4.2		3.1
90		1.8		5.6		3.9		3.1
f1 Limit: 0-15	f1 = 4.8				f1 = 2.0			
f2 Limit: 50-100	f2 = 67.4				f2 = 88.5			

⁸ Table 6 is located in Attachment 5, Report No. ADSR-06-50: Development of an In-vitro dissolution method for the apparatus USP 4 (Flow-Through-Cell), pp. 13 (145).

2. The firm's proposed dissolution method using the non-conventional Apparatus IV (Flow-through-cell) is the most appropriate for the firm's Methylprednisolone Acetate Injection Suspension drug product. The experimental conditions for dissolution testing are provided in [Table 7](#). However, the firm does not propose any specifications for its Methyl Methylprednisolone Acetate Injectable Suspension, USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials). Therefore, based on the submitted data, the DBE recommends the following specifications:

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

Table 7. Experimental conditions for the Dissolution Testing⁹

Parameters	Conditions
Apparatus	USP 4 (Flow-through cell)
System Mode	Open loop system
Medium	0.55% SDS
Dissolution Flow Rate	8 mL/min
Temperature	37°C
Type of Cell	22.6 mm
Glass Beads	1 mm
Glass Beads Loading	2S (equivalent to 13 g)
Type of filter	2 filters GF/C (Whatman), glass microfiber, 1.2 µm, 25 mm diameter
Sample load	1 mL for 80 mg/mL 2 mL for 40 mg/mL
Split ratio	10%
Size of sample tubes	65 mL
Sampling Time	5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 mins

3. The application is still incomplete.

⁹ Contents of Table 7 are located in Attachment 5, Report No. ADSR-06-50: Development of an In-vitro dissolution method for the apparatus USP 4 (Flow-Through-Cell), pp. 22 (154). Sampling time has been added by the reviewer.

Deficiency Comment

The firm's dissolution method for its proposed drug product, Methylprednisolone Acetate Injectable Suspensions, 40 mg/mL and 80 mg/mL (Multiple Dose Vials), using the non-conventional Apparatus IV (Flow-through cell), is acceptable. However, the firm does not propose any specifications. Therefore, based on the submitted data, the Division of Bioequivalence (DBE) recommends the following specifications:

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

The firm should acknowledge and accept the DBE-recommended dissolution specifications for its proposed dissolution method.

Recommendation

The amendment provided by Sandoz Canada, Inc. for its proposed drug product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) is still incomplete for the reason provided in the deficiency comment.

The Division of Bioequivalence (DBE) requests the firm to acknowledge and accept the DBE-recommended dissolution specifications for its test product using its proposed dissolution method.

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

Additional Attachments

Report No. ADSR-06-43: Analytical Development Summary Report

Dissolution Profile of Pharmacia Depo-Medrol and Sandoz Canada products¹⁰

Table 2. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 40 mg/mL (Sandoz Canada, lot # 1090401)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												10.1	1.7
10	(b) (4)												26.5	1.5
15	(b) (4)												38.7	1.9
20	(b) (4)												46.9	2.3
30	(b) (4)												58.1	3.0
40	(b) (4)												66.1	3.3
50	(b) (4)												72.3	3.4
60	(b) (4)												77.0	3.1
70	(b) (4)												80.9	3.1
80	(b) (4)												83.8	3.1
90	(b) (4)												86.3	3.1

Table 3. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 80 mg/mL (Sandoz Canada, lot # 1810312)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												11.9	4.2
10	(b) (4)												28.0	5.4
15	(b) (4)												41.1	6.9
20	(b) (4)												52.1	6.7
30	(b) (4)												70.7	3.4
40	(b) (4)												81.5	3.8
50	(b) (4)												87.0	4.5
60	(b) (4)												90.0	4.9
70	(b) (4)												91.9	5.2
80	(b) (4)												93.0	5.4
90	(b) (4)												93.7	5.8

¹⁰ The dissolution profiles of Pharmacia Depo-Medrol and Sandoz Canada products are located in Attachment 3, Report ADSR-06-43: Dissolution profiles of Pharmacia Depo-Medrol and Sandoz Canada products, pp. 8-10 (100-2).

Table 4. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 40 mg/mL
(Pharmacia Depo-Medrol, lot # 37MPJ)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												10.2	8.1
10	(b) (4)												27.8	4.1
15	(b) (4)												41.2	3.1
20	(b) (4)												50.5	3.0
30	(b) (4)												64.3	4.0
40	(b) (4)												74.0	5.0
50	(b) (4)												80.6	5.3
60	(b) (4)												85.1	5.1
70	(b) (4)												88.2	4.7
80	(b) (4)												90.4	4.3
90	(b) (4)												92.0	4.0

Table 5. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 80 mg/mL
(Pharmacia Depo-Medrol, lot # 59JMX)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												8.6	25.3
10	(b) (4)												18.8	27.1
15	(b) (4)												22.9	25.2
20	(b) (4)												28.4	24.0
30	(b) (4)												41.6	20.8
40	(b) (4)												58.5	15.9
50	(b) (4)												70.2	13.0
60	(b) (4)												80.6	9.7
70	(b) (4)												88.1	6.7
80	(b) (4)												93.1	4.4
90	(b) (4)												96.2	2.9

Table 6. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 80 mg/mL
(Pharmacia Depo-Medrol, lot # 01KUJ)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD (%)
5	(b) (4)												5.8	38.1
10	(b) (4)												9.1	37.2
15	(b) (4)												12.8	36.2
20	(b) (4)												16.8	34.1
30	(b) (4)												27.8	28.9
40	(b) (4)												42.3	22.3
50	(b) (4)												57.0	18.0
60	(b) (4)												69.8	14.3
70	(b) (4)												79.8	10.8
80	(b) (4)												88.8	7.3
90	(b) (4)												91.8	5.0

BIOEQUIVALENCE DEFICIENCY

ANDA: 40-719

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP 40 mg/mL and 80 mg/mL
(Multiple-dose vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet and has identified the following deficiency:

We agree with your proposed dissolution method using Apparatus IV for your test products, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/ml (Multiple Dose Suspension). We propose the specifications shown below based on submitted dissolution results. Please provide acknowledgement and acceptance of the following dissolution method and specifications:

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	IV (Flow-through cell)	IV (Flow-through cell)
System (Open/Closed):	Open	Open
Medium:	0.55% SDS	0.55% SDS
Temperature:	37°C ± 0.5°C	37°C ± 0.5°C
Sampling Times:	15, 30, 60 and 90 mins	15, 30, 60 and 90 mins
Specifications:	30 min: (b) (4) % 90 min: NLT (b) (4)	30 min: (b) (4) % 90 min: NLT (b) (4)

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

A. Outcome Page

ANDA: 40-719

1.	Study Amendment	Strength(s):	40 mg/mL and 80 mg/mL
	(STA)	Outcome:	IC
	Submission Date(s)	March 09, 2007	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit
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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.**

/s/

April Braddy
3/27/2007 12:11:04 PM
BIOPHARMACEUTICS

Moheb H. Makary
3/27/2007 12:48:24 PM
BIOPHARMACEUTICS

Barbara Davit
3/27/2007 04:32:41 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-719
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials)
Strength(s)	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz Canada, Inc.
Address	145 Jules Leger Street, Boucherville (QC) Canada, J4B 7K8
Applicant's Point of Contact	Ms. Beth Brannan, U.S. Authorized Agent c/o Sandoz, Inc., 2555 W. Midway Blvd., P.O. Box 446, Broomfield, CO 80038
Contact's Telephone Number	303-438-4237
Contact's Fax Number	303-438-4600
Original Submission Date(s)	March 08, 2006 - Refuse to File (Original Submission date: December 19, 2005)
Submission Date(s) of Amendment(s) Under Review	June 01, 2007
Reviewer	April C. Braddy, Ph.D.
Study Number (s)	3034 (b) (4) Study No. 50529
Study Type (s)	Fasting (STF)
Strength (s)	80 mg/mL
Clinical Site	Biovail Contract Research
Clinical Site Address	460 Comstock Road, Toronto, ON, M1L 4S4 Canada 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada
Analytical Site	(b) (4)
Analytical Site Address	(b) (4)

Review of an Amendment

Executive Summary

In this amendment, the authorized US agent, Sandoz Inc., submitted a response for the firm, Sandoz Canada, Inc., to the deficiency letter received on April 05, 2007, from the Division of Bioequivalence (DBE). The firm's application is for Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials), 40 mg/mL and 80 mg/mL. The DBE requested the firm acknowledge and accept the DBE-recommended dissolution specifications for its proposed dissolution method using the non-conventional Apparatus IV (Flow-through cell) with an open system in 0.55% Sodium Dodecyl Sulfate @ 37°C ± 0.5°C. The DBE-recommended dissolution specifications for the firm's test product were as follows:

Initial DBE-Recommended Specifications (03/07)	For 40 mg/mL	For 80 mg/mL
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

The firm did not accept the DBE-recommended dissolution specifications. Instead, the firm has proposed the following specifications for its test product:

Firm's Proposed Specifications (06/07)	40 mg/mL	For 80 mg/mL
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

The firm based its proposed specifications on the *in vitro* dissolution testing data for its test product and the reference-listed drug (RLD) product, Depo-Medrol® (methylprednisolone acetate) Injectable Suspension by Pharmacia & UpJohn. However, the DBE recommends the dissolution specifications be based **only** on the dissolution testing data for the test product.

After further review of the submitted *in vitro* dissolution testing data for the firm's test product, the DBE-recommended dissolution specifications for the firm's proposed dissolution method are as follows:

Current DBE-Recommended Specifications (06/07)	40 mg/mL	For 80 mg/mL
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

Once again, the DBE requests the firm acknowledge and accept the DBE-recommended dissolution specifications for its test product using its proposed dissolution method. The application is **incomplete**.

Background¹

The firm has previously submitted two (2) amendments concerning the dissolution testing for its proposed drug product, Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials), 40 mg/mL and 80 mg/mL. The firm's most recent amendment was submitted on March 09, 2007. The DBE determined that the firm's proposed dissolution method using the non-conventional Apparatus IV (Flow-through cell) was acceptable. However, the firm did not propose any specifications for its test product.

¹ 1. Division of System Files v 2.0. ANDA #40-719. Bioequivalence Review. N 040719 N 000 19-Dec-2005 (N 040719 N 000 AC 08-Mar-2006 and N 000 AB 15-Sep-2006).
2. Division of System Files v 2.0. ANDA #40-719. Bioequivalence Dissolution Review. N 040719 N 000 19-Dec-2005 (N 000 AB 15-Sep-2006).
3. Division of System Files v 2.0. ANDA #40-719. Bioequivalence Review. N 040719 N 000 AB 09-Mar-2007.

Therefore, based on the submitted data the DBE recommended the following specifications:

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

The firm was asked to acknowledge and accept the DBE-recommended specifications for its test product. As stated before, the fasting BE study No. 3034 is acceptable. However, the wavier request of *in vivo* bioequivalence study requirements for the lower strength, 40 mg/mL Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials) is still pending acceptable dissolution testing.

DBE Deficiency Comment

We agree with your proposed dissolution method using Apparatus IV for your test products, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/ml (Multiple Dose Suspension). We propose the specifications shown below based on submitted dissolution results. Please provide acknowledgement and acceptance of the following dissolution method and specifications:

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	<i>IV (Flow-through cell)</i>	<i>IV (Flow-through cell)</i>
System (Open/Closed):	<i>Open</i>	<i>Open</i>
Medium:	<i>0.55% SDS</i>	<i>0.55% SDS</i>
Temperature:	<i>37°C ± 0.5 °C</i>	<i>37°C ± 0.5 °C</i>
Sampling Times:	<i>15, 30, 60 and 90 mins</i>	<i>15, 30, 60 and 90 mins</i>
Specifications:	30 min: (b) (4) % 90 min: NLT (b) (4) %	30 min: (b) (4) % 90 min: NLT (b) (4) %

Firm’s Response: We acknowledge Division of Bioequivalence’s proposed dissolution method and specifications. However, we would like to propose different limits for the specifications based on the dissolution results submitted in our previous amendment dated March 09, 2007, for both Sandoz products and the Reference listed drug product, Depo-Medrol®, Lots No. 37MPJ & 59JMX from Pharmacia & Upjohn. As *in vivo* bioequivalence studies have shown the Sandoz product to be bioequivalent to the RLD, the proposed dissolution specifications limits are representative of the observed data.

The tables below summarize the dissolution results previously filed and support the proposed specifications limits for both strengths. To further assist in this review, the 12 point dissolution results are provided in **Attachment 1** of this amendment.

Methylprednisolone Acetate Injectable Suspension, Multiple dose formulation: 40 mg

Time (min):	RLD Product 37MPJ EXP. 08 (12 unit Avg. %)	Sandoz Product Lot # 1090401 (12 unit Avg. %)	Range of Individual results observed	Proposed OGD Specification limits	Proposed Sandoz Specification limits
15	41.2	38.7	(b) (4) %	NA	NA
30	64.3	58.1	%	(b) (4) %	(b) (4) %
60	85.1	77.0	%	NA	NA
90	92.0	86.3	%	NLT (b) (4) %	NLT (b) (4)

Methylprednisolone Acetate Injectable Suspension, Multiple dose formulation: 80 mg

Time (min):	RLD Product 59JMX EXP. 08 (12 unit Avg. %)	Sandoz Product Lot for clinical study # 1810312 (12 unit Avg. %)	Range of Individual results observed	Proposed OGD Specification limits	Proposed Sandoz Specification limits
15	22.9	41.1	(b) (4)	NA	NA
30	41.6	70.7	%	(b) (4) %	(b) (4) %
60	80.6	90.0	%	NA	NA
90	96.2	93.7	%	NLT (b) (4)	NLT (b) (4)

For post approval stability protocol, dissolution testing is proposed for the annual timepoints (0, 12, 24, 36 months and expiry date if different) of Methylprednisolone stability batches.

Summary of proposed specification limits:

Strengths:	40 mg/mL	80 mg/mL
Specifications:	30 min: (b) (4) % 90 min: NLT (b) (4) %	30 min: (b) (4) % 90 min: NLT (b) (4) %

Please find enclosed in **Attachment 2**, the revised drug product specifications and post-approval stability protocols with the new limits.

The revised dissolution method DI-0002 with new dissolution parameters is also provided.

Reviewer's Comments:

1. The firm's response to the deficiency comment is incomplete.
 - a. The firm's proposed specifications for both strengths of its test product are based on the *in vitro* dissolution testing results for the test and RLD products. However, the dissolution specifications should be based solely on the dissolution testing data obtained for the firm's test product.
 - b. The minimum, maximum, range, mean, and %RSD values for the % dissolved of methylprednisolone acetate in Sandoz's Methylprednisolone

Acetate Injection Suspension USP, 40 mg/mL, Lot No. 1090401 and 80 mg/mL, Lot No. 1810312 in 30 minutes are provided in the table below.

% Dissolved methylprednisolone acetate @ 30 minutes		
	40 mg/mL Lot No. 1090401	80 mg/mL Lot No. 1810312
Minimum	(b) (4)	(b) (4)
Maximum		
Range		
Mean	58.1	70.7
%RSD	3.0	3.4

- c. The minimum, maximum, range, mean, and %RSD values for the % dissolved of methylprednisolone acetate for Sandoz's Methylprednisolone Acetate Injection Suspension USP, 40 mg/mL, Lot No. 1090401 and 80 mg/mL, Lot No. 1810312 in 90 minutes are provided in the table below.

% Dissolved methylprednisolone acetate @ 90 minutes		
	40 mg/mL Lot No. 1090401	80 mg/mL Lot No. 1810312
Minimum	(b) (4)	(b) (4)
Maximum		
Range		
Mean	86.3	93.7
%RSD	3.1	5.6

- d. After further review, of the submitted dissolution testing the DBE has modified the recommended specifications for the 40 mg/mL injectable suspension at 30 minutes from (b) (4)% to (b) (4)%. All other previously recommended specifications for both strengths of the firm's test product remain the same.
- e. The *in vitro* dissolution testing data for the test and RLD product are provided in the [Additional Attachments](#) section of the review.
2. The DBE-recommends the following specifications for the firm's proposed test product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL (Multiple Dose Vials):

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

The DBE requests the firm acknowledge and accept the DBE-recommended specifications for its proposed dissolution method.

Deficiency Comment

The firm's proposed dissolution specifications for its proposed drug product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL (Multiple Dose Vials), are not acceptable. Based on the submitted *in vitro* testing data for the firm's test product, the Division of Bioequivalence (DBE) recommends the following specifications:

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4) %	NLT (b) (4) %

The firm should acknowledge and accept the DBE-recommended dissolution specifications for its proposed dissolution method.

Recommendations

The amendment provided by Sandoz Canada, Inc. for its proposed drug product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) is still incomplete for the reason provided in the deficiency comment.

The Division of Bioequivalence (DBE) requests the firm to acknowledge and accept the DBE-recommended dissolution specifications for its test product using its proposed dissolution method.

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

Additional Attachments^{1,2}

Dissolution Profiles of Pharmacia Depo-Medrol and Sandoz Canada products

Table 2. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 40 mg/mL
(Sandoz Canada, lot # 1090401)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												10.1	1.7
10	(b) (4)												26.5	1.5
15	(b) (4)												38.7	1.9
20	(b) (4)												46.8	2.3
30	(b) (4)												58.1	3.0
40	(b) (4)												66.1	3.3
50	(b) (4)												72.3	3.4
60	(b) (4)												77.0	3.1
70	(b) (4)												80.9	3.1
80	(b) (4)												83.8	3.1
90	(b) (4)												86.3	3.1

Table 3. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 80 mg/mL
(Sandoz Canada, lot # 1810312)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												11.9	4.2
10	(b) (4)												28.0	5.4
15	(b) (4)												41.1	6.9
20	(b) (4)												52.1	6.7
30	(b) (4)												70.7	3.4
40	(b) (4)												81.5	3.8
50	(b) (4)												87.0	4.5
60	(b) (4)												90.0	4.9
70	(b) (4)												91.9	5.2
80	(b) (4)												93.0	5.4
90	(b) (4)												93.7	5.8

² The dissolution profiles of Pharmacia Depo-Medrol and Sandoz Canada products are located in Attachment 1 of the firm's amendment dated June 01, 2007.

Table 4. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 40 mg/mL
(Pharmacia Depo-Medrol, lot # 37MPJ)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												10.2	8.1
10	(b) (4)												27.8	4.1
15	(b) (4)												41.2	3.1
20	(b) (4)												50.5	3.0
30	(b) (4)												64.3	4.0
40	(b) (4)												74.0	5.0
50	(b) (4)												80.6	5.3
60	(b) (4)												85.1	5.1
70	(b) (4)												88.2	4.7
80	(b) (4)												90.4	4.3
90	(b) (4)												92.0	4.0

Table 5. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 80 mg/mL
(Pharmacia Depo-Medrol, lot # 59JMX)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												8.6	25.3
10	(b) (4)												18.8	27.1
15	(b) (4)												22.9	25.2
20	(b) (4)												28.4	24.0
30	(b) (4)												41.6	20.8
40	(b) (4)												58.5	15.9
50	(b) (4)												70.2	13.0
60	(b) (4)												80.6	9.7
70	(b) (4)												88.1	6.7
80	(b) (4)												93.1	4.4
90	(b) (4)												96.2	2.9

BIOEQUIVALENCE DEFICIENCY

ANDA: 40-719

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP 40 mg/mL and 80 mg/mL
(Multiple-dose vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet and identified the following deficiency:

As stated in the previous correspondence to you dated April 05, 2007, we agree with your proposed dissolution method using Apparatus IV for your test product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/ml (Multiple Dose Suspension). However, your proposed specifications are not acceptable. You based your proposed dissolution specifications on the dissolution data for your test product and the reference-listed drug (RLD) product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, by Pharmacia & UpJohn. The DBE-recommended specifications for your test product are based **only** on the *in vitro* dissolution testing results of your test product. Therefore, based on the submitted dissolution testing data please provide acknowledgement and acceptance of the following dissolution method and specifications:

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	IV (Flow-through cell)	IV (Flow-through cell)
System (Open/Closed):	Open	Open
Medium:	0.55% SDS	0.55% SDS
Temperature:	37°C ± 0.5°C	37°C ± 0.5°C
Sampling Times:	15, 30, 60 and 90 mins	15, 30, 60 and 90 mins
Specifications:	30 min: (b) (4) % 90 min: NLT (b) (4)	30 min: (b) (4) % 90 min: NLT (b) (4),

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

Outcome Page

ANDA: 40-719

1.	Study Amendment	Strength(s):	40 mg/mL and 80 mg/mL
	(STA)	Outcome:	IC
	Submission Date(s)	June 01, 2007	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit
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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.**

/s/

April Braddy
6/20/2007 08:02:36 AM
BIOPHARMACEUTICS

Moheb H. Makary
6/20/2007 08:04:53 AM
BIOPHARMACEUTICS

Barbara Davit
6/20/2007 04:55:22 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-719
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials)
Strength(s)	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz Canada, Inc.
Address	145 Jules Leger Street, Boucherville (QC) Canada, J4B 7K8
Applicant's Point of Contact	Ms. Beth Brannan, U.S. Authorized Agent c/o Sandoz, Inc., 2555 W. Midway Blvd., P.O. Box 446, Broomfield, CO 80038
Contact's Telephone Number	303-438-4237
Contact's Fax Number	303-438-4600
Original Submission Date(s)	March 08, 2006 (Refuse to File- December 19, 2005)
Submission Date(s) of Amendment(s) Under Review	August 29, 2007
Reviewer	April C. Braddy, Ph.D.
Study Number (s)	3034 (b) (4) Study No. 50529)
Study Type (s)	Fasting (STF)
Strength (s)	80 mg/mL
Clinical Site	Biovail Contract Research
Clinical Site Address	460 Comstock Road, Toronto, ON, M1L 4S4 Canada 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada
Analytical Site	(b) (4).
Analytical Site Address	(b) (4)
OUTCOME DECISION	INCOMPLETE

Review of an Amendment

Executive Summary

On August 29, 2007, the U.S. Authorized Agent, Sandoz Inc., submitted an amendment on the behalf of Sandoz Canada, Inc., for its application for Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials), 40 mg/mL and 80 mg/mL. The amendment is in response to the deficiency letter sent to the firm on June 27, 2007 from the Division of Bioequivalence (DBE). The DBE previously acknowledged and accepted the firm's proposed dissolution method. However, the DBE requested the firm acknowledge and accept the following dissolution specifications for its proposed dissolution method:

Current DBE-Recommended Specifications (06/07 & 10/07)	40 mg/mL	For 80 mg/mL
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NL (b) (4)	NLT (b) (4)

The firm did not comply with the DBE's request. For the 80 mg/mL strength of its test product, the firm proposed a specification of (b) (4) % at the 30 minute time point instead of the FDA-recommended (b) (4) %.

After additional review of the firm's rationale for requesting a change in the dissolution specification and the submitted dissolution testing data for both strengths of the firm's test product, the DBE-recommended dissolution specifications for the firm's proposed dissolution method remain unchanged. Alternatively, the firm may submit dissolution data for three (3) production lots, to determine if a revision of the dissolution specification is warranted.

Once again, the DBE requests the firm acknowledge and accept the DBE-recommended dissolution specifications for its test product using its proposed dissolution method.

The application is **incomplete** with a deficiency.

Background¹

On June 01, 2007, the firm submitted its third amendment concerning the dissolution testing for its proposed drug product, Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials), 40 mg/mL and 80 mg/mL. The amendment was in response to the deficiency letter sent to the firm on April 05, 2007. At that time the firm was asked to acknowledge and accept the DBE-recommended dissolution specifications for its proposed dissolution method using the non-conventional Apparatus IV (Flow-through cell) with an open system in 0.55% Sodium Dodecyl Sulfate @ 37°C ± 0.5°C.

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4)	NLT (b) (4)

The firm did not accept the DBE-recommended dissolution specifications. Instead, the firm proposed the following specifications for its test product:

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4)	NLT (b) (4)

Upon further review of the data the firm was asked to acknowledge and accept the following specifications:

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4)	NLT (b) (4)

As stated before, the fasting BE study No. 3034 is acceptable. However, the wavier request of *in vivo* bioequivalence study requirements for the lower strength, 40 mg/mL Methylprednisolone Acetate Injectable Suspension, USP (Multiple-Dose Vials) is still pending acceptable dissolution testing.

¹ 1. Division of System Files v 2.0. ANDA #40-719. Bioequivalence Review. N 040719 N 000 AB 01-Jun-2007.
2. Division of System Files v 2.0. ANDA #40-719. Bioequivalence Review. N 040719 N 000 AB 09-Mar-2007.
3. Division of System Files v 2.0. ANDA #40-719. Bioequivalence Review. N 040719 N 000 19-Dec-2005 (N 040719 N 000 AC 08-Mar-2006 and N 000 AB 15-Sep-2006)
4. Division of System Files v 2.0. ANDA #40-719. Bioequivalence Dissolution Review. N 040719 N 000 19-Dec-2005 (N 000 AB 15-Sep-2006).

Deficiency Comment

*As stated in the previous correspondence to you dated April 05, 2007, we agree with your proposed dissolution method using Apparatus IV for your test product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/ml (Multiple Dose Suspension). However, your proposed specifications are not acceptable. You based your proposed dissolution specifications on the dissolution data for your test product and the reference-listed drug (RLD) product, Depo-Medrol® (methylprednisolone acetate) Injectable Suspension, by Pharmacia & UpJohn. The DBE-recommended specifications for your test product are based **only** on the in vitro dissolution testing results of your test product. Therefore, based on the submitted dissolution testing data please provide acknowledgement and acceptance of the following dissolution method and specifications:*

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	<i>IV (Flow-through cell)</i>	<i>IV (Flow-through cell)</i>
System (Open/Closed):	<i>Open</i>	<i>Open</i>
Medium:	<i>0.55% SDS</i>	<i>0.55% SDS</i>
Temperature:	<i>37°C ± 0.5 °C</i>	<i>37°C ± 0.5 °C</i>
Sampling Times:	<i>15, 30, 60 and 90 mins</i>	<i>15, 30, 60 and 90 mins</i>
Specifications:	30 min: (b) (4) % 90 min: NLT (b) (4)	30 min: (b) (4) % 90 min: NLT (b) (4)

Firm's Response: The firm stated that the dissolution specifications proposed by the FDA were based on the results of the dissolution testing on one lot from each strength made with the same active pharmaceutical ingredient (API; lot 1810312 for the 80 mg/mL and lot 1090401 for the 40 mg/mL), (see [Additional Attachments](#) section). Sandoz agreed with the set specifications for its 40 mg/mL product according to the FDA recommendation. However, the firm did not agree with the set specifications for its 80 mg/mL product. Considering that the same formulation is used for both strengths, Sandoz preferred to set the 30 minute lower limit at (b) (4) % for the 80 mg/mL formulation which they believed is aligned with physiochemical characteristics of the active ingredient. In support of its proposal, the firm provided literature and referenced FDA guidelines to support its requested change.

1. The firm referenced the 1997 FDA Guidance for Industry, SUPAC_MR: Modified Release Solid Oral Dosage Forms (pg. 33), 'the average difference at any dissolution sampling time point should not be greater than 15% between the changed drug product and the biobatch or marketed batch (unchanged drug product) dissolution profiles.' The firm stated this statement suggested that ± 15% variation from the biobatch dissolution curve is considered acceptable variability.

2. Other supporting statements in the literature (US patents): included: “it is also normally agreed for controlled released drug product that a “uniform release rate” or “zero order release rate” is meant to be a variation that varies positively or negatively by no more than about 30%, preferably no more than about 25%, and most preferably no more than 10%, where the cumulative release is between about 25% to about 75%².

By “uniform rate of release” of “uniform release rate” is meant a rate of release of the active agent from a dosage form that does not vary positively or negatively by more than 30% from the mean rate of release of the active agent over a prolonged period of time, as determined in a USP Type 7 Interval Release Apparatus. Preferred uniform rates of release will vary by not more than 25% (positively or negatively) from the mean rate of release determined over a prolonged period of time³.

The firm stated that both statements suggested that positive and negative variability around the mean release of the active is an expected outcome.

3. The firm referenced the 1997 FDA Guidance to Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (pg 17), ‘In certain cases, reasonable deviations from the \pm 10% range can be accepted provided that the range at any time point does not exceed 25%.’

Therefore, the firm stated that considering the both formulations are similar (40 and 80 mg/mL), they believe that a (b) (4) allowance of the lower limit from the average obtained in the dissolution of the 80 mg/mL strength is expected and justifiable and would be adequate while still minimizing the possibility of releasing lots that would present difference in *in vivo* performance. Thus, the firm proposes a (b) (4)% limit at 30 minutes for the 80 mg/mL formulation.

Reviewer’s Comments:

1. Based on the submitted data, the firm’s proposed specification of (b) (4)% at the 30 minute time point, instead of the FDA-recommended specification of (b) (4)% for its Methylprednisolone Acetate Injectable Suspension, USP, 80 mg/mL is not acceptable.
2. The literature and reference to FDA guidance’s do not provide sufficient evidence to support the changing of the specifications for the 80 mg/mL strength of firm’s test product. The literature provided by the firm addressed inventions for novel means of delivering drug products.
3. Upon additional review of the submitted dissolution testing data, the previous recommended dissolution specifications remain unchanged.

² United States Patent 20030224051: Dosage forms and compositions for osmotic delivery of variable dosages of oxycodone

³ United States Patent 6342249: Controlled release liquid active ingredient formulation dosage forms

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4)	NLT (b) (4)

The DBE request the firm acknowledge and accept the DBE-recommended specifications for its proposed dissolution method.

Deficiency Comment

The firm’s proposed dissolution specifications for its proposed drug product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) are not acceptable. Based on the submitted *in vitro* testing data for the firm’s test product, the Division of Bioequivalence (DBE) recommends the following specifications:

	<u>40 mg/mL</u>	<u>For 80 mg/mL</u>
30 minutes	(b) (4) %	(b) (4) %
90 minutes	NLT (b) (4)	NLT (b) (4)

The firm should acknowledge and accept the DBE-recommended dissolution specifications for its proposed dissolution method.

Recommendations

The amendment provided by Sandoz Canada, Inc. for its proposed drug product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL (Multiple Dose Vials) is still incomplete for the reason provided in the deficiency comment.

The Division of Bioequivalence (DBE) requests the firm to acknowledge and accept the DBE-recommended dissolution specifications for its test product using its proposed dissolution method.

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

Dissolution Consult

(NOT TO BE RELEASED UNDER FOI)

From: Seo, Paul
Sent: Monday, October 15, 2007 12:59 PM
To: Braddy, April
Cc: Seo, Paul
Subject: RE: ANDA 40-719: Dissolution Consult

Follow Up Flag: Follow up
Flag Status: Orange

Hi April,

As discussed, my opinion regarding the matter remains unchanged. I believe that the firm's points in argument for changing the spec to (b) (4)% are reasonable, but do not warrant a change of the specs on their own. If the data supported the need for a (b) (4) spec of (b) (4)%, we could consider their request, however the data they submitted does not support this. Both their dissolution data and PK parameters are very good and do not warrant changing the specifications to the (b) (4)% for the 80 mg/mL strength.

This is just a recommendation, please consult with your TL as well.

Thanks,
Paul

From: Braddy, April
Sent: Monday, October 15, 2007 10:53 AM
To: Seo, Paul
Subject: ANDA 40-719: Dissolution Consult

Good morning Paul,

As per our conversation on this morning, Sandoz's proposed specification at 30 min of (b) (4) (b) (4) for its 80 mg/mL Methylprednisolone Acetate Injectable Suspension is not acceptable. Based on the submitted data, the firm is once again requested to acknowledge the FDA-recommended specification of NLT (b) (4)% in 30 minutes. Also, the rationale provided by the firm does not support changing the specification.

Do you concur with this assessment?

Thanks,

April

April C. Braddy, Ph.D.
Pharmacologist
FDA/CDER/OPS/OGD/DBE
PH 240-276-8794
FAX 240-276-8766
April.Braddy@fda.hhs.gov

Additional Attachments^{1,4}

Dissolution Profiles of Pharmacia Depo-Medrol and Sandoz Canada products

Table 2. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 40 mg/mL
(Sandoz Canada, lot # 1090401)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												10.1	1.7
10	(b) (4)												26.5	1.5
15	(b) (4)												38.7	1.9
20	(b) (4)												46.8	2.3
30	(b) (4)												58.1	3.0
40	(b) (4)												66.1	3.3
50	(b) (4)												72.3	3.4
60	(b) (4)												77.0	3.1
70	(b) (4)												80.9	3.1
80	(b) (4)												83.9	3.1
90	(b) (4)												86.3	3.1

Table 3. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 80 mg/mL
(Sandoz Canada, lot # 1810312)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												11.9	4.2
10	(b) (4)												28.0	5.4
15	(b) (4)												41.1	6.9
20	(b) (4)												52.1	6.7
30	(b) (4)												70.7	3.4
40	(b) (4)												81.5	3.8
50	(b) (4)												87.0	4.5
60	(b) (4)												90.0	4.9
70	(b) (4)												91.9	5.2
80	(b) (4)												93.0	5.4
90	(b) (4)												93.7	5.8

⁴ The dissolution profiles of Pharmacia Depo-Medrol and Sandoz Canada products are located in Attachment 1 of the firm's amendment dated June 01, 2007.

Table 4. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 40 mg/mL
(Pharmacia Depo-Medrol, lot # 37MPJ)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												10.2	8.1
10	(b) (4)												27.8	4.1
15	(b) (4)												41.2	3.1
20	(b) (4)												50.5	3.0
30	(b) (4)												64.3	4.0
40	(b) (4)												74.0	5.0
50	(b) (4)												80.6	5.3
60	(b) (4)												85.1	5.1
70	(b) (4)												88.2	4.7
80	(b) (4)												90.4	4.3
90	(b) (4)												92.0	4.0

Table 5. Dissolution profile for 12 units of Methylprednisolone Acetate Injectable Suspension 80 mg/mL
(Pharmacia Depo-Medrol, lot # 59JMX)

Time (min)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)	11 (%)	12 (%)	Aver. (%)	RSD. (%)
5	(b) (4)												8.6	25.3
10	(b) (4)												18.8	27.1
15	(b) (4)												22.9	25.2
20	(b) (4)												28.4	24.0
30	(b) (4)												41.6	20.8
40	(b) (4)												58.5	15.9
50	(b) (4)												70.2	13.0
60	(b) (4)												80.6	9.7
70	(b) (4)												88.1	6.7
80	(b) (4)												93.1	4.4
90	(b) (4)												96.2	2.9

BIOEQUIVALENCE DEFICIENCY

ANDA: 40-719

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP 40 mg/mL and 80 mg/mL
(Multiple-dose vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet and identified the following deficiency:

Your proposed specification of NLT (b)(4)% at 30 minutes for your Methylprednisolone Acetate Injectable Suspension USP, 80 mg/ml is not acceptable. The information you provided does not support changing the specification at this particular time point. Upon additional review of the dissolution testing data you submitted, please provide acknowledgement and acceptance of the following dissolution method and specifications:

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	IV (Flow-through cell)	IV (Flow-through cell)
System (Open/Closed):	Open	Open
Medium:	0.55% SDS	0.55% SDS
Temperature:	37°C ± 0.5°C	37°C ± 0.5°C
Sampling Times:	15, 30, 60 and 90 mins	15, 30, 60 and 90 mins
Specifications:	30 min: (b)(4)% 90 min: NLT (b)(4)	30 min: (b)(4)% 90 min: NLT (b)(4)

Alternatively, you may submit dissolution data for three (3) production lots, to determine if a revision of the dissolution specification is warranted.

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

Outcome Page

ANDA: 40-719

*Completed Assignment for 040719 ID: 659***Reviewer:** Braddy, April**Date Completed:****Verifier:****Date Verified:****Division:** Division of Bioequivalence**Description:**

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
659	8/29/2007	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

April Braddy
10/29/2007 02:11:06 PM
BIOPHARMACEUTICS

Moheb H. Makary
10/29/2007 02:57:40 PM
BIOPHARMACEUTICS

Barbara Davit
10/30/2007 04:09:43 PM
BIOPHARMACEUTICS

**DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT
REVIEW**

ANDA No.	40-719
Drug Product Name	Methylprednisolone Acetate Injectable Suspension USP
Strength	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz Inc.
Submission Date	November 28, 2007
Reviewer	Beth Fabian-Fritsch, R.Ph.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing and the application is approvable.

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

/s/

Beth Fabian-Fritsch
12/28/2007 11:27:47 AM
BIOPHARMACEUTICS

Lizzie Sanchez
1/2/2008 12:59:10 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-719

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

June 19, 2008

ANDA: 40-719

Drug Product Name

Proprietary: N/A

Non-proprietary: Methylprednisolone Acetate Injectable Suspension,
USP (multi-dose)

Drug Product Classification: N/A

Review Number: #1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
December 19, 2005	December 21, 2005	N/A	March 20, 2008
December 10, 2007*	December 11, 2007	N/A	March 20, 2008

*Gratuitous Amendment

Submission History (for amendments only) – None

Applicant/Sponsor

Name: Sandoz Canada Inc.

Address: 145 Jules Leger Street
Boucherville, (QC)
Canada J4B 7K8

Representative: Beth Brennan
c/o Sandoz Inc.
2555 W. Midway Blvd., P. O. Box 446
Broomfield, Colorado 80038

Telephone: 303-438-4237

Name of Reviewer: George K. Arhin, 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 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:** Sterile injectable solution, supplied as 40 mg/ml and 80 mg/ml strengths in fill volumes of (b) (4) (multi-dose), given by IM.
- 5. METHOD(S) OF STERILIZATION:** (b) (4)
- 6. PHARMACOLOGICAL CATEGORY:** Steroidal anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection.
- B. SUPPORTING/RELATED DOCUMENTS:** ANDA 40-794 - Sandoz Canada Inc. Single-dose form of the drug product which is (b) (4) (b) (4) was reviewed by the same Microbiology Reviewer (G. Arhin). Portions of the validation data and sterility assurance information of ANDA 40-719 and 40-794 are similar.
- C. REMARKS:** None

filename: 40-719.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 are provided in the "Product Quality Microbiology Assessment" 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

(b) (4)
 data are incomplete. Data are required for (b) (4)
 . Data for the (b) (4)
 are incomplete.

C. Assessment of Risk Due to Microbiology Deficiencies

The safety risk associated with the microbiology deficiencies is considered high.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / George K. Arhin, Ph.D.
 Microbiology Secondary Reviewer/Brenda Pillari, Ph.D.

C. CC Block

cc: Field Copy

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}

Brenda Pillari, Ph.D.
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
this page is the manifestation of the electronic signature.**

/s/

George K. Arhin
7/21/2008 12:21:15 PM
MICROBIOLOGIST

Kun Shen
7/21/2008 12:33:26 PM
MICROBIOLOGIST

Neal Sweeney
7/21/2008 01:06:15 PM
MICROBIOLOGIST

Brenda Pillari
7/21/2008 01:11:11 PM
MICROBIOLOGIST

Product Quality Microbiology Review

September 15, 2008

ANDA: 40-719

Drug Product Name

Proprietary: N/A

Non-proprietary: Methylprednisolone Acetate Injectable Suspension,
USP (multi-dose)

Drug Product Classification: N/A

Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
September 3, 2008	September 4, 2008	N/A	September 10, 2008

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Microbiology Review Date
December 19, 2005	1	July 19, 2008
December 10, 2007*	1	July 19, 2008

*Gratuitous Amendment

Applicant/Sponsor

Name: Sandoz Canada Inc.

Address: 145 Jules Leger Street
Boucherville, (QC), Canada J4B 7K8

Representative: Beth Brennan
c/o Sandoz Inc.
2555 W. Midway Blvd., P. O. Box 446
Broomfield, Colorado 80038

Telephone: 303-438-4237

Name of Reviewer: George K. Arhin, Ph.D.

Conclusion: The submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original Amendment

- 2. **SUBMISSION PROVIDES FOR:** Response to Agency’s Microbiology deficiency letter.

- 3. **MANUFACTURING SITE:**
 Sandoz Canada Inc.
 145 Jules-Leger Street
 Boucherville, (QC),
 Canada J4B 7K8

- 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injectable solution, supplied as 40 mg/ml and 80 mg/ml strengths in fill volumes of (b) (4) (multi-dose), given by IM.

- 5. **METHOD(S) OF STERILIZATION:** (b) (4)

- 6. **PHARMACOLOGICAL CATEGORY:** Steroidal anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection.

- B. **SUPPORTING/RELATED DOCUMENTS:** None

- C. **REMARKS:** The subject amendment provides a response to the microbiology deficiencies conveyed to the applicant in the Agency’s July 21, 2008 deficiency letter.

filename: 40-719a1.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

No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / George K. Arhin, Ph.D.

Microbiology Secondary Reviewer/Brenda Pillari, Ph.D.

C. CC Block

cc: Field Copy

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/s/

George K. Arhin
9/15/2008 03:03:31 PM
MICROBIOLOGIST

Mark Anderson
9/15/2008 04:12:41 PM
MICROBIOLOGIST

checked for correct linking

Neal Sweeney
9/16/2008 12:49:02 PM
MICROBIOLOGIST

Brenda Pillari
9/17/2008 03:49:36 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-719

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



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

DEC 19 2005

Handwritten notes:
205-10-10
Methylpred
27-10-2005
40719
N-000

Gary J. Buehler, RPh
Director, HFD-600
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: Original ANDA
Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)**

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 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA in CTD format consists of 21 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.

Given that this is a sterile injectable product, the sterility assurance data is included in Module 3 under the Regional Information section with an additional separate review copy of Sections 3.2.R.1-3 provided.

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 21 2005

CGD / CDER

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

Electronic Media: Immediately following this cover letter, Sandoz is providing one CD entitled "ELECTRONIC LABELING SUBMISSION" which includes the draft physician insert and draft container labels in pdf format. Additionally, we are providing one separate CD with in-vivo study data, dissolution data, and formulation data summarized as requested by the Division of Bioequivalence.

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

ANDA 40-719

Sandoz Inc.
U.S. Agent for: Sandoz Canada Inc.
Attention: Beth Brannan
2555 West Midway Boulevard
Broomfield, CO 80038

Dear Madam:

MAR 02 2006

Please refer to your abbreviated new drug application (ANDA) dated December 19, 2005, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b)(4) 10 mL vials and 80 mg/mL, 5 mL vials

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to provide complete comparative *in vitro* dissolution data for your products. A complete dissolution report should contain the individual data for twelve dosage units, including means, range and relative standard deviation (RSD) at each time point, a description of the methodology being used, and the lot numbers being tested.

You have failed to provide (b)(4) data as part of your manufacturing and processing instructions. (b)(4)

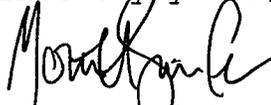
(b)(4)
This data is required to be finished and complete upon submission of the application to the office.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Christine Bina
Project Manager
(301) 827-5839

Sincerely yours,



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

ANDA 40-719

cc: DUP/Jackets

HFD-600/Division File

Field Copy

HFD-610/

HFD-92

Endorsement:

HFD-615/MShimer, Chief, RSB *M. Shimer* date *27 Feb 06*

HFD-615/CBina, CSO *Chantel M Bina* *02/27/06* date

Word Document V:\Firmsnz\sandoz\Itrs&rev\40719.rtf

F/T CMB 2/27/2006

ANDA Refuse to File!



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

505 (b)(4)
10/10/2006
AMENDMENT

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

N/A/C

MAR 08 2006

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Response to Refusal to File**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 2, 2006. The following is provided in response to this request:

FDA: *You have failed to provide complete comparative in vitro dissolution for your products. A complete dissolution report should contain the individual data for twelve dosage units, including means, range and relative standard deviation (RSD) at each time point, a description of the methodology being used, and the lot numbers being tested.*

Sandoz Response: Sandoz is providing complete 12 unit dissolution profiles of the Methylprednisolone Acetate Injectable Suspension Lots 1090401 (40 mg/mL) and 1810312 (80 mg/mL) including mean, range, and RSD at each time point. Additionally, a validation report for the dissolution, method DI-0002, and a validation report for the assay of the dissolution samples are enclosed in this submission. Please incorporate this information into section 3.2.P.5.3 Validation of Analytical Procedures.

FDA: *You have failed to provide (b) (4) data as part of your manufacturing and processing instructions. (b) (4)*

RECEIVED

MAR 09 2006

OGD / CDER

(b) (4) This data is required to be finished and complete upon submission of the application to the office.

Sandoz Response: Although the methylprednisolone acetate injectable suspension is

(b) (4)

in the original application for a more detailed description.

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

ANDA 40-719

Sandoz Inc.
U.S. Agent for: Sandoz Canada Inc.
Attention: Beth Brannan
2555 West Midway Boulevard
Broomfield, CO 80038

Dear Madam:

APR 13 2006

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

Reference is made to our "Refuse to Receive" letter dated March 2, 2006 and your amendment dated March 8, 2006.

NAME OF DRUG: Methylprednisolone Acetate Injectable
Suspension USP, 40 mg/mL (b)(4) 10 mL vials
and 80 mg/mL, 5 mL vials

DATE OF APPLICATION: December 19, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 9, 2006

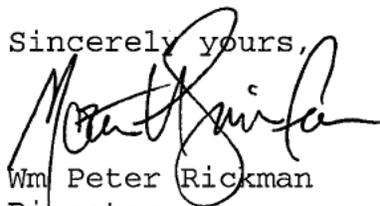
We will correspond with you further after we have had the opportunity to review the application.

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

Should you have questions concerning this application, contact:

Ben Danso
Project Manager
301-827-5763

Sincerely yours,



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

ANDA 40-719

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/
HFD-143/OIM/DRM

Endorsement:

HFD-615/M.Shimer, Chief, RSB

HFD-615/C.Bina, CSO



date 12 April 2006

M. Shimer 4/10/06 date

Word File V:\CDSNAS\OGDS11\FIRMSNZ\SANDOZ\LTRS&REV\40719.ACK.DOC

F/T

ANDA Acknowledgment Letter!



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

ORIG AMENDMENT

N/AF

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
(including electronic labeling)

JUN 1 2 2006

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Labeling**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 May 10, 2006. The following is provided in response to the FDA comments (*in italics*):

1. CONTAINER

A. Assure the text is at least 4 point type.

Sandoz Response: Sandoz has verified the text to be not less than 4.25 point type in FuturaEF-Book font.

B. Please provide the complete NDC number. If the NDC number is not available at the time you submit your final printed labels, please delete "NDC 0781-XXXX-XX". You can add the NDC number to your labels when it is available.

Sandoz Response: The correct NDC numbers have been added to all containers.

2. CARTON

A. Refer to CONTAINER comment 1.B.

Sandoz Response: The correct NDC numbers have been added to all cartons.

RECEIVED

JUN 1 3 2006

CGD / CDER

B. Please add the statement "Sterile".

Sandoz Response: The statement "Sterile" has been added to all cartons.

3. PACKAGE INSERT

A. *General Comment:* We encourage you to update the section heading to be in accord with 21 CFR 201.56(d)(1).

Sandoz Response: Sandoz has revised the package insert section headings to be in accord with 21 CFR 201.56(d)(1).

B. *TITLE:* We encourage you to add the phrase "Rx only" to a location just under the *TITLE* of the package insert.

Sandoz Response: Sandoz has revised the package insert to add the phrase "Rx only" just under the *TITLE* of the package insert.

C. DESCRIPTION

i. Please add a statement that the product is sterile [refer to 21 CFR 201.57(a)(iv)].

Sandoz Response: The statement "Sterile" has been added to the description section of the package insert.

ii. *First paragraph, last sentence:* delete the extra colon.

Sandoz Response: Sandoz has deleted the extra colon.

iii. *Second paragraph, first sentence:* "Methylprednisolone acetate injectable suspension is an..."

Sandoz Response: Sandoz has revised sentence to use the established name.

D. WARNINGS

i. *Multidose use of methylprednisolone acetate injectable suspension, USP from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. The preservative in methylprednisolone acetate injectable suspension, USP will prevent growth of most pathogenic organisms, but certain ones (e.g., Serratia marcescens) may remain viable. Particular care, such as use of disposable sterile syringes and needles is necessary.*

Sandoz Response: Sandoz has revised paragraph accordingly.

ii. *While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients*

who are on corticosteroids, especially in high doses, because of possible hazard of neurological complications and lack of antibody response.

Sandoz Response: Sandoz has revised paragraph accordingly.

E. DOSAGE AND ADMINISTRATION: *Please use the established name throughout this section.*

Sandoz Response: Sandoz has revised section to use the established name throughout.

F. HOW SUPPLIED: *Refer to CONTAINER comment 1.B.*

Sandoz Response: Sandoz has added the correct NDC numbers to all strengths and package sizes.

In addition to the above mentioned changes, the deficiency letter included an attached mocked-up copy of the package insert, including additional labeling recommendations. Sandoz has updated the package insert in accordance to the FDA recommendations.

The revised labeling is attached electronically. The package insert is provided in both pdf and word, the SPL will not be submitted at this time. Additionally, a side-by-side comparison of the proposed labeling with the last submission is provided electronically and in hard copy.

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/lah

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No. 40-719
Drug Product Name Methylprednisolone Acetate Injectable Suspension USP
Strength 40 mg/mL & 80 mg/mL
Applicant Name Sandoz Canada
Submission Date(s) December 19, 2005
First Generic No
Reviewer Hoainhon Nguyen
File Location V:\firmnsz\sandoz\ltrs&rev\40719d1205 .doc
Clinical Site Biovail Contract Research, Toronto Canada
Analytical Site (b) (4)

Table 1. Submission Content Checklist

Information		YES	NO	N/A	
Did the firm use the FDA-recommended dissolution method		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Did the firm use the USP dissolution method		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Did the firm use 12 units of both test and reference in dissolution testing		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Did the firm provide complete dissolution data (all raw data, range, mean, % CV)		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Did the firm conduct dissolution testing with its own proposed method		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is FDA method in the public dissolution database (on the web)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
		Plasma concentrations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
	Fed BE study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Other study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Are all eight electronic summary biotables present		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Are electronic summary biotables in pdf format		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

NOTE: The FDA-recommended method is as follows (ANDA 40-557):

USP Apparatus: II(paddle) @ 50 rpm
 Dissolution Medium: water
 Volume of Dissolution Medium: 900 mL



7/6/06

Hoainhon Nguyen
Team I
Division of Bioequivalence
Office of Generic Drugs



7/7/06

Moheb H. Makary
Team I
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA #40-719

V:\firmsnz\sandoz\ltrs&rev\40719d1205.doc

Endorsements: (Final with Dates)

HFD-650/HNguyen *WML*

HFD-650/MMakary *MM 7/7/06*

BIOEQUIVALENCE - INCOMPLETE Submission date: 12-19-05

[NOTE: The in vitro testing is incomplete. The fasting BE study and waiver request are pending review]

1. DISSOLUTION (Dissolution Data)

Strength: 40 mg/mL & 80 mg/mL

Outcome: IC

Outcome Decisions: IC – Acceptable or Incomplete

WinBio Comments: IC

BIOEQUIVALENCY AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



JUL 26 2006

APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Aaron Sigler 

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 19, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 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 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:

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

JUL 26 2006

ANDA: 40-719

APPLICANT: Sandoz Canada

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP, 40 mg/mL & 80 mg/mL

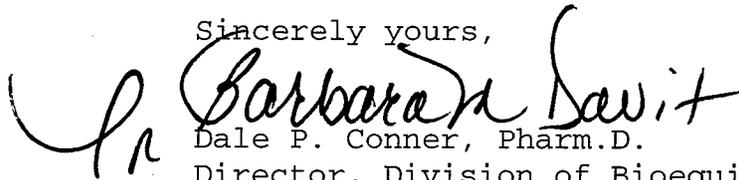
The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

Please conduct and submit dissolution testing on all strengths of the test and reference products (12 units each) using the following FDA-recommended method:

USP Apparatus:	II(paddle)@ 50 rpm
Dissolution Medium:	water(@ 37°C)
Volume of Dissolution Medium:	900 mL
Sampling Times:	15, 20, 30, 45, 60, 120 and 240 minutes

The results should be submitted in electronic CTD format, with individual data as well as mean, range and CV% data included.

Sincerely yours,



Dale P. Conner, Pharm.D.

Director, Division of Bioequivalence
Office of Generic Drugs

Center for Drug Evaluation and Research



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

**MINOR AMENDMENT
(including electronic labeling)**

AUG 3 2006

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Labeling**

Dear Mr. Buehler:

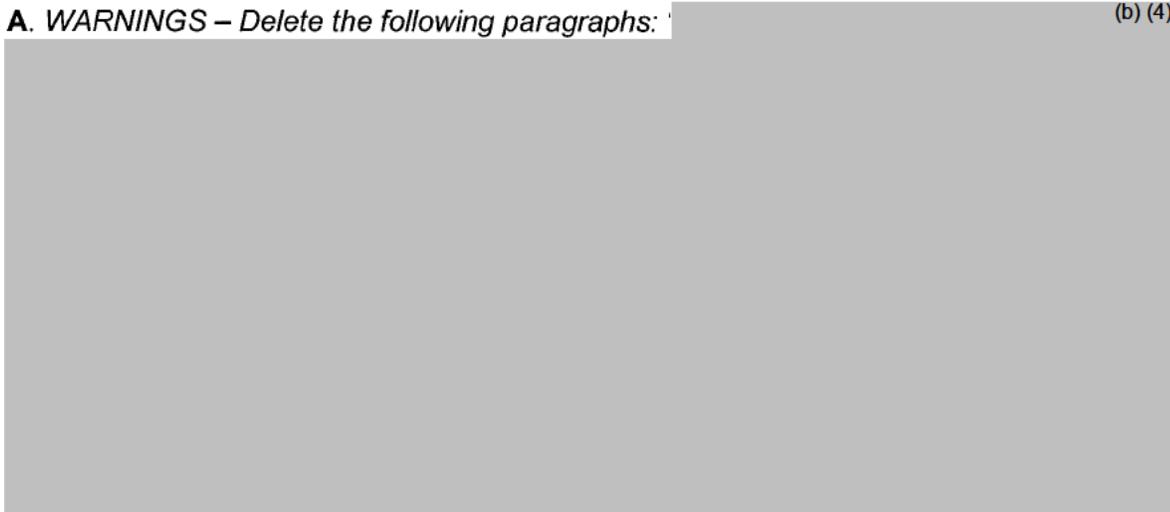
On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. is hereby submitting an amendment to unapproved Abbreviated New Drug Application 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the communication dated July 3, 2006. The following is provided in response to the FDA comments (*in italics*):

PACKAGE INSERT

A. WARNINGS – Delete the following paragraphs:

(b) (4)



AUG 04 2006

OGD/CDER

Sandoz Response: Sandoz has deleted the above mentioned paragraphs.

B. PRECAUTIONS, General Precautions – add the following as the seventh paragraph
“Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.”

Sandoz Response: Sandoz has added the sentence as the seventh paragraph in the PRECAUTIONS, General Precautions insert section.

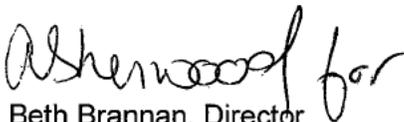
The revised labeling is attached electronically. The package insert is provided in both pdf and word, the SPL will not be submitted at this time. Additionally, a side-by-side comparison of the proposed labeling with the last submission is provided in electronic and hard copy.

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/lah

cc: Peggy Leary (Amendment)



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**

ORIG AMENDMENT

N/AB

SEP 15 2006

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Bioequivalence Amendment – Dissolution Data**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from the Division of Bioequivalence dated Jul 26, 2006. Sandoz Canada Inc. has provided their response on the pages following this cover letter.

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. Peggy Levy (CL)

RECEIVED

SEP 18 2006

OGD/CDER

MINOR AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Benjamin Danso

PROJECT MANAGER: (301) 827-5763

SEP 27 2006

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 19, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the 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. 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.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

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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.

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

[Handwritten signature]
9/27/06

Please provide a response to the labeling deficiencies.

3. The microbiology information you have provided is under review. After the review is complete, any deficiencies found will be communicated to you under separate cover.
4. The USP methods for the drug substance and the drug product are the regulatory methods and they will prevail in the event of any dispute.
5. Please provide all available long-term stability data to update your studies.
6. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

Sincerely yours,

for 
Rashmikant M. Patel, Ph.D.
Director

Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research



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

ORIG AMENDMENT

WAF

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)

OCT 04 2006

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Labeling**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 August 30, 2006. The following is provided in response to the FDA comments (*in italics*):

1. CONTAINER –[40 mg/mL (b) (4) 10mL MDV) and 80 mg/mL (5 mL MDV)]

Upon further review, we ask that you make the following revisions:

A. *Revise labels to visually differentiate the established name from "Methyltestosterone" with the use of "Tall Man" letters, such as "MethylPREDNISolone". Refer to [Http://www.fda.gov/cder/drug/mederrors/namediff.htm](http://www.fda.gov/cder/drug/mederrors/namediff.htm) for guidance.*

Sandoz Response: Sandoz has revised the established name to use the recommended "Tall Man" lettering in accordance with this request.

B. *Revise the expression of strength in the principal display panel so that the entire contents/mL is the primary expression of strength followed immediately by contents per mL. For Example: (b) (4) (40 mg/mL)*

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OCT 05 2006
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Sandoz Response: The expression of strength has been revised so that the entire content is the primary expression of strength followed by the "per mL concentration" in parenthesis.

2. CARTON

A. *Refer to CONTAINER comments*

Sandoz Response: The cartons have all been revised in accordance with the changes described above for the vials.

3. PACKAGE INSERT

A. *Refer to CONTAINER comments*

Sandoz Response: The Physician Insert Title and How Supplied section have been revised in accordance with the changes described above for the vials.

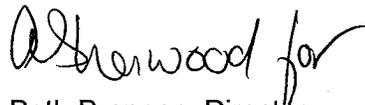
In addition to the revisions described above, the Sandoz vial and carton labels have been updated to the current Sandoz formatting. A new color scheme is now being used to better differentiate the strengths.

The revised labeling is attached electronically. The DRAFT package insert is provided in both pdf and word, the SPL will not be submitted at this time. Additionally, a side-by-side comparison of the proposed labeling with the last submission is provided electronically and in hard copy.

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

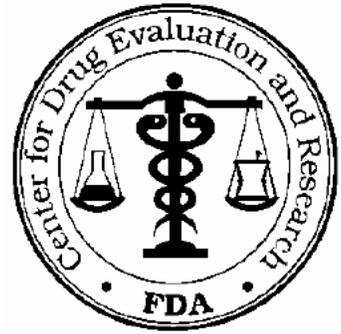
Enclosures
BB/ags

cc: Peggy Levy (whole submission)

Telephone Fax

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (301-827-7351)



TO: Sandoz Canada Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Agent

FAX: 303-438-4600

FROM: Ruby Wu

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 Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose 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**

ANDA Number: 40-719

Date of Submission: October 4, 2006 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the October 4, 2006 submission.
2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
40 mg/mL (1 x 5 mL carton only): The NDC number on the top lid is incorrect. Please revise.
3. PACKAGE INSERT
HOW SUPPLIED: "...multi-dose vials of XX mL in..." [add a space]

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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}

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

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

/s/

John Grace
11/1/2006 02:22:33 PM
for Wm Peter Rickman



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

ORIGINAL

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
(including electronic labeling)

ORIG AMENDMENT
N/A/T

NOV 30 2006

RE: **ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Labeling- Response to November 1, 2006 Deficiency**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 November 1, 2006. The following is provided in response to the FDA comments (*in italics*):

1. CONTAINER- 40 mg/mL (b)(4) 10 mL MDV) and 80 mg/mL (5 mL MDV)
Satisfactory in final print as submitted in the October 4, 2006 submission.

Sandoz Response: Sandoz acknowledges this comment.

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DEC 01 2006

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2. CARTON- [40 mg/mL (b)(4) 1 x 10mL, 10 x 10mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)] 40 mg/mL (b)(4): *The NDC number on the top lid is incorrect, please revise.*

Sandoz Response: Sandoz has corrected the NDC number on the 40 mg/mL (b)(4) carton and is providing a revised copy of this carton label.

3. PACKAGE INSERT

HOW SUPPLIED: "... multi-dose vials of XX mL in" [add space]

Sandoz Response: Sandoz has added a space as requested to the HOW SUPPLIED section.

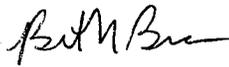
The revised labeling (carton and insert) are provided electronically. The draft package insert is provided in both pfd and word, the SPL will be included upon submission of final print. Additionally, a side-by-side comparison of the proposed insert with the last submission is provided electronically.

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

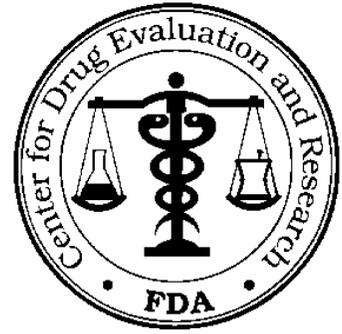
BB/ags

cc: Peggy Levy (submission)

BIOEQUIVALENCY AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Aaron Sigler

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 19, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL.

Reference is also made to your amendment dated September 15, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 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:

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 40-719

APPLICANT: Sandoz

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver request will be conducted later. The following deficiencies have been identified in the dissolution testing:

1. The dissolution data based on the your proposed method appear to be discriminating and promising. However, no data for the RLD product, Depo-Medrol[®] (methylprednisolone acetate aqueous suspension), were submitted for comparison with the test product.
2. In addition, you have not shown that an exhaustive experiment with the conventional USP apparatus II (paddle) has been conducted for the drug product. No method development data comparing USP apparatus II (paddle) and IV (flow-through-cell) were submitted. You stated that *"the USP Apparatus II (Paddle) and rotational speed (50 rpm), recommended by FDA, didn't provide adequate mixing to disperse the drug product in the Medium and to get a homogeneous mixture for sampling."* Please submit dissolution data based on USP apparatus II (paddle), using the same medium chosen for USP apparatus IV (flow-through-cell), i.e., 0.55% SDS, to support the above statement.
3. Please also provide method development data showing that dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration.
4. Since solubility of the drug in dissolution medium is the primary focus of the method development, and filtration of dissolution samples is used to separate the soluble from insoluble particles, please justify the selection of filter size (0.45 μ m nylon filter) used for the sample preparation. It was also noted that you used 0.45 μ m nylon filter for your proposed method, but used 0.2 μ m nylon filter for the FDA-recommended method in sample preparation. Please explain the reason for selecting

different filters for the two methods, and provide additional dissolution data based on your proposed dissolution method but with 0.2 μm nylon filter used in sample preparation.

The dissolution data of the RLD product, the comparative dissolution data based on both USP apparatus, the dissolution medium optimization data and the filtration optimization data are essential in assisting the DBE to determine whether your proposed method is indeed the most appropriate method for the drug product. Please provide these additional method development data.

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

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

/s/

Barbara Davit
11/20/2006 02:41:14 PM
Signing for Dale P Conner

Telephone Fax

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (301-827-7351)



TO: Sandoz Canada Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Agent

FAX: 303-438-4600

FROM: Ruby Wu

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 Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b)(4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling comments

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

ANDA Number: 40-719

Date of Submission: November 30, 2006 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the October 4, 2006 submission.

2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
40 mg/mL (b) (4) Satisfactory in final print as submitted in the November 30, 2006 amendment.

40 mg/mL (b) (4), 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL): Satisfactory in final print as submitted in the October 4, 2006 submission.

3. PACKAGE INSERT
Satisfactory in draft. You are reminded that final printed labels submitted in electronic format must be actual size, color and clarity.

Please submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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}

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

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

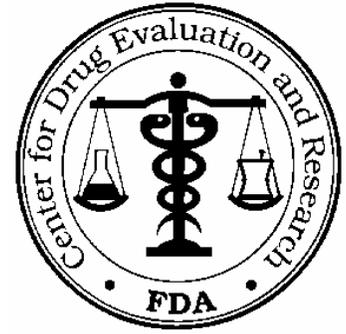
/s/

John Grace
12/7/2006 06:07:06 PM
for Wm Peter Rickman

BIOEQUIVALENCY AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Aaron Sigler

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on March 08, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL.

Reference is also made to your amendment dated September 15, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 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.

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 40-719

APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP,
40 mg/mL and 80 mg/mL (Multiple Dose Vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please provide sufficient long-term stability for methylprednisolone in human plasma. The long-term stability data should cover the timeframe from the first blood sample collection until the last plasma sample is analyzed (February 19, 2005 to November 30, 2005, i.e., 285 days). You stated in your bioanalytical report, "Additional long-term stability of methylprednisolone in human plasma NaF/potassium oxalate plasma under storage conditions at a nominal temperature of -80°C will be evaluated in the near future."
2. Please clearly identify the seven (7) methylprednisolone plasma samples that were reassayed for the analytical reason coded (G), sample reanalyzed to obtain confirming value. In the analytical report, Table 3: Repeat Analysis Results for Methylprednisolone in Human Plasma (Study LBI) we could only identify four (4) plasma samples as being reassayed for the reasons coded as: 9 (Code D, G, G), 10 (Code D, G) and 12 (Code G, G) The table below contains the information for the four (4) samples identified.

Subject No.	Period	Time, hr	Reason
35	1	8.5	9
35	1	12	10
63	2	PRE	12
71	2	PRE	12

3. Please provide the potency data for the reference-listed drug product, Depo-Medrol® (methylprednisolone acetate) Injectable Suspension, Lot No. 59JMX by Pharmacia & Upjohn.
4. As per the deficiency letter faxed on November 20, 2006, please provide all of the requested additional method development data, for your in vitro dissolution method as outlined below:
 - a. The dissolution data based on your proposed method appear to be discriminating and promising. However, no data for the RLD product, Depo-Medrol® (methylprednisolone acetate aqueous suspension), were submitted for comparison with the test product.
 - b. In addition, you have not shown that an exhaustive experiment with the conventional USP apparatus II (paddle)

has been conducted for the drug product. No method development data comparing USP apparatus II (paddle) and IV (flow-through-cell) were submitted. You stated that "the USP Apparatus II (Paddle) and rotational speed (50 rpm), recommended by FDA, didn't provide adequate mixing to disperse the drug product in the Medium and to get a homogeneous mixture for sampling." Please submit dissolution data based on USP apparatus II (paddle), using the same medium chosen for USP apparatus IV (flow-through cell), i.e., 0.55% SDS, to support the above statement.

- c. Please also provide method development data showing that dissolution profiles have been optimized with the selected dissolution medium as well as at the selected SDS concentration.
- d. Since solubility of the drug in dissolution medium is the primary focus of the method development, and filtration of dissolution samples is used to separate the soluble from insoluble particles, please justify the selection of filter size (0.45 μm nylon filter) used for the sample preparation. It was also noted that you used 0.45 μm nylon filter for your proposed method, but used 0.2 μm nylon filter for the FDA-recommended method in sample preparation. Please explain the reason for selecting different filters for the two methods, and provide additional dissolution data based on your proposed dissolution method but with 0.2 μm nylon filter used in sample preparation.

The dissolution data of the RLD product, the comparative dissolution data based on both USP apparatus, the dissolution medium optimization data and the filtration optimization data are essential in assisting the DBE to determine whether your proposed method is indeed the most appropriate method for the drug product.

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

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

/s/

Dale Conner

1/23/2007 09:36:40 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
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

**MINOR
AMENDMENT**

ORIG AMENDMENT

N/AM

JAN 30 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Minor Amendment- CMC**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from FDA dated September 27, 2006. Sandoz Canada Inc. has provided their response on the pages following this cover letter.

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. Peggy Levy (CL and responses)

**RECEIVED
JAN 31 2007
UGD / CDER**



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

ORIGINAL

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
(electronic labeling)**

ORIG AMENDMENT
N/AF

FEB 23 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Labeling (Response to Dec. 8, 2006 deficiency letter)**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 December 8, 2006. The following is provided in response to the FDA comments (*in italics*):

- 1. CONTAINER- 40 mg/mL (b)(4) 10 mL MDV) and 80 mg/mL (5 mL MDV)
Satisfactory in final print as submitted in the October 4, 2006 submission.

Sandoz Response: Sandoz is re-submitting the final print vial labels prepared using the proposed commercial size and layout. Additionally, the "manufactured by" statement has been revised as part of a general reformatting from :

(b)(4)

to

(b)(4)

RECEIVED
FEB 26 2007
OGD / CDER

2. CARTON- [40 mg/mL (b) (4) 1 x 10mL, 10 x 10mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]

40 mg/mL (b) (4): Satisfactory in final print as submitted in the November 30, 2006 submission.

40 mg/mL (b) (4) 1 x 10mL, 10 x 10mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]: Satisfactory in final print as submitted in the October 4, 2006 submission.

Sandoz Response: Sandoz is re-submitting the final print carton labels prepared using the proposed commercial size and layout. Additionally, the "manufactured by" statement has been revised as described above for the vial labels.

3. PACKAGE INSERT

Satisfactory in draft. You are reminded that final printed labels submitted in electronic format must be actual size, color and clarity.

Sandoz Response: Sandoz is submitting the final print package insert prepared using the proposed commercial size and layout. Additionally, the electronic files are provided in the following 8.5 x 11 formats: SPL, pdf, and MSword.

The revised labeling is attached electronically. Additionally, a side-by-side comparison of the proposed insert with the last submission is provided electronically. Differences noted pertain to reformatting of the document to fit with the SPL requirements.

Included on the CD are the following files:

Document	File Name on CD
Physician Insert in SPL	SPL folder
Physician Insert in MSWord format	MethylPREDNISolone Injectable.doc
Physician Insert in pdf format	MethylPREDNISolone Injectable.pdf
Side by Side Comparison of previous filed and current proposed Physician Insert	Previous vs Current PI.doc
Final Print Insert – actual size	M-1003055 136x296mm 01-2007.pdf
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
40 mg/mL - 400mg/10mL vial label	Methylpred 3136-70 vial.pdf
40 mg/mL - 400mg/10mL 1 count carton	Methylpred 3136-70 Ctn.pdf
40 mg/mL - 400mg/10mL 10 count carton	Methylpred 3136-92 Ctn.pdf
80 mg/mL - 400mg/5mL vial label	Methylpred 3137-75 vial.pdf
80 mg/mL - 400mg/5mL 1 count carton	Methylpred 3137-75 Ctn.pdf
80 mg/mL - 400mg/5mL 10 count carton	Methylpred 3137-95 Ctn.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.

A handwritten signature in black ink, appearing to read "Beth Brannan". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Beth Brannan, Director
Regulatory Affairs

Enclosures

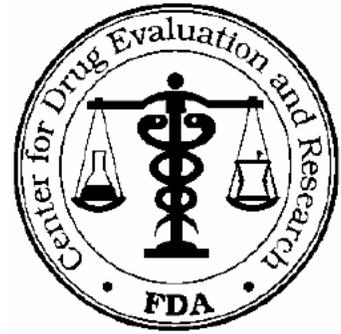
BB/ags

cc: Peggy Levy (submission)

Telephone Fax

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (301-827-7351)



TO: Sandoz Canada Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Agent

FAX: 303-438-4600

FROM: Ruby Wu

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 Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b)(4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling comments

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

ANDA Number: 40-719

Date of Submission: February 23, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Satisfactory in final print as submitted in the February 23, 2007 submission.
2. CARTON- [40 mg/mL (b) (4) 1 x 10 mL, 10 x 10 mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Satisfactory in final print as submitted in the February 23, 2007 submission.
3. PACKAGE INSERT
DESCRIPTION: Please update the pH range of the drug product to be in accord with the USP as well as your finished product specification.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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}

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

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

/s/

John Grace
3/6/2007 11:49:22 AM
for Wm Peter Rickman



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

**BIOEQUIVALENCY
AMENDMENT**

ORIG AMENDMENT

N/A/B

MAR 9 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Bioequivalence Amendment – Dissolution Data**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 communications from the Division of Bioequivalence dated November 20, 2006 and January 23, 2007. Sandoz Canada Inc. has provided their response on the pages following this cover letter.

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.

Asherwood for
Beth Brannan, Director
Regulatory Affairs

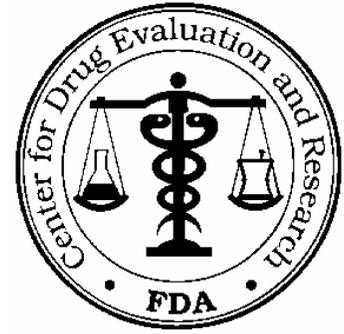
Enclosures
BB/ags
cc. Peggy Levy (CL)

RECEIVED
MAR 12 2007
OGD / CDER

BIOEQUIVALENCY AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Aaron Sigler

PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on March 08, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL.

Reference is also made to your amendment dated March 09, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 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.

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BIOEQUIVALENCE DEFICIENCY

ANDA: 40-719

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP 40 mg/mL and 80 mg/mL
(Multiple-dose vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet and has identified the following deficiency:

We agree with your proposed dissolution method using Apparatus IV for your test products, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/ml (Multiple Dose Suspension). We propose the specifications shown below based on submitted dissolution results. Please provide acknowledgement and acceptance of the following dissolution method and specifications:

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	IV (Flow-through cell)	IV (Flow-through cell)
System (Open/Closed):	Open	Open
Medium:	0.55% SDS	0.55% SDS
Temperature:	37°C ± 0.5°C	37°C ± 0.5°C
Sampling Times:	15, 30, 60 and 90 mins	15, 30, 60 and 90 mins
Specifications:	30 min: (b) (4) _s 90 min: NLT (b) (4) _s	30 min: (b) (4) _s 90 min: NLT (b) (4) _s

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

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

/s/

Barbara Davit
4/5/2007 04:30:24 PM
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

ORIG AMENDMENT

N/AF

AMENDMENT
(including electronic labeling)

APR 9 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Labeling – Response to March 6, 2007 Deficiency Letter**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 6, 2007. The following is provided in response to the FDA comments (*in italics*):

1. CONTAINER – [40 mg/mL (b)(4) 10ml MDV) and 80 mg/mL (5ml MDV)]
Satisfactory in final print as submitted in the February 23, 2007 submission.

2. CARTON [40 mg/mL (b)(4) 10ml MDV) and 80 mg/mL (5ml MDV)]
Satisfactory in final print as submitted in the February 23, 2007 submission.

3. PACKAGE INSERT

DESCRIPTION: Please update the pH range of the drug product to be in accord with the USP as well as your finished product specification.

Sandoz Response: The pH in the description section has been revised to reflect the range of 3.0 to 7.0 as requested. The final print PI is provided in SPL, MS word, and final print artwork pdf. Additionally, the "manufactured by" statement has been revised, the (b)(4) distribution channel has been removed.

RECEIVED
APR 10 2007
OGD / CDER

The revised labeling is attached electronically. Included on the CD are the following files:

Document	File Name on CD
Physician Insert in SPL	SPL folder (xml and jpg files)
Physician Insert in MSWord format	MethylPREDNISolone Injectable.doc
Physician Insert in pdf format	MethylPREDNISolone Injectable.pdf
Side by Side Comparison of previous filed and current proposed Physician Insert	PI compare rev01-2007 vs rev032007.doc
Final Print Insert – actual size	M-1003055 136x296mm 03-2007.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: Peggy Levy (whole submission)

Telephone Fax

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (301-827-7351)



TO: Sandoz Canada Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Agent

FAX: 303-438-4600

FROM: Ruby Wu

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 Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b)(4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose 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**

ANDA Number: 40-719

Date of Submission: April 9, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4)
10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Labeling Deficiencies

1. CONTAINER –[40 mg/mL (b) (4) 10 mL MDV) and 80 mg/mL (5 mL MDV)]
Please update your “manufactured by” statement to be consistent with the insert labeling.
2. CARTON- [40 mg/mL (b) (4), 1 x 10 mL, 10 x 10 mL]; 80 mg/mL (1 x 5 mL, 10 x 5 mL)]
Please update your “manufactured by” statement to be consistent with the insert labeling.
3. PACKAGE INSERT
Satisfactory in final print as submitted in the April 9, 2007 e-amendment.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html>

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}

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

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

/s/

John Grace
4/15/2007 11:12:28 AM
for Wm Peter Rickman



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

MINOR AMENDMENT
(including electronic labeling)

ORIG AMENDMENT

N/AF

MAY 22 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Amendment – Labeling- Response to April 15, 2007 Deficiency**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 April 15, 2007. The following is provided in response to the FDA comments (*in italics*):

1. CONTAINER- 40 mg/mL (b)(4) 10 mL MDV) and 80 mg/mL (5 mL MDV)
Please update your "manufactured by" statement to be consistent with the insert labeling.
2. CARTON- [40 mg/mL (b)(4) 1 x 10mL, 10 x 10mL); 80 mg/mL (1 x 5 mL, 10 x 5 mL)] 40 mg/mL (b)(4); *Please update your "manufactured by" statement to be consistent with the insert labeling.*
3. PACKAGE INSERT
Satisfactory in final print as submitted in the April 9, 2007 e-amendment.

RECEIVED

MAY 23 2007

OGD

Sandoz Response: Sandoz has revised the manufacturer statement on the vials and cartons to match the insert as follows:

Previous Statement	Revised Statement
 (b) (4)	Manufactured in Canada by Sandoz Canada Inc. for Sandoz Inc. Princeton, NJ 08540

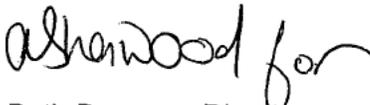
The revised labeling (vials and cartons) are provided electronically.

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: Peggy Levy (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

**BIOEQUIVALENCY
AMENDMENT**

ORIG AMENDMENT

N/A/B

JUN 1 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Bioequivalence Amendment – Dissolution Data**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from the Division of Bioequivalence dated April 5, 2007. Sandoz Canada Inc. has provided their response on the pages following this cover letter.

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. Peggy Levy (CL)

RECEIVED

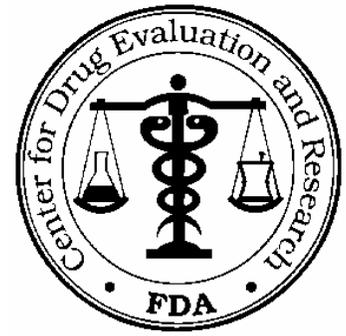
JUN 4 2007

OGD

BIOEQUIVALENCY AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Aaron Sigler

PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on March 08, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL.

Reference is also made to your amendment dated June 01, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 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:

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: 40-719

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP 40 mg/mL and 80 mg/mL
(Multiple-dose vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet and identified the following deficiency:

As stated in the previous correspondence to you dated April 05, 2007, we agree with your proposed dissolution method using Apparatus IV for your test product, Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/ml (Multiple Dose Suspension). However, your proposed specifications are not acceptable. You based your proposed dissolution specifications on the dissolution data for your test product and the reference-listed drug (RLD) product, Depo-Medrol[®] (methylprednisolone acetate) Injectable Suspension, by Pharmacia & UpJohn. The DBE-recommended specifications for your test product are based **only** on the *in vitro* dissolution testing results of your test product. Therefore, based on the submitted dissolution testing data please provide acknowledgement and acceptance of the following dissolution method and specifications:

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	IV (Flow-through cell)	IV (Flow-through cell)
System (Open/Closed):	Open	Open
Medium:	0.55% SDS	0.55% SDS
Temperature:	37°C ± 0.5°C	37°C ± 0.5°C
Sampling Times:	15, 30, 60 and 90 mins	15, 30, 60 and 90 mins
Specifications:	30 min: (b) (4) _s 90 min: NLT (b) (4) _s	30 min: (b) (4) _s 90 min: NLT (b) (4) _s

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

**This is a representation of an electronic record that was signed electronically and
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/s/

Barbara Davit
6/26/2007 05:54:08 PM
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

**BIOEQUIVALENCY
AMENDMENT**

ORIG AMENDMENT
N/AB

AUG 29 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Bioequivalence Amendment – Response to June 27, 2007 Deficiency Letter**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from the Division of Bioequivalence dated June 27, 2007. Sandoz Canada Inc. has provided their response on the pages following this cover letter.

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. Peggy Levy (CL)

RECEIVED

AUG 30 2007

OGD

MINOR AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Benjamin Danso

PROJECT MANAGER: (301) 827-5763

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 08, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 page). 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.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

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.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-719 APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL (Multiple Dose Vials)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF [REDACTED] (b) (4), is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the Agency.
2. [REDACTED] (b) (4)
Please clarify.
3. Your proposed [REDACTED] (b) (4)
4. Please set specifications for [REDACTED] (b) (4)
[REDACTED] (b) (4) is not acceptable.
5. You have indicated that the results of the [REDACTED] (b) (4)
[REDACTED] (b) (4) This is not acceptable. Please submit data to support the [REDACTED] (b) (4)

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

1. Bioequivalence deficiencies were communicated to you on June 26, 2007 and have not been responded. Please provide a response to the bioequivalence deficiencies.
2. Please provide all available long-term stability data to update your studies.

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/

Gururaj Bykadi
9/11/2007 11:26:23 AM



Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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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

ORIG AMENDMENT

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

N/A

**MINOR
AMENDMENT**

NOV 5 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Minor Amendment- Response to Chemistry Deficiency Letter**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from FDA dated September 11, 2007. Sandoz Canada Inc. has provided their response on the pages following this cover letter.

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)

RECEIVED

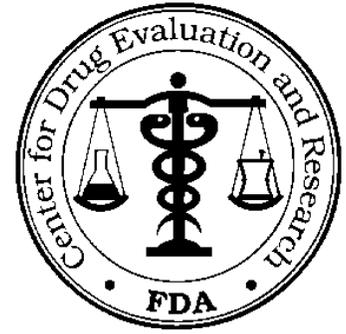
NOV 06 2007

OGD

BIOEQUIVALENCY AMENDMENT

ANDA 40-719

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs

FAX: 303-438-4600

FROM: Aaron Sigler

PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on March 08, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL & 80 mg/mL.

Reference is also made to your amendment dated August 29, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 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:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

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: 40-719

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable
Suspension USP 40 mg/mL and 80 mg/mL
(Multiple-dose vials)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet and identified the following deficiency:

Your proposed specification of NLT (b)(4)% at 30 minutes for your Methylprednisolone Acetate Injectable Suspension USP, 80 mg/ml is not acceptable. The information you provided does not support changing the specification at this particular time point. Upon additional review of the dissolution testing data you submitted, please provide acknowledgement and acceptance of the following dissolution method and specifications:

Strengths:	40 mg/mL	80 mg/mL
USP Apparatus:	IV (Flow-through cell)	IV (Flow-through cell)
System (Open/Closed):	Open	Open
Medium:	0.55% SDS	0.55% SDS
Temperature:	37°C ± 0.5°C	37°C ± 0.5°C
Sampling Times:	15, 30, 60 and 90 mins	15, 30, 60 and 90 mins
Specifications:	30 min: (b)(4)% 90 min: NLT (b)(4)%	30 min: (b)(4)% 90 min: NLT (b)(4)%

Alternatively, you may submit dissolution data for three (3) production lots, to determine if a revision of the dissolution specification is warranted.

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

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

/s/

Barbara Davit
11/19/2007 03:59:13 PM
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
Internet:
Beth.Brannan@sandoz.com

RECEIVED

NOV 23 2007

OVERNIGHT DELIVERY

OGD

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

**GRATUITOUS AMENDMENT
(including electronic labeling)**

ORIG AMENDMENT

NIAE

NOV 21 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Gratuitous Amendment – Revision to Labeling- Withdrawal of**

(b) (4)

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. is hereby submitting a gratuitous amendment to unapproved Abbreviated New Drug Application 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

On November 5, 2007, in response to chemistry deficiencies, Sandoz communicated to the Office of Generic Drugs that we are withdrawing

(b) (4)

Additionally, we have revised our physician insert to

(b) (4)

(b) (4)

section. No other changes have been made to the insert.

Included on the CD are the following files:

Document	File Name on CD
Physician Insert in SPL	SPL folder (xml and jpg files)
Physician Insert in MSWord format	MethylPREDNISolone Injectable 1003055.doc
Physician Insert in pdf format	MethylPREDNISolone Injectable 1003055.pdf
Side by Side Comparison of previous filed and current proposed Physician Insert	MethylPREDNISolone Injectablerev032007 vs rev112007.doc
Final Print Physician Insert – actual size	1003055 136x296 11-2007 R.pdf



SANDOZ

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 (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
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

**BIOEQUIVALENCY
AND CHEMISTRY
AMENDMENT**

N/AB

NOV 28 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Bioequivalence and Chemistry Amendment-
Response to Bioequivalence Deficiency Letter (DISSOLUTION)**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from FDA dated November 19, 2007. Sandoz Canada Inc. has provided their response on the pages following this cover letter.

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)

RECEIVED

NOV 29 2007

OGD



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

ORIG AMENDMENT

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

N/AS

**GRATUITOUS
AMENDMENT**
(Microbiology)

DEC 10 2007

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Gratuitous Amendment: Microbiology Amendment**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. is hereby submitting a gratuitous amendment to unapproved Abbreviated New Drug Application 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Sandoz Canada is submitting a complete sterility assurance package for the manufacture of the (b) (4) sterile Methylprednisolone Acetate Injectable Suspension, USP. This gratuitous amendment supersedes all of the previously filed sterility assurance information provided in the Regional section of the original ANDA.

There are no changes to the manufacturing process or analytical portion of this ANDA reported in this amendment. This amendment provides only for the re-organization and updates to the sterility assurance information based on previous communications from OGD's microbiology reviewers. Additionally, we have incorporated the contents of the sterility assurance information into the CTD according to MAPP 5040.1. Enclosed in front of each of the 2 volumes is the microbiology table of contents.

RECEIVED

DEC 11 2007

OGD



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)

Chemistry Assessment Section

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-719

APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP 40 mg/mL
(10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

Please respond to the comments presented below as a Telephone Amendment followed by a hard copy:

1. Please submit complete dissolution data for the drug product using the third month accelerated stability study samples.

cc: ANDA 40-719
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/K.Woodland/4/22/08
HFD-620/R.Bykadi, Ph.D./ April 29, 2008
HFD-617/Benjamin Danso, Pharm.D./

V:\CHEMISTRY DIVISION I\TEAM 5\PM FOLDER\40719.RV3.DOC

NOT APPROVABLE

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

/s/

Kathy P. Woodland
4/30/2008 08:54:56 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
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

**CHEMISTRY
TELEPHONE AMENDMENT
(electronic)**

MAY 9 2008

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Chemistry Amendment- Response to Chemistry Deficiency Letter (DISSOLUTION)**

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 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from FDA dated April 29, 2008. Provided is a complete response to this request.

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	anda40719
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Response to Deficiency	cmc folder response to 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)

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)



TO: Beth Brannan	FROM: Kun Shen
Sandoz Canada Inc.	Microbiology Project Manager
PHONE: (303) 438-4237	PHONE: (240) 276-8722
FAX: (866) 301-6408	FAX: (240) 276-8428

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 40-719, Methylprednisolone Acetate Injectable Suspension USP (multi-dose)**. The submissions reviewed were submitted on 12/19/2005 and 12/10/2007. 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: 40-719 APPLICANT: Sandoz Canada Inc

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP (multi-dose)

A. Microbiology Deficiencies:

1.

2.

3.

4.

(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}

Brenda Pillari, Ph.D.
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
this page is the manifestation of the electronic signature.**

/s/

Brenda Pillari
7/21/2008 01:58:38 PM

COMPLETE RESPONSE -- MINOR

ANDA 40-719

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

FAX: (303) 438-4600

FROM: Benjamin Danso

FDA CONTACT PHONE: (240) 276-8527

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 19, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Injectable, 40 mg/mL and 80 mg/mL.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

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 (1 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.

36. Chemistry Comments to be Provided to the Applicant:

ANDA: 40-719

APPLICANT: Sandoz Canada Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP
40 mg/mL and 80 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. USP <467> became effective July 1, 2008. Please refer to the OGD website at <http://www.fda.gov/cder/ogd/ResidualSolvents.pdf> for important information about this change.

Please submit the following:

- A statement in the Drug Product specification, "Meets USP <467> requirements for residual solvents" along with the method used to establish permitted daily exposure for residual solvents (Options 1 or 2).
 - A statement from the excipient/drug substance manufacturer for following two scenarios:
 - (1) If solvents are used in the manufacturing process:
 - ❖ Names of the residual solvents and specifications. Certificates of Analysis (your COAs and the manufactures' COAs)
 - ❖ A statement from the manufacturer stating that no other solvents are used in the manufacturing process.
 - (2) If solvents are NOT used in the manufacturing process:
 - ❖ A statement from the manufacturer that no solvents are used in the manufacturing process.
 - Submit copies of the revised drug substance/excipient specifications.
 - Submit a commitment to re-assess your compliance with USP<467> if you change ingredient suppliers in the post approval period including implementing revised controls, if appropriate.
2. Microbiology deficiencies were communicated to you on or about June 24, 2008 and have not been responded. Please provide a response to the Microbiology deficiencies.

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

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

/s/

Gururaj Bykadi
8/25/2008 05:41:49 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
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

MINOR AMENDMENT
(microbiology)
(electronic)

SEP 03 2008

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Minor Amendment – Response to Microbiology Deficiency Letter dated July 21, 2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. is hereby submitting a minor amendment to unapproved Abbreviated New Drug Application 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 microbiology deficiency letter dated July 21, 2008. Provided in this amendment is a complete response to all deficiencies.

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 40-719
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Response to 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.

A handwritten signature in cursive script that reads 'Beth Brannan'.

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
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

**CHEMISTRY
MINOR AMENDMENT
(electronic)**

SEP 17 2008

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Chemistry Amendment- Response to Deficiency Letter dated August 25, 2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. is hereby submitting a minor amendment to unapproved Abbreviated New Drug Application 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 from FDA dated August 25, 2008. Provided is a complete response to this request.

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	anda40719
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Response to Deficiency	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)



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
Internet:
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

TELEPHONE AMENDMENT
(electronic)

DEC 12 2008

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL (Multiple Dose Vials)
Telephone Amendment – Response to Chemistry Telephone Deficiency emailed Dec 10,
2008**

Dear Mr. Buehler:

On behalf of Sandoz Canada Inc., as their U.S. Authorized Agent, Sandoz Inc. is hereby submitting a telephone amendment to unapproved Abbreviated New Drug Application 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Multiple Dose Vials) 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 chemistry deficiency emailed to Sandoz by Benjamin Danso of FDA on December 10, 2008.

FDA Deficiency:

We noted that you have submitted

(b) (4)

Sandoz Response:

As requested, Sandoz Canada Inc. is providing in the enclosed electronic attachment revised statements from the

(b) (4)



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 40-719
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Response to deficiency	cmc folder telephoneamendment.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.
P.O. Box 446
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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

Telephone Amendment

January 13, 2009

**RE: ANDA 40-719 Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL**

Response to FDA telephone request dated 1/13/09 – Revised API specs.

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 40-719 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 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 conversation between Kathy Woodland (FDA) and Alison Sherwood (Sandoz) on January 13, 2009. Per FDA's request, revised API Specifications are provided.

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 40-719
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder (bookmarked) telephone amendment.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.

A handwritten signature in black ink that reads 'ASherwood'.

Alison Sherwood, Manager
Regulatory Affairs

Enclosures

AS/slc



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

New Correspondence

N/me

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

OGD APPROVAL ROUTING SUMMARY

ANDA # 40-719 Applicant Sandoz Canada Inc
Drug Methylprednisolone Acetate Inj Susp USP Strength(s) 40 mg/mL, and 80 mg/mL

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

<u>REVIEWER:</u>	<u>DRAFT Package</u>	<u>FINAL Package</u>
1. Martin Shimer		Date <u>12 January 2009</u>
Chief, Reg. Support Branch		Date <u>1/29/09</u>
		Initials <u>MHS</u>
		Initials <u>rlw</u>

Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Depo-Medrol NDA#11-757
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: _____

Comments: ANDA submitted on 12/21/2005, BOS=Depo-Medrol NDA 11-757, no relevant patent cert provided, no unexpired exclusivity. ANDA RTR'd on 3/2/2006. Firm addressed deficiency and ANDA was ACK for filing on 3/9/2006. There are no remaining unexpired patents or exclusivities which preclude approval of this ANDA. ANDA is eligible for immediate Full Approval.

2. Project Manager , <u>Benjamin Danso Team 5</u>	Review Support Branch	Date <u>1-9-09</u>
		Date _____
		Initials <u>sb</u>
		Initials _____

Original Rec'd date <u>11-19-05</u>	EER Status Pending <input type="checkbox"/> Acceptable <input checked="" type="checkbox"/> OAI <input type="checkbox"/>
Date Acceptable for Filing <u>12-21-05</u>	Date of EER Status <u>11-13-06</u>
Patent Certification (type) <u>P2</u>	Date of Office Bio Review <u>1-2-08</u>
Date Patent/Exclus. expires _____	Date of Labeling Approv. Sum <u>12-10-07</u>
Citizens' Petition/Legal Case Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Date of Sterility Assur. App. <u>9-17-08</u>
(If YES, attach email from PM to CP coord)	Methods Val. Samples Pending Yes <input type="checkbox"/> No <input type="checkbox"/>
First Generic Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	MV Commitment Rcd. from Firm Yes <input type="checkbox"/> No <input type="checkbox"/>
Priority Approval Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Modified-release dosage form: Yes <input type="checkbox"/> No <input type="checkbox"/>
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)	Interim Dissol. Specs in AP Ltr: Yes <input type="checkbox"/>
Acceptable Bio reviews tabbed Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Bio Review Filed in DFS: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
Suitability Petition/Pediatric Waiver	
Pediatric Waiver Request Accepted <input type="checkbox"/> Rejected <input type="checkbox"/> Pending <input type="checkbox"/>	
Previously reviewed and tentatively approved <input type="checkbox"/>	Date _____
Previously reviewed and CGMP def. /NA Minor issued <input type="checkbox"/>	Date _____

Comments:

3. **Labeling Endorsement**

Reviewer: _____ Labeling Team Leader: _____
Date _____ Date 1/29/09
Name/Initials _____ Name/Initials rlw/for

Comments:

Final-printed labeling (FPL) found acceptable for approval 12/10/07.

4. **David Read (PP IVs Only)** Pre-MMA Language included Date 1/29/09
OGD Regulatory Counsel, Post-MMA Language Included Initials rlw/for
Comments: N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. **Div. Dir./Deputy Dir.**
Chemistry Div. I

Date 1/27/09
Initials RMP

Comments: CMC section is satisfactory for AP.

6. **Frank Holcombe** **First Generics Only**
Assoc. Dir. For Chemistry

Date 1/29/09
Initials rlw/for

Comments: (First generic drug

review)
N/A. TEVA Parenteral's ANDA 40-557, 40-620 were approved for this drug product on Febuaqry 23, 2005 and October 27, 2006.

7. Vacant
Initials _____
RLD = Depo Medrol Injectable Suspension, 40 mg/mL and 80 mg/mL
Pharmacia & Upjohn Co. NDA 11-757

Date _____ Deputy Dir., DLPS

8. **Peter Rickman**
Director, DLPS

Date 1/29/09
Initials rlw/for

Comments: Bioequivalence

study Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
(fasting) on the 80 mg/mL strength found acceptable.
In-vitro dissolution testing for both strengths also found acceptable. Waiver granted to the 40 mg/mL strength under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 10/30/07 and 1/2/08 (dissolution).

Final-printed labeling (FPL) found acceptable for approval 5/31/07; 12/10/07.

Microbiology/Sterility Assurance found acceptable for approval (Micro Review #2) 9/16/08.

CMC found acceptable for approval (Chemistry Review #4).

OR

8. **Robert L. West** Date 1/29/09
 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 11/13/06 (Verified 1/29/09). no "OAI" Alerts noted.

There are no patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

9. **Gary Buehler** Date 1/29/09
 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, Benjamin Danso Team 5 Date _____
 Review Support Branch Initials _____
 _____ Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
 _____ Time notified of approval by phone
 _____ Time approval letter faxed

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

EER DATA :

EES Data for: 040719

***** Compliance Recommendations *****

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

/s/

Benjamin Danso
2/12/2009 02:09:29 PM