CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 40-794

Name: Methylprednisolone Acetate Injectable Suspension USP
40 mg/mL and 80 mg/mL
Packaged in 1 mL Single-dose Vials

Sponsor: Sandoz Canada, Inc.

Approval Date: March 5, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 40-794

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 July 21, 2006, 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 and 80 mg/mL, packaged in 1 mL Single-dose Vials.

Reference is also made to your amendments dated February 12, March 9, March 28, August 9, September 5, and December 10, 2007; August 22, October 7, and December 24, 2008.

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 40-794"***.

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
3/5/2009 12:42:07 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

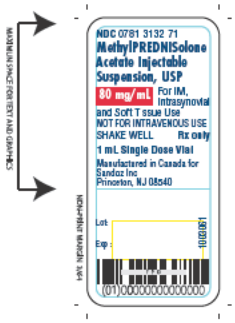
LABELING

MAC DX 4647

DIE FORMAT

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

ANDA Submission



(b) (4)

MAC DX 4647

DIE FORMAT

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

ANDA Submission

(b) (4)

(b) (4)

ANDA Submission

NDC 0781-3132-95

MethylPREDNISolone Acetate Injectable Suspension, USP

80 mg/mL

Rx only

10 x 1 mL Single Dose Vials

SANDOZ

LOT

EXP

N 3 0781-3132-95 0

NDC 0781-3132-95

MethylPREDNISolone Acetate Injectable Suspension, USP

80 mg/mL

Rx only

10 x 1 mL Single Dose Vials

SANDOZ

Each mL contains:

Methylprednisolone acetate ..... 80 mg

Also

Polyethylene glycol 3350 ..... 28 mg

Myristyl-gamma-picolinium Chloride ..... 0.19 mg

Sodium chloride was added to adjust tonicity.

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

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

Rev. 03-2007M

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

NDC 0781-3132-95

MethylPREDNISolone Acetate Injectable Suspension, USP

80 mg/mL

For intramuscular, intrasynovial and soft tissue injection only.
NOT FOR INTRAVENOUS USE

Sterile

Rx only 10 x 1 mL Single Dose Vials

SANDOZ

1003062

(b) (4) 10 x 1 mL Carton

(b) (4) arton
Carton
Carton

ANDA Submission

(b) (4)

1003060

SANDOZ

80 mg/mL

MethylPREDNISolone
Acetate Injectable
Suspension, USP

NDC 0781-3132-71

(b) (4)

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 acetate . . . . . 80 mg

Also

Polyethylene glycol 3350 . . . . . 28 mg

Myristyl-gamma-picolinium chloride . . . . . 0.19 mg

Sodium chloride was added to adjust tonicity.

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

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

Rev. 03-2007M

SANDOZ

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

NDC 0781-3132-71

MethylPREDNISolone Acetate Injectable Suspension, USP

80 mg/mL

Sterile

For intramuscular, intrasynovial and soft tissue injection only.

NOT FOR INTRAVENOUS USE

R_x only

One 1 mL Single Dose Vial

SANDOZ

N 3 0781-3132-71 4

(b) (4)

3060

(b) (4)

ANDA Submission

NDC 0781-3131-95

MethylPREDNISolone Acetate Injectable Suspension, USP

40 mg/mL

Rx only

10 x 1 mL Single Dose Vials

SANDOZ

LOT

EXP

Each mL contains:
Methylprednisolone acetate ..... 40 mg
Also
Polyethylene glycol 3350 ..... 29 mg
Myristyl-gamma-picolinium Chloride ..... 0.19 mg
Sodium chloride was added to adjust tonicity.
When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

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

Rev. 03-2007M

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

NDC 0781-3131-95

MethylPREDNISolone Acetate Injectable Suspension, USP

40 mg/mL

For intramuscular, intrasynovial and soft tissue injection only.
NOT FOR INTRAVENOUS USE

Sterile

Rx only 10 x 1 mL Single Dose Vials

SANDOZ

1003050

3050

(b) (4) 10 x 1 mL Carton

(b) (4) arton
Carton
Carton

ANDA Submission

(b) (4)

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SANDOZ

40 mg/mL

MethylPREDNISolone
Acetate Injectable
Suspension, USP

NDC 0781-3131-71

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 acetate . . . . . 40 mg

Also

Polyethylene glycol 3350 . . . . . 29 mg

Myristyl-gamma-picolinium chloride . . . . . 0.19 mg

Sodium chloride was added to adjust tonicity.

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

(b) (4)

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

Rev. 03-2007M

SANDOZ

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

NDC 0781-3131-71

MethylPREDNISolone Acetate Injectable Suspension, USP

40 mg/mL

Sterile

For intramuscular, intrasynovial and soft tissue injection only.

NOT FOR INTRAVENOUS USE

R_x only

One 1 mL Single Dose Vial

SANDOZ

N 3 0781-3131-71 7

????

SANDOZ

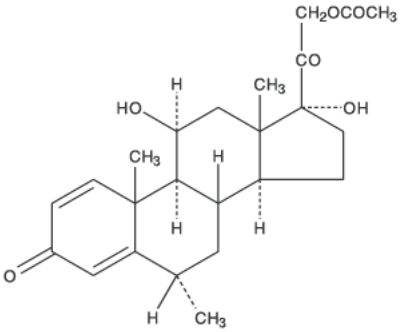
MethylPREDNISolone Acetate Injectable Suspension, USP

℞ 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-, (6α, 11β)- 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 intralesional injection. It is available as single dose vials 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 mg	28 mg
Myristyl gamma picolinium chloride	0.19 mg	0.19 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
Hypercalcemia 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

5. Allergic States:

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
Chorioretinitis
Diffuse posterior uveitis and choroiditis
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 (autoimmune) 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 Intralesional Administration:

Methylprednisolone acetate injectable suspension is indicated for intralesional 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 diabeticorum
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 also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS:

This product is not suitable for multi-dose use. Following administration of the desired dose, any remaining suspension should be discarded.

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 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.

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

Methylprednisolone acetate injectable suspension is not recommended for intrathecal administration.

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 intratendinous 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.

Allergic skin reactions have been reported apparently related to the excipients in the formulation (see **DESCRIPTION**). Rarely has skin testing demonstrated a reaction to methylprednisolone acetate, per se.

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.

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 patients suffering from hypoprothrombinemia.

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.)

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.

(See Reverse)

(Continued)

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
Petechiae 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:

Intrathecal/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 periocular 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. Procaine 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.

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

40 mg per mL
NDC 0781-3131-71 single-dose vial of 1 mL in boxes of 1
NDC 0781-3131-95 single-dose vial of 1 mL in boxes of 10

80 mg per mL
NDC 0781-3132-71 single-dose vial of 1 mL in boxes of 1
NDC 0781-3132-95 single-dose vial of 1 mL in boxes of 10

Store at 20° to 25°C (68° to 77°F) (see USP Controlled Room Temperature).

Rev. 03-2007M
1003052

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

LABELING REVIEWS

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

ANDA Number: 40-794

Date of Submission: October 18, 2006

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (1 mL single-dose vials) and 80 mg/mL (1 mL single-dose vials)

Labeling Deficiencies (based on labeling submitted July 21, 2006)

1. CONTAINER –(1 mL single-dose vial)
   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. Ensure that "NOT" appears on the same line as "FOR INTRAVENOUS USE."

2. CARTON- (1 x 1 mL vial and 10 x 1 mL vials)
   a. Refer to CONTAINER comment 1.a.
   b. Please add the statement "Sterile"
   c. 40 mg/mL 1 x 1 mL vial only: '(b) (4)" is listed in the "Each mL contains" statement. However, this ingredient is not found in your composition statement. Please comment.

3. PACKAGE INSERT
   a. CONTRAINDICATIONS: Revise this section to read as "Methylprednisolone acetate injectable suspension is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents."
   b. WARNINGS:
      i. Add "**Methylprednisolone acetate injectable suspension, USP is Not Recommended For Intrathecal Administration**." after "It is critical that…" paragraph.
      ii. Delete '(b) (4)
      "
      iii. Replace (b) (4)
      with "**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."**
      iv. Replace (b) (4)
      ." with "Allergic skin reactions have been reported apparently related to the excipients in the formulation (see DESCRIPTION). Rarely has skin testing demonstrated a reaction to methylprednisolone acetate, per se."
   c. PRECAUTIONS
      i. Delete (b) (4)
      "
      ii. Add "Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia." after "Psychic derangements…" paragraph.
      iii. Delete the (b) (4)" and (b) (4)" subsections.

d. ADVERSE REACTIONS
   i. Delete "(b) (4)"
   ii. Delete (b) (4) ."
e. (b) (4) delete this section.

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.

   Related ANDA: 40-719 for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

   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.	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

   [10/18/06 patent amendment]

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 & 80 mg/mL (single dose vials)
   1 mL single dose vials; Box of 1 vial and box of 25 vials

   ANDA: 40 mg/mL & 80 mg/mL
   1 mL single dose vials; Box of 1 vial and box of 10 vials

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. **However, the carton for 40 mg/mL (1 vial) is not consistent.**

Ingredients	**40 mg/mL each mL contains: (mg)**	**80 mg/mL each mL contains: (mg)**
Methylprednisolone Acetate, USP	40	80
Polyethylene Glycol 3350	29.0	28.0
Myristil-gamma-picolinium chloride	0.19	0.19
Sodium Chloride USP	(b) (4)	
Sodium Hydroxide NF (b) (4) Hydrochloric Acid	To adjust pH	To adjust pH
(b) (4)		

   [Vol. A1.3, section 3.2.P.1, pg. 2-3]

6. Container/Closure [Vol. A1.4, section 3.2.P.7, 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 2 mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
   pH 3.0-7.0
   [Vol. A1.4, section 3.2.P.5.1, pg. 4-8]

8. Bioequivalency: 12/5/2006 - Bio dissolution deficiencies given to document room for faxing / KAS

9. All manufacturing will be done by
   Sandoz Canada Inc.
   Boucherville, Canada [A1.3, section 3.2.P.3.1, pg. 2]

Date of Review: December 21, 2006 Date of Submission: October 18, 2006

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-794
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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
12/21/2006 12:41:54 PM
MEDICAL OFFICER

John Grace
1/3/2007 10:51:53 AM
MEDICAL OFFICER

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

ANDA Number: 40-794

Date of Submission: February 12, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (1 mL single-dose vials) and 80 mg/mL (1 mL single-dose vials)

Labeling Deficiencies

1. CONTAINER –(1 mL single-dose vial)
   Satisfactory in final print as submitted in the February 12, 2007 e-amendment.

2. CARTON- (1 x 1 mL vial and 10 x 1 mL vials)
   Satisfactory in final print as submitted in the February 12, 2007 e-amendment.

3. PACKAGE INSERT
   Satisfactory in draft.

Please submit final printed insert 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.

   Related ANDA: 40-719 for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

   USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass (checked (2/22/07)

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.	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

   [10/18/06 patent amendment]

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 & 80 mg/mL (single dose vials)
   1 mL single dose vials; Box of 1 vial and box of 25 vials

   ANDA: 40 mg/mL & 80 mg/mL
   1 mL single dose vials; Box of 1 vial and box of 10 vials

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	29.0	28.0
Myristil-gamma-picolinium chloride	0.19	0.19
Sodium Chloride USP	(b) (4)	
Sodium Hydroxide NF (b) (4) Hydrochloric Acid	To adjust pH	To adjust pH
(b) (4)		

   [Vol. A1.3, section 3.2.P.1, pg. 2-3]

6. Container/Closure [Vol. A1.4, section 3.2.P.7, 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 2 mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
   pH 3.0-7.0
   [Vol. A1.4, section 3.2.P.5.1, pg. 4-8]

8. Bioequivalency: 12/5/2006 - Bio dissolution deficiencies given to document room for faxing / KAS

9. All manufacturing will be done by
   Sandoz Canada Inc.
   Boucherville, Canada [A1.3, section 3.2.P.3.1, pg. 2]

Date of Review: February 22, 2007 Date of Submission: February 12, 2007

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-794
V:\FIRMSNZ\SANDOZ\LTRS&REV\40794.na2.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
2/22/2007 02:59:09 PM
MEDICAL OFFICER

John Grace
2/23/2007 07:00:19 AM
MEDICAL OFFICER

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

ANDA Number: 40-794

Date of Submission: March 28, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (1 mL single-dose vials) and 80 mg/mL (1 mL single-dose vials)

APPROVAL SUMMARY:

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER –(1 mL single-dose vial)
   Satisfactory in final print as submitted in the March 28, 2007 e-amendment.

2. CARTON- (1 x 1 mL vial and 10 x 1 mL vials)
   Satisfactory in final print as submitted in the March 28, 2007 e-amendment.

3. PACKAGE INSERT
   Satisfactory in final print as submitted in the March 28, 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-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.

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); 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 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.

   Related ANDA: 40-719 for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (b) (4) (b) (4) 10 mL multiple-dose vials) and 80 mg/mL (5 mL multiple-dose vials)

   USP Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass (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.	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

   [10/18/06 patent amendment]

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 & 80 mg/mL (single dose vials)
   1 mL single dose vials; Box of 1 vial and box of 25 vials

   ANDA: 40 mg/mL & 80 mg/mL
   1 mL single dose vials; Box of 1 vial and box of 10 vials

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	29.0	28.0
Myristil-gamma-picolinium chloride	0.19	0.19
Sodium Chloride USP	(b) (4)	
Sodium Hydroxide NF (b) (4) Hydrochloric Acid	To adjust pH	To adjust pH
(b) (4)		

   [Vol. A1.3, section 3.2.P.1, pg. 2-3]

6. Container/Closure [Vol. A1.4, section 3.2.P.7, 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 2 mL clear vial, with a 13 mm rubber stopper and a flip-off closure.
pH 3.0-7.0
[Vol. A1.4, section 3.2.P.5.1, pg. 4-8]

8. Bioequivalency: 12/5/2006 - Bio dissolution deficiencies given to document room for faxing / KAS

9. All manufacturing will be done by
Sandoz Canada Inc.
Boucherville, Canada [A1.3, section 3.2.P.3.1, pg. 2]

Date of Review: April 13, 2007 Date of Submission: March 28, 2007

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 40-794
V:\FIRMSNZ\SANDOZ\LTRS&REV\40794.ap.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 05:56:00 PM
MEDICAL OFFICER

John Grace
4/15/2007 11:15:00 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

CHEMISTRY REVIEWS

ANDA 40-794

Methylprednisolone Acetate Injectable Suspension, USP

40 mg/mL (1mL single-dose vial) and
80 mg/mL (1mL single-dose vial)

Sandoz Canada Inc.

Aijin Shen, Ph.D.
Chemistry Division I

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The Executive Summary **7**

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II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

The ANDA is not approvable at this time for the following reasons: 8

III. Administrative 9

Chemistry Assessment **10**

Chemistry Review Data Sheet

1. ANDA 40-794

2. REVIEW #: 1

3. REVIEW DATE: January 25, 2007

4. REVIEWER: Aijin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA	July 21, 2006
Acceptable for filing	Nov 17, 2006
Amendment (AC)	Oct 18, 2006
Amendment (AC)	Nov 6, 2006

7. NAME & ADDRESS OF APPLICANT:

Name	Sandoz Canada Inc.
Address	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8
US Representative	Ms. Beth Brannan, Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, Colorado 80038 Tel : 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:

Reference Product: Depo-Medrol®
Manufacturer: Pharmacia and Upjohn
NDA # 011-757

	Patent #	Expiration Date	Use Code
Patent	None		
Exclusivity	None		

a. The firm has provided a patent certification (v1.1,1.3.5.2 and v2.1, attachment 2). As required by 21 CFR 314.94(a)(12)(i)(A) and (ii), Sandoz Canada Inc., certifies that, in its opinion and to the best knowledge that there are no patents that claim the listed drug referred to in this application, or that claim a use of the listed drug referred to in this application, or that claim the use of the listed drug.

b. The basis for Sandoz Canada Inc. proposed ANDA for Methylprednisolone Acetate Injectable Suspension USP is the approved, reference listed drug, Depo-Medrol, the subject of NDA #011-757 (001 and 004), held by Pharmacia and Upjohn.

c. The holder states that the proposed drug product has the same active ingredient in the same concentration, dosage form and strength as the RLD and has the same inactive ingredients in the same concentrations as the RLD in single dose vials, except for changes as allowed for in 314.94(a)(9)(ii). (1.12.11)

10. PHARMACOLOGIC CATEGORY: Steroidal Anti-inflammatory Agent

11. DOSAGE FORM: Injectable Suspension

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

13. ROUTE OF ADMINISTRATION: Intramuscular, intrasynovial, soft tissue or intralesional Injection.

14. Rx/OTC DISPENSED: _X_Rx ___OTC

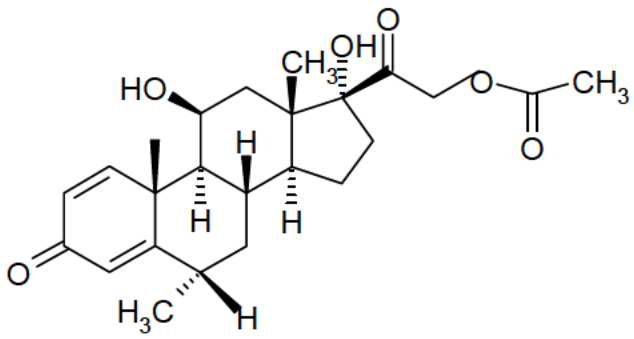
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (Authorization letters section 1.4):

DMF#	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	*Comments
(b) (4)	II		(b) (4)	1	Inadequate	03/23/2007	A. Shen
	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
N/A		

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
Methods Validation	N/A		
Labeling	Acceptable	04/15/2007	R. Wu
EES	Acceptable	11/20/2006	
Bioequivalence	Pending		
DBE dissolution	Deficient	12/04/2006	KAS
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:

QbR based submission, used for reviewer training.

The Chemistry Review for ANDA 40-794

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 40-794 is not approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance
Methylprednisolone Acetate is a white or practically white, odorless, crystalline powder which melts at about 215°C with some decomposition (Form II polymorphism). 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. It is 6-methyl derivative of prednisolone. The chemical name for methylprednisolone acetate is Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6α,11β)- and molecular weight is 416.51. It has specific optical rotation between +97° to +105° in dioxane.

Drug Product
Methylprednisolone Acetate injectable suspension, USP is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available as single-dose vials in two strengths: 40 mg/mL and 80 mg/mL. Each mL of these preparations contains: active, Methylprednisolone acetate, USP (40 mg and 80 mg), and following inactive ingredients, polyethylene glycol 3350 (29 mg and 28 mg), myristyl-gamma-picolinium chloride (0.19 mg and 0.19 mg) and sodium chloride is 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 of between 3.5 and 7.0. (Labeling Insert)

Note: According to current USP, the pH specification is 3.0 to 7.0. RLD label has a spec of 3.5 to 7.0 which is not in agreement with USP. Decision needs to be made as to how address this labeling issue.

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

Methylprednisolone acetate has a strong and prolonged anti-inflammatory , immunosuppressive and anti-allergic activity.

- Intramuscular administration:

  It is indicated for endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states, nervous system.

- Intrasynovial or soft tissue administration:

  As an adjunctive therapy for short-term administration in: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute non-specific tenosynovitis, post-traumatic osteoarthritis.

- Intralesional administration

  Keloids, localized hypertrophic infiltrated, inflammatory
  IT and QT based on MDD (200 mg/day)
  (Reference: vol 1.1, pkg insert section 1.14.1.3, page 14)

	ID	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

- Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
- HOW SUPPLIED
  Methylprednisolone acetate sterile injectable suspension is available as single-dose vials in the following strengths and package sizes:
  40 mg per mL
  NDC 0781-3131-71 single-dose vial of 1 mL in boxes of 1
  NDC 0781-3131-95 single-dose vial of 1 mL in boxes of 10
  80 mg per mL
  NDC 0781-3132-71 single-dose vial of 1 mL in boxes of 1
  NDC 0781-3132-95 single-dose vial of 1 mL in boxes of 10

C. Basis for Approvability or Not-Approval Recommendation

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

- MINOR Chemistry Issues
- Pending Bioequivalence review

III. Administrative

Reviewer: Aijin Shen

Following this page, 48 pages withheld in full - (b)(4)

3. Please note that your bio-equivalency information is pending review. Deficiencies, if any, will be communicated to you separately. Additionally, please respond to the DBE's dissolution deficiency comments and provide data to support the dissolution limit.

4. Please note that drug substance and drug product have a USP monograph. In the event of dispute, the methods listed in the USP monograph will be considered as a regulatory methods.

5. In response to the questions in the 2.3.S.4 and 2.3.P.5 sections, you have mainly listed the analytical test methods. In your future submission, please give a summary of the method validation. In addition, a discussion of the drug substance attributes that are important to achieve bioequivalence, as described in the model QbR, would be useful.

6. Please provide any additional long term stability data that may be available.

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 40-794
ANDA DUP 40-794
DIV FILE
Field Copy

Endorsements:

HFD-620/Aijin Shen, Ph.D./
HFD-620/Raj Bykadi, Ph.D/ 3/15/07; 3/30/07/ 4/3/07
HFD-617/Benjamin Danso, Pharm. D /5-2-07

V:\Chemistry Division I\Team 5\Final Version For DFS\40794.CR01.QBR.doc 5/21/2007
F/T by:

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Aijen Shen
5/21/2007 01:49:23 PM
CHEMIST

Gururaj Bykadi
5/21/2007 02:01:52 PM
CHEMIST

Benjamin Danso
5/31/2007 09:34:45 AM
CSO

Gururaj Bykadi
5/31/2007 11:31:33 AM
CHEMIST

ANDA 40-794

Methylprednisolone Acetate Injectable Suspension, USP

40 mg/mL (1mL single-dose vials) and
80 mg/mL (1mL single-dose vials)

Sandoz Canada Inc.

Aijin Shen, Ph.D.
Chemistry Division I

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A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 9

The ANDA is not approvable at this time for the following reasons: 9

III. Administrative 9

Chemistry Assessment **20**

Chemistry Review Data Sheet

1. ANDA 40-794

2. REVIEW #: 2

3. REVIEW DATE: January 15, 2008

4. REVIEWER: Aijin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original ANDA	July 21, 2006
Acceptable for filing	Nov 17, 2006
Amendment (AC)	Oct 18, 2006
Amendment (AC)	Nov 6, 2006
Amendment (AF)	February 12, 2007
Amendment (AF)	March 28, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	November 8, 2007
Telephone Amendment	February 8, 2008
Telephone Amendment	February 28, 2008

7. NAME & ADDRESS OF APPLICANT:

Name	Sandoz Canada Inc.
Address	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8

Chemistry Review Data Sheet

Name	**Sandoz Canada Inc.**
US Representative	Ms. Beth Brannan, Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, Colorado 80038 Tel : 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:

Reference Product: Depo-Medrol®
Manufacturer: Pharmacia and Upjohn
NDA # 011-757

	Patent #	Expiration Date	Use Code
Patent	None		
Exclusivity	None		

a. The firm has provided a patent certification (v1.1,1.3.5.2 and v2.1, attachment 2). As required by 21 CFR 314.94(a)(12)(i)(A) and (ii), Sandoz Canada Inc., certifies that, in its opinion and to the best knowledge that there are no patents that claim the listed drug referred to in this application, or that claim a use of the listed drug referred to in this application, or that claim the use of the listed drug.

b. The basis for Sandoz Canada Inc. proposed ANDA for Methylprednisolone Acetate Injectable Suspension USP is the approved, reference listed drug, Depo-Medrol, the subject of NDA #011-757 (001 and 004), held by Pharmacia and Upjohn.

c. The holder states that the proposed drug product has the same active ingredient in the same concentration, dosage form and strength as the RLD and has the same inactive ingredients in the same concentrations as the RLD in single dose vials, except for changes as allowed for in 314.94(a)(9)(ii). (1.12.11)

10. PHARMACOLOGIC CATEGORY: Steroidal Anti-inflammatory Agent

11. DOSAGE FORM: Injectable Suspension

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

13. ROUTE OF ADMINISTRATION: Intramuscular, intrasynovial, soft tissue or intralesional Injection.

14. Rx/OTC DISPENSED: _X_Rx ___OTC

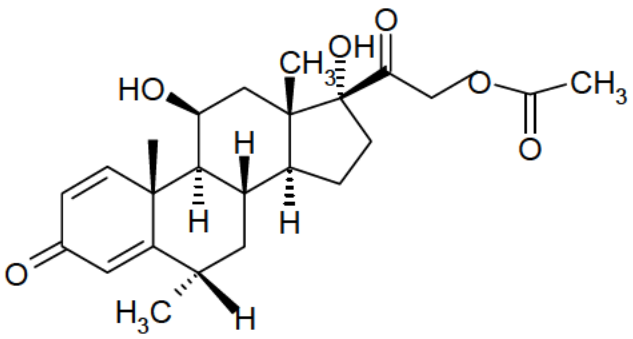
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

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-, (6α,11β)-. 11b,17,21-Trihydroxy-6a-methylpregna-1,4-diene-3,20-dione 21-acetate.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (Authorization letters section 1.4):

DMF#	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	*Comments
(b) (4)	II		(b) (4)	1	Adequate	03/21/2008	A. Shen
	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
N/A		

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Deficient	07/21/2008	George Arhin (DFS)
Methods Validation	N/A		
Labeling	Acceptable	04/15/2007	MQ/R. Wu
EES	Acceptable	11/20/2006	MQ
Bioequivalence-clinical	Incomplete	08/30/2007	S. Shrivastava (DFS)
DBE dissolution	Satisfactory	09/17/2007	KAS
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:

The Chemistry Review for ANDA 40-794

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 40-794 is not approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance
Methylprednisolone Acetate is a white or practically white, odorless, crystalline powder which melts at about 215°C with some decomposition (Form II polymorphism). 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. It is 6-methyl derivative of prednisolone. The chemical name for methylprednisolone acetate is Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6α,11β)- and molecular weight is 416.51. It has specific optical rotation between +97° to +105° in dioxane.

Drug Product
Methylprednisolone Acetate injectable suspension, USP is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available as single-dose vials in two strengths: 40 mg/mL and 80 mg/mL. Each mL of these preparations contains: active, Methylprednisolone acetate, USP (40 mg and 80 mg), and following inactive ingredients, polyethylene glycol 3350 (29 mg and 28 mg), myristyl-gamma-picolinium chloride (0.19 mg and 0.19 mg) and sodium chloride is 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 of between 3.0 and 7.0.

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

Methylprednisolone acetate has a strong and prolonged anti-inflammatory , immunosuppressive and anti-allergic activity.

- Intramuscular administration:

  It is indicated for endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states, nervous system.

- Intrasynovial or soft tissue administration:

  As an adjunctive therapy for short-term administration in: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute non-specific tenosynovitis, post-traumatic osteoarthritis.

- Intralesional administration

  Keloids, localized hypertrophic infiltrated, inflammatory
  IT and QT based on MDD (200 mg/day)
  (Reference: vol 1.1, pkg insert section 1.14.1.3, page 14)

	ID	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

- Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
- HOW SUPPLIED
  Methylprednisolone acetate sterile injectable suspension is available as single-dose vials in the following strengths and package sizes:

  40 mg per mL
  NDC 0781-3131-71 single-dose vial of 1 mL in boxes of 1
  NDC 0781-3131-95 single-dose vial of 1 mL in boxes of 10

  80 mg per mL
  NDC 0781-3132-71 single-dose vial of 1 mL in boxes of 1
  NDC 0781-3132-95 single-dose vial of 1 mL in boxes of 10

C. Basis for Approvability or Not-Approval Recommendation

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

- MINOR Chemistry Issues
- Deficient Microbiology and Bioequivalence

III. Administrative

Reviewer: Aijin Shen

Following this page, 43 pages withheld in full - (b)(4)

	DS	DP
		(b) (4)

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

A. Labeling & Package Insert

The labeling is acceptable as of 04/15/2007.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Categorical exclusion from the requirement to prepare an Environmental Assessment is requested (v1.1, 1.12.14, p2).
It is satisfactory.

III. List Of Deficiencies To Be Communicated

See the section below for details.

III. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-794 APPLICANT: Sandoz Canada Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.

7. Effective July 1, 2008, all ANDAs must provide information and data as necessary to demonstrate that the drug product is in compliance with USP Residual Solvents <467> requirement. Please refer to the letter posted on the Office of Generic Drugs website for additional information:
.http://www.fda.gov/cder/ogd/residualsolvents.pdf
Your drug product release specifications need to include "Residual Solvents" with acceptance criteria as "Complies with USP<467> if applicable.

8. Please submit commitment to reassess your compliance with USP <467> if you change ingredient suppliers in the post approval period including implementing revised controls.

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

1 Please follow ICH guideline for method precision validation.

2 Please be diligent in generating various data, specifically stability data for FDA submission and reduce any human error during data generation.

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 40-794
ANDA DUP 40-794
DIV FILE
Field Copy

Endorsements:

HFD-620/Aijin Shen, Ph.D./07/03/08
HFD-620/Raj Bykadi, Ph.D./ April 11; July3, 2008
HFD-617/Benjamin Danso, Pharm. D /7-6-08

V:\Chemistry Division I\Team 5\Final Version For DFS (Original)\40794.CR02.QBR.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Aijen Shen
7/22/2008 09:56:46 PM
CHEMIST

Benjamin Danso
7/23/2008 11:40:25 AM
CSO

Gururaj Bykadi
7/23/2008 02:11:07 PM
CHEMIST

ANDA 40-794

Methylprednisolone Acetate Injectable Suspension, USP
40 mg/mL (1mL single-dose vials) and
80 mg/mL (1mL single-dose vials)

Sandoz Canada Inc.

Aijin Shen, Ph.D.
Chemistry Division I

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C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 8

Chemistry Assessment **9**

Part II **14**

Chemistry Review Data Sheet

1. ANDA 40-794

2. REVIEW #: 3

3. REVIEW DATE: December 16, 2008

4. REVIEWER: Aijin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original ANDA	July 21, 2006
Acceptable for filing	Nov 17, 2006
Amendment (AC)	Oct 18, 2006
Amendment (AC)	Nov 6, 2006
Amendment (AF)	February 12, 2007
Amendment (AF)	March 28, 2007
Amendment	November 8, 2007
Telephone Amendment	February 8, 2008
Telephone Amendment	February 28, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	October 07, 2008
Telephone Amendment	December 24, 2008

7. NAME & ADDRESS OF APPLICANT:

Name	Sandoz Canada Inc.
Address	145 Jules Leger Street Boucherville (QC) Canada J4B 7K8

Chemistry Review Data Sheet

Name	**Sandoz Canada Inc.**
US Representative	Ms. Beth Brannan, Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, Colorado 80038 Tel : 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:

Reference Product: Depo-Medrol®
Manufacturer: Pharmacia and Upjohn
NDA # 011-757

	Patent #	Expiration Date	Use Code
Patent	None		
Exclusivity	None		

a. The firm has provided a patent certification (v1.1,1.3.5.2 and v2.1, attachment 2). As required by 21 CFR 314.94(a)(12)(i)(A) and (ii), Sandoz Canada Inc., certifies that, in its opinion and to the best knowledge that there are no patents that claim the listed drug referred to in this application, or that claim a use of the listed drug referred to in this application, or that claim the use of the listed drug.

b. The basis for Sandoz Canada Inc. proposed ANDA for Methylprednisolone Acetate Injectable Suspension USP is the approved, reference listed drug, Depo-Medrol, the subject of NDA #011-757 (001 and 004), held by Pharmacia and Upjohn.

c. The holder states that the proposed drug product has the same active ingredient in the same concentration, dosage form and strength as the RLD and has the same inactive ingredients in the same concentrations as the RLD in single dose vials, except for changes as allowed for in 314.94(a)(9)(ii). (1.12.11)

10. PHARMACOLOGIC CATEGORY: Steroidal Anti-inflammatory Agent

11. DOSAGE FORM: Injectable Suspension

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

13. ROUTE OF ADMINISTRATION: Intramuscular, intrasynovial, soft tissue or intralesional Injection.

14. Rx/OTC DISPENSED: __X__Rx __OTC

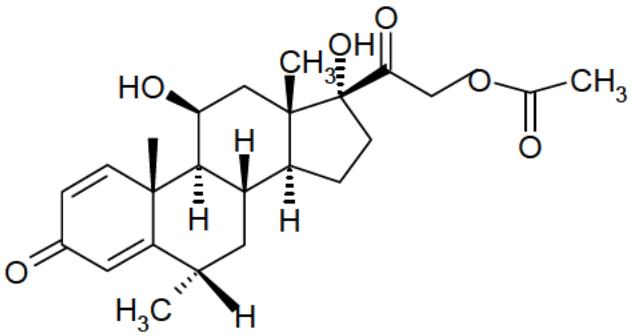
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

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-, (6α,11β)-.
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)	1	Adequate	02/03/2009	A. Shen
	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
N/A		

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	01/12/2008	
Methods Validation	N/A		
Labeling	Acceptable	04/15/2007	MQ/R. Wu
EES	Acceptable	11/20/2006	MQ
Bioequivalence	Acceptable	09/17/2007	S. Shrivastava (DFS)
DBE dissolution	Satisfactory	09/17/2007	KAS
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:

The Chemistry Review for ANDA 40-794

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 40-794 is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance
Methylprednisolone Acetate is a white or practically white, odorless, crystalline powder which melts at about 215°C with some decomposition (Form II polymorphism). 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. It is 6-methyl derivative of prednisolone. The chemical name for methylprednisolone acetate is Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6α,11β)- and molecular weight is 416.51. It has specific optical rotation between +97° to +105° in dioxane.

Drug Product
Methylprednisolone Acetate injectable suspension, USP is an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available as single-dose vials in two strengths: 40 mg/mL and 80 mg/mL. Each mL of these preparations contains: active, Methylprednisolone acetate, USP (40 mg and 80 mg), and following inactive ingredients, polyethylene glycol 3350 (29 mg and 28 mg), myristyl-gamma-picolinium chloride (0.19 mg and 0.19 mg) and sodium chloride is 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 of between 3.0 and 7.0.

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

Methylprednisolone acetate has a strong and prolonged anti-inflammatory , immunosuppressive and anti-allergic activity.

- Intramuscular administration:

It is indicated for endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states, nervous system.

- Intrasynovial or soft tissue administration:

  As an adjunctive therapy for short-term administration in: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute non-specific tenosynovitis, post-traumatic osteoarthritis.

- Intralesional administration

  Keloids, localized hypertrophic infiltrated, inflammatory
  IT and QT based on MDD (200 mg/day)

	ID	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

- Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
- HOW SUPPLIED
  Methylprednisolone acetate sterile injectable suspension is available as single-dose vials in the following strengths and package sizes:

  40 mg per mL
  NDC 0781-3131-71 single-dose vial of 1 mL in boxes of 1
  NDC 0781-3131-95 single-dose vial of 1 mL in boxes of 10

  80 mg per mL
  NDC 0781-3132-71 single-dose vial of 1 mL in boxes of 1
  NDC 0781-3132-95 single-dose vial of 1 mL in boxes of 10

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable.

III. Administrative

Reviewer: Aijin Shen

Following this page, 23 pages withheld in full - (b)(4)

Reviewer's Assessment and comment: Satisfactory As Per CR #1.

Additional information complied by the Reviewer:

R REGIONAL INFORMATION

R1 Executed Batch Records (Review #1 for details)

R2 Comparability Protocols: (Review #1 and 2 for details)

R3 Methods Validation Package: (Review #1 for details)

(b) (4)

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

A. Labeling & Package Insert

The labeling is approved on 04/15/2007.

B. Environmental Assessment Or Claim Of Categorical Exclusion

It is satisfactory.

III. List Of Deficiencies To Be Communicated

None

Approvable.

cc: ANDA 40-794
ANDA DUP 40-794
DIV FILE
Field Copy

Endorsements:

HFD-620/Aijin Shen, Ph.D./ Jan 28, 2009
HFD-620/Raj Bykadi, Ph.D./ Feb 19, 2009
HFD-617/Benjamin Danso, Pharm. D /2-20-09

V:\Chemistry Division I\Team 5\Final Version For DFS (Original)\40794.CR03.AP.doc

TYPE OF LETTER: APPROVABLE

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

/s/

Aijen Shen
3/3/2009 01:42:30 PM
CHEMIST

Gururaj Bykadi
3/3/2009 02:15:16 PM
CHEMIST

Benjamin Danso
3/5/2009 12:40:59 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	40-794
Drug Product Name	Methylprednisolone Acetate Injectable Suspension
Strength	40 and 80 mg/mL
Applicant Name	Sandoz Canada, Inc.
Address	145 Jules Leger street, Boucherville (QC), Canada
Point of Contact **Telephone Number** **Fax Number**	Ms. Beth Brannan 303-438-4237 303-438-4600
Submission Date(s)	October 18, 2006
First Generic	No
Reviewer	S. P. Shrivastava, Ph.D.
Clinical Site	SFBC Anapharm, Quebec, Canada,
Analytical Site	SFBC Anapharm, Quebec, Canada,

Table 1. Submission Content Checklist

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

Comments

- There is no USP/FDA Dissolution method available for this product. Therefore, the DBE requested firm to develop a dissolution method for its product (e.g., ANDA 40-557, Sicor Pharmaceuticals; CD 04-058, (b) (4)).

- The firm has proposed a dissolution method using USP Apparatus IV (flow-through cell) and 0.55% SDS. However, it has provided data for test products only. Complete comparative dissolution data for 40 and 80 mg/mL test and reference products are requested.

- Additionally, the firm is requested to conduct comparative dissolution testing on 40 and 80 mg/mL test and reference products using the following FDA-recommended method (v:\firmsnz\(b) (4)\ltrs&rev\04058P1204.doc):

Source of Method	FDA
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	Paddle
Rotation (rpm)	50 rpm
Sampling Times	15, 30, 45, 60, 120 and 240 minutes

S. P. Shrivastava, Ph.D. Team II Date

Shriniwas G. Nerurkar, Ph.D. Team II Date
Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCIES

ANDA:40-794 APPLICANT: Sandoz, Inc.

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

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(ies) has (have) been identified:

1. You have proposed a dissolution method using USP Apparatus IV (flow-through cell) and 0.55% SDS. However, you have provided data for test products only. Complete comparative dissolution data for 40 and 80 mg/mL test and reference products are requested.

2. Additionally, please conduct comparative dissolution testing on 40 and 80 mg/mL test and reference products using the following FDA-recommended method:

Medium:	Water
Volume (mL):	900 mL
USP Apparatus:	II (Paddle) at 50 rpm
Sampling Times:	15, 30, 45, 60, 120 and 240 minutes
Dosage Units:	12 each for the test and reference

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

BIOEQUIVALENCE - INCOMPLETE Submission date: 10/18/06

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

1. DISSOLUTION (BDI – 10/18/06)	Strength:	40 and 80 mg/mL
	Outcome:	**IC**

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

/s/

Surendra P. Shrivastava
12/4/2006 02:45:07 PM
BIOPHARMACEUTICS

Xiaojian Jiang
12/4/2006 05:36:08 PM
BIOPHARMACEUTICS
On behalf of Shriniwas G. Nerurkar

Barbara Davit
12/4/2006 06:39:57 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	40-794
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP
Strength	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz Canada, Inc.
Address	145 Jules Leger street, Boucherville (QC), Canada
Point of Contact **Telephone Number** **Fax Number**	Ms. Beth Brannan 303-438-4237 303-438-4600
Submission Date(s)	**March 9, 2007**
First Generic	No
Reviewer	S. P. Shrivastava, Ph.D.
Clinical Site	SFBC Anapharm, Quebec, Canada,
Analytical Site	SFBC Anapharm, Quebec, Canada,

I. EXECUTIVE SUMMARY

This is a review of the dissolution amendment only.

The dissolution review (see Shrivastava, S.P., Bioequivalence Dissolution Review, DFS) indicated deficiencies in dissolution testing data. In this amendment the firm has adequately responded to the dissolution deficiencies.

There is no USP/FDA Dissolution method available for this product. Therefore, the firm developed a dissolution method for its product The firm's dissolution testing are incomplete pending firm's acknowledgement of the acceptance of DBE recommended dissolution specifications. The DBE recommends the following dissolution method and specifications for this product:

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading	2 mL for 40 mg/mL; 1 mL for 80 mg/mL

The test product should meet the following specifications:

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

The DBE will review the fasted BE study and waiver requests at a later date.

The firm has provided the CTD Summary Tables.

II. DISSOLUTION CHECKLIST

The dissolution review (see Shrivastava, S.P., Bioequivalence Dissolution Review, DFS) indicated two deficiencies as follows:

1. You have proposed a dissolution method using USP Apparatus IV (flow-through cell) and 0.55% SDS. However, you have provided data for test products only. Complete comparative dissolution data for 40 and 80 mg/mL test and reference products are requested.

2. Additionally, please conduct comparative dissolution testing on 40 and 80 mg/mL test and reference products using the following FDA-recommended method:

   Medium: Water
   Volume (mL): 900 mL
   USP Apparatus: II (Paddle) at 50 rpm
   Sampling Times: 15, 30, 45, 60, 120 and 240 minutes
   Dosage Units: 12 each for the test and reference

In this amendment, the firm has adequately responded to both the deficiencies by providing requested data. The dissolution data are reviewed and results are discussed in Sections below.

Table 1. SUBMISSION CONTENT CHECKLIST

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

III. DISSOLUTION TESTING

Source of Method (USP/FDA/Firm)	FDA*	Firm
Medium	Water at 37 ^{0}C	0.55 % SDS**
Volume (mL)	900 mL	N/A
USP Apparatus type	II (Paddle)	IV (Flow-through cell)
Rotation (rpm)	50 rpm	N/A
Sampling Time	15, 30, 45, 60, 120 and 240 minutes	5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 minutes
Firm's proposed specifications	Not available	
FDA-recommended specifications (ANDA 40-557, using 900 mL water and Paddle at 50 rpm method)	40 mg: 1 Hr-(b) (4)%, 4 Hr–NLT (b) (4)% 80 mg: 1 Hr %, 4 Hr–NLT	
F2 metric calculated?	Yes	
If no, reason why F2 not calculated	N/A	
Is method acceptable?	Yes	
If not then why?	N/A	

* The FDA-recommended method (ANDA 40-557, Sicor Pharmaceuticals; CD 04-058, (b) (4)). ** SDS: Sodium Dodecyl Sulfate

Table 2. Summary of In Vitro Dissolution Studies – USP Apparatus IV (Flow-through Cell) and 40 mg Strength

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative, Range (RSD%)											Difference (f1) and similarity (f2) values
					5 min	10 min	15 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min	
ADSR-06-37	**Test product** Methylprednisolone Acetate Injectable Suspension (single dose) Lot # 1100402-C	40 mg/mL	Dissolution Apparatus 4 Flow rate : 8 mL/min Medium 0.55% SDS* Open loop and off line Temperature : 37°C	12	11.0%	28.0%	39.9%	47.5%	56.6%	63.3%	68.6%	73.1%	76.9%	80.1%	82.8%	
					(3.5%)	(1.4%)	(2.7%)	(3.4%)	(3.9%)	(4.1%)	(4.2%)	(4.3%)	(4.3%)	(4.3%)	(4.1%)	
ADSR-06-37	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# 96MDT	40 mg/mL		12	10.2	26.6	39.4	49.1	62.8	72.0	76.5	83.2	86.6	89.1	90.9	
					1.6	2.3	2.1	1.7	1.9	2.1	2.2	2.1	2.0	1.9	1.8	

(b) (4)

* SDS: Sodium Dodecyl Sulfate (references: book 127 p. 20-26, binder V-14)

Table 3. Summary of In Vitro Dissolution Studies - USP Apparatus IV (Flow-through Cell) and 80 mg Strength

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative, Range (RSD%)											Difference (f1) and similarity (f2) values
					5 min	10 min	15 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min	
ADSR-06-37	**Test product** Methylprednisolone Acetate Injectable Suspension Lot # 124943 Manuf Date: 02/10/2005	80 mg/mL	Dissolution Apparatus 4 Flow rate : 8 mL/min Medium 0.55% SDS Open loop and off line Temperature : 37°C	12	10.8 11.8	25.9 9.0	39.3 6.2	49.6 4.1	64.5 3.0	74.5 4.6	80.4 4.6	84.2 5.3	86.8 5.4	88.6 5.4	89.9 (b) (4) 5.2	
ADSR-06-37	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# 08MCA	80 mg/mL		12	10.4 26.9	21.1 24.5	30.8 24.6	39.0 23.3	56.1 15.5	72.7 9.6	84.5 6.0	91.6 3.9	96.0 2.7	99.0 2.0	100.8 (b) (4) 1.5	
ADSR-06-37	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# 05MHJ Exp. Date: 09/2007	80 mg/mL		6*	9.2 8.1	18.6 6.1	27.2 4.2	34.6 3.7	48.9 6.9	64.2 7.9	78.0 5.2	86.7 4.2	92.1 3.3	95.5 2.7	97.6 (b) (4) 1.9	

* Additional dosage units of this lot were not available.

Table 4. F2 Metrix for Dissolution in SDS Medium Using USP Apparatus IV (Flow-through Cell)

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
80 mg/mL Suspension	40 mg/mL Suspension	55.04	55.20

Table 5. Summary of In Vitro Dissolution Studies - USP Apparatus II (Paddle) and 40 mg Strength, (0.2 µm Nylon Filter)

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative (RSD%)						Difference (f1) and similarity (f2) values
					15 min	30 min	45 min	60min	120 min	240 min	
ADSR-07-04	**Test product** Methylprednisolone Acetate Injectable Suspension (single dose) Lot # 1100402-C	40 mg/mL	Dissolution Apparatus 2 (Paddle) at 50 rpm Volume: 900 mL Medium: Water Temperature : 37°C 0.2 µm filter	3	16.3 0.0	16.7 0.3	16.6 0.9	16.8 2.1	16.8 0.6	16.0 8.5	
ADSR-07-04	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# AAOHB	40 mg/mL		3	15.4 1.7	15.7 1.3	15.8 0.6	16.0 1.0	16.1 0.9	16.4 0.6	

Table 6. Summary of In Vitro Dissolution Studies - USP Apparatus II (Paddle) and 80 mg Strength, (0.2 µm Nylon Filter)

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative (RSD%)						Difference (f1) and similarity (f2) values
					15 min	30 min	45 min	60min	120 min	240 min	
ADSR-07-04	**Test product** Methylprednisolone Acetate Injectable Suspension (single dose) Lot # 124943	80 mg/mL	Dissolution Apparatus 2 (Paddle) at 50 rpm Volume: 900 mL Medium: Water Temperature : 37°C 0.2 µm filter	3	16.0 1.0	16.5 2.1	16.2 1.1	16.8 0.3	16.5 1.0	17.0 0.6	
ADSR-07-04	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# 83PTU	80 mg/mL		3	15.3	15.1	16.1	16.3	16.5	16.6	

Table 7. Summary of In Vitro Dissolution Studies - USP Apparatus II (Paddle) and 40 mg Strength (0.45 µm Nylon Filter)

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative (RSD%)														Difference (f1) and similarity (f2) values
					5 min	10 min	15 min	20 min	30 min	40 min	45 min	50 min	60 min	70 min	80 min	90 min	120 min	240 min	
ADSR-07-04	**Test product** Methylprednisolone Acetate Injectable Suspension (single dose) Lot # 1100402-C	40 mg/mL	Dissolution Apparatus 2 (Paddle) at 50 rpm Volume 900mL Medium 0.55% SDS Temperature : 37°C 0.45 µm filter	3	99.0 0.5	99.1 0.4	99.1 0.5	99.4 1.0	99.3 0.8	99.1 0.8	99.1 1.0	99.3 0.6	99.5 0.6	98.9 0.9	99.5 0.9	99.0 1.4	99.7 0.7	99.5 1.3	
ADSR-07-04	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# AAOHB	40 mg/mL		3	92.3 2.5	93.3 1.7	93.1 1.5	93.5 2.8	93.7 2.4	93.3 2.5	93.6 2.3	93.5 2.2	93.7 1.6	93.6 2.1	93.6 1.9	93.3 2.3	93.4 2.6	93.7 2.0	

Table 8. Summary of In Vitro Dissolution Studies - USP Apparatus II (Paddle) and 80 mg Strength (0.45 µm Nylon Filter)

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative (RSD%)														Difference (f1) and similarity (f2) values
					5 min	10 min	15 min	20 min	30 min	40 min	45 min	50 min	60 min	70 min	80 min	90 min	120 min	240 min	
ADSR-07-04	**Test product** Methylprednisolone Acetate Injectable Suspension (single dose) Lot #124943	80 mg/mL	Dissolution Apparatus 2 (Paddle) at 50 rpm Volume 900mL Medium 0.55% SDS Temperature : 37°C 0.45 µm filter	3	99.7 0.3	99.8 0.6	99.9 0.3	99.6 0.8	100.1 0.4	100.1 0.3	99.7 0.9	99.8 0.7	99.5 0.9	99.4 0.8	99.7 0.5	99.8 0.7	99.7 1.3	100.1 1.2	
ADSR-07-04	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# 83PTU	80 mg/mL		3	94.2 0.9	94.4 1.1	94.0 0.6	94.1 1.0	94.5 1.1	94.2 1.3	94.1 0.8	94.3 0.9	94.1 1.0	93.9 0.2	93.5 1.1	94.2 1.3	93.9 0.3	94.4 0.9	

Table 9. Summary of In Vitro Dissolution Studies - USP Apparatus II (Paddle) and 40 mg Strength (0.2 µm Nylon Filter)

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative (RSD%)														Difference (f1) and similarity (f2) values
					5 min	10 min	15 min	20 min	30 min	40 min	45 min	50 min	60 min	70 min	80 min	90 min	120 min	240 min	
ADSR-07-04	**Test product** Methylprednisolone Acetate Injectable Suspension (single dose) Lot # 1100402-C	40 mg/mL	Dissolution Apparatus 2 (Paddle) at 50 rpm Volume 900mL Medium 0.55% SDS Temperature : 37°C 0.2 µm filter	3	98.6 1.1	99.0 1.0	99.1 1.0	99.4 1.1	99.2 1.3	99.0 1.3	99.0 0.9	99.3 0.8	99.3 0.7	99.5 1.2	99.9 0.6	100.0 0.8	100.0 0.7	99.9 0.9	
ADSR-07-04	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# AAOHB	40 mg/mL		3	92.2 1.8	93.6 1.7	93.1 2.2	93.6 1.7	93.8 2.0	93.8 2.2	93.5 2.1	93.8 2.6	93.7 2.1	94.0 2.6	94.0 1.7	94.2 2.5	94.0 1.7	94.4 2.5	

Table 10. Summary of In Vitro Dissolution Studies - USP Apparatus II (Paddle) and 80 mg Strength (0.2 µm Nylon Filter)

Study reference report	Product ID/Batch No.	Dosage Form	Conditions (DI-0002)	No. of Dosage Units	% dissolution cumulative (RSD%)														Differenc (f1) and similarity (f2) values
					5 min	10 min	15 min	20 min	30 min	40 min	45 min	50 min	60 min	70 min	80 min	90 min	120 min	240 min	
ADSR-07-04	**Test product** Methylprednisolone Acetate Injectable Suspension (single dose) Lot #124943	80 mg/mL	Dissolution Apparatus 2 (Paddle) at 50 rpm Volume 900mL Medium 0.55% SDS Temperature : 37°C 0.2 µm filter	3	100.6 0.3	100.6 0.6	100.5 0.6	100.8 0.9	100.6 0.2	101.2 0.2	100.9 0.6	101.0 0.7	100.7 0.6	100.9 0.5	100.7 0.7	100.1 0.7	100.9 0.3	101.3 0.7	
ADSR-07-04	**Reference Product** Methylprednisolone Acetate Injectable Suspension Lot# 83PTU	80 mg/mL		3	94.3 1.0	95.2 1.1	95.1 0.9	95.1 0.8	95.0 0.7	94.9 0.6	94.8 0.5	94.4 0.5	94.4 0.7	94.4 0.8	94.6 0.6	94.7 0.6	94.2 1.2	94.9 1.3	

IV. COMMENTS:

1. There is no USP/FDA Dissolution method available for this product. Therefore, the DBE requested firms to develop a dissolution method for its products (e.g., ANDA 40-557, Sicor Pharmaceuticals; CD 04-058, (b) (4)).

2. The firm has proposed a dissolution method using USP Apparatus IV (flow-through cell) and 0.55% SDS (Table 2, Table 3). The similarity factor F2 values were >50 for both test and reference products (Table 4). Since the firm ran out of the Bio reference batch (80 mg/mL, Lot #05MHJ), it has conducted dissolution on another Reference batch (Lot # 08MCA), and has also provided dissolution data on six dosage units of Bio reference Lot (Table 3).

3. Additionally, the firm has provided dissolution testing data, as requested by the DBE (Letter, dated 12/5/06), in water and SDS media using Paddle at 50 rpm (Tables 5-10).The dissolution testing results showed a slow (16-17% dissolution in water in 6 hours, Table 5), and a fast dissolution in SDS medium (92-101% in 5 minutes, Table 7-10). The sponsor found only ~17% dissolution of the brand name products in six hours while Sicor (ANDA 40-557) observed a dissolution of over 80% in one hour in the same medium. The reason for the difference may be the use of filters by Sandoz, which probably filters out any fine particles in samples.

4. Although the number of dosage units used in these studies were only 3 (n=3), the results clearly indicate that these methods (900 mL water or 0.55% SDS with Paddle at 50 rpm) are not appropriate for the products.

5. The firm's dissolution method using 0.55% SDS medium as follows is acceptable:

Medium	0.55 % Sodium Dodecyl Sulfate
Temperature	37 ^{0}C
USP Apparatus type	IV (Flow-through Cell)
Type of cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2, Glass microfiber GF/C (Whatman), 25 mm diameter
Sample load	1 mL for 80 mg/mL strength 2 mL for 40 mg/mL strength
Flow rate	8 mL/minute
Sampling Times	15, 30, 45, 60, 120 and 240 minutes

6. The firm has not proposed any dissolution specifications for its products. Based on the data submitted, following dissolution specifications are recommended for 40 mg/mL and 80 mg/mL strength products:

Dissolution Specifications:

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

V. DEFICIENCY COMMENTS:

1. The firm has not proposed any dissolution specifications for its products. The firm is requested to acknowledge the acceptance of DBE recommended dissolution specifications for its 40 mg/mL and 80 mg/mL strength products as mentioned above (see Comment #5).

VI. RECOMMENDATIONS:

1. The dissolution testing conducted by Sandoz on its methylprednisolone acetate injectable suspension, 40 mg/mL and 80 mg/mL comparing it to Depo-Medrol® 40 mg/mL and 80 mg/mL, respectively, manufactured by Pharmacia Upjohn, is incomplete pending acknowledgement of the acceptance of dissolution specifications.

2. The dissolution testing should be conducted in 0.55% sodium dodecyl sulfate (SDS) using USP Apparatus IV (Flow-through Cell) as follows:

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading	2 mL for 40 mg/mL; 1 mL for 80 mg/mL

The test product should meet the following specifications:

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

BIOEQUIVALENCE DEFICIENCIES

ANDA:40-794 APPLICANT: Sandoz, Inc.

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

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence study and the waiver request will be conducted later. The following comments/deficiency has been identified:

1. Your request to use the following dissolution method is acceptable:

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading	2 mL for 40 mg/mL; 1 mL for 80 mg/mL

2. You have not proposed any dissolution specifications for your products. Please acknowledge your acceptance of the following dissolution specifications:

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

CC: ANDA 40-794

[NOTE: The in vitro testing is incomplete pending acceptance of dissolution specification by the firm. The fasting and/or fed BE studies and waiver request are pending review]

1. DISSOLUTION AMENDMENT (DA)

Submission date: 03/09/2007
Strength: 40 mg/mL, 80 mg/mL
Outcome: IC

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

/s/

Surendra P. Shrivastava
6/6/2007 03:33:20 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
6/6/2007 04:32:18 PM
BIOPHARMACEUTICS

Barbara Davit
6/6/2007 04:39:27 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	**40-794**
Drug Product Name	**Methylprednisolone Acetate Injectable Suspension, USP, Single-Dose Vial Formulation**
Strength(s)	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz Canada, Inc.
Address	Boucherville (QC), Canada
Applicant's Point of Contact	Ms. Beth Brannan, Director, Reg. Affairs
Contact's Telephone Number	303-438-4237
Contact's Fax Number	303-438-4600
Original Submission Date(s)	**October 18, 2006**
Submission Date(s) of Amendment(s) Under Review	**August 9, 2007 (Tele. Amendment - Potency Data)** **March 9, 2007 (Dissolution Amend. – Completed, 6/6/07)**
Reviewer	**S. P. Shrivastava, Ph.D.**
Study Number (s)	1
Study Type (s)	Single-dose Fasting Parallel Design Study
Strength (s)	80 mg/mL Injectable Suspension
Clinical Site	SFBC Anapharm
Clinical Site Address	Quebec, Canada
Analytical Site	SFBC Anapharm
Analytical Site Address	Quebec, Canada

1. EXECUTIVE SUMMARY

Pharmacia and Upjohn Pharms (innovator) market two formulations of methylprednisolone acetate injectable suspension, single-dose-vials and multiple-dose-vials, under the brand name Depo-Medrol®. The single-dose-vials are available in 40 mg and 80 mg/mL strengths, and multiple-dose-vials are available in 20, 40 and 80 mg/mL strengths (PDR). The Orange Book does not differentiate the single-dose-vials from the multi-dose-vials and list them together under one NDA (11-757). Even though the Orange Book lists three strengths 20, 40 and 80 mg/mL under one NDA, from the DBE's perspective there are five viable strengths. Those are 2 single-dose-vials (40mg/ml and **RLD 80mg/ml**) and 3 multi-dose-vials (20mg/ml, 40mg/ml and **RLD**

80mg/ml). Thus if a generic firm plans submit ANDA(s) for all five strengths, it needs to conduct two separate fasting BE studies using the 2 RLDs mentioned above in the **bold font**. **The DBE does not request a fed BE study.**

The firm has submitted a single-dose, 4-period (in 2 Groups) parallel fasting bioequivalence study comparing the test product, methylprednisolone acetate injectable suspension, 80 mg/mL (single-dose vial) with the RLD product, Pharmacia and Upjohn's Depo-Medrol® Injectable Suspension, 80 mg/mL (single-dose-vial). **The firm did not submit a fed BE study.**

Single-dose Fasting BE study (50534): It is a single-dose parallel study using 146 normal healthy male and female volunteers (Test n=70, Ref n=76) given a dose of 80 mg of the formulation. The results for methylprednisolone acetate (point estimate, 90% CI) are: Methylprednisolone acetate- LAUCt of 94, 86.38-101.37%; LAUCi of 95, 88.71-102.24% and LCmax of 102, 89.76-115.16%. The study is **acceptable**.

The In vitro dissolution testing has previously been reviewed and was found acceptable (see DFS sign off date 6-6-2007). However, the dissolution testing is **incomplete** pending acceptance of the dissolution specifications by the firm.

The DBE recommended the following dissolution method and specifications for this product

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading	2 mL for 40 mg/mL; 1 mL for 80 mg/mL

The test product should meet the following specifications:

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

Methylprednisolone acetate 40 mg/mL strength injectable suspension is formulated proportionally to the 80 mg/mL strength. However, due to the deficiency cited above, the waiver of BE study for 40 mg/mL strength injectable suspensions cannot be granted at this time.

The application is **incomplete**.

This ANDA is not scheduled for a DSI inspection.

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3. SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Methylprednisolone acetate injectable suspension USP, 80 mg/mL
Reference Product	Depo-Medrol® Injectable suspensions, 80 mg/mL (RLD) & 40 mg/mL
RLD Manufacturer	Pharmacia and Upjohn
NDA (ANDA) No.	11-757
RLD Approval Date	09/09/1975
Indication	Is an anti-inflammatory glucocorticoid for intra muscular, intrasynovial or soft tissue injection in a number of organ system disorders, e.g., endocrine, rheumatic collagen, dermatologic, etc.

3.2 PK/PD Information (PDR)

Bioavailability	Not available
Food Effect	Food effects not discussed in the labeling
T_{max}, Hrs.	24
Metabolism	Extensive metabolized in the liver
Excretion	Excreted primarily as metabolites
Half-life, Hrs.	139 (58-866)
Agency Guidance	None
Drug Specific Issues (if any)	Per general BA/BE Guidance, the bioequivalence assessment should be based on the parent compound methylprednisolone.

3.3 OGD Recommendations for Drug Product

Pharmacia and Upjohn Pharms (innovator) markets two formulations of methylprednisolone acetate injectable suspensions, single-dose-vials and mult-dose-vials, under the brand name Depo-Medrol®. The single-dose vials are available in 40 mg and 80 mg/mL strengths, and multiple-dose vials are available in 20, 40 and 80 mg/mL strengths (PDR). The Orange Book does not differentiate between the two formulations (NDA 11-757) and all three strengths, 20, 40 and 80 mg/mL strengths are designated as the RLDs.

Number of studies recommended:		1 Fasting BE study for single-dose-vials (**applicable for this ANDA**) And 1 fasting BE study for multi-dose-vials (**not applicable for this ANDA**) No fed BE study
1.	**Type of study:**	Single-dose fasting
	Design:	Single-dose, two-treatment, two-period crossover, in vivo
	Strength:	80 mg/Ml
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None
Analytes to measure (in appropriate biological fluid):		Methylprednisolone acetate in plasma
Bioequivalence based on (90% CI):		Yes
Waiver request of in-vivo testing (appropriate strengths):		Yes, 40 mg/mL injectable suspensions
Current Recommendations: **Source of most recent recommendations**[1]		1. Conduct only a single-dose fasting BE study on 80 mg/mL strength. (**NOTE: if a firm plans to market single-dose-vials and multi-dose-vials, it needs to conduct 2 separate BE studies. One with single-dose-vial of the 80 mg/ml RLD and the other with multi-dose-vial of the 80 mg/ml RLD**). A fed BE study is not necessary. 2. Measure only the parent drug methylprednisolone acetate. 3. Waiver for 40 mg/mL strength may be granted under 21 CFR 320.22(d)(2) 4. Develop dissolution as follows (P04-058, CD06-0452): Medium : 900 mL water Apparatus: 2 (Paddle) at 50 rpm Sampling time: 1 and 4 hrs.

[1] See v:\firmsam\ (b) (4) \Conttrols\060452.doc

Summary of OGD or DBE History	**CD:** 01-569 (Sabex, conduct only single-dose IM injection study on 80 mg/mL), 02-298 (Gensia/Sicor, conduct two separate BE studies on single-dose and multiple-dose vials), 06-0452 ((b) (4) two BE studies, one on single-dose vials and one on multi-dose vials). **Protocols:** 93-044 (b) (4)), 00-049 (Sicor), 02-064 (Gensia/Sicor), 03-011 (Sabex), 04-058 ((b) (4) SD on 80 mg/mL strength), 05-063 ((b) (4) two SD fasting, 2-way crossover BE studies on single-dose and multi-dose vials using 80 mg/mL strengths of T and R). Recently, protocols, [P00-049, 02-064, (Gensia Sicor), P03-011 (Sabex), P04058 ((b) (4) and 05-063 ((b) (4) have been reviewed by the DBE. The DBE concurred with the first two firms' (Sicor and Sabex) proposal to conduct single-dose, crossover fasting BE studies using 80-mg dose. Gensia Sicor and (b) (4) submitted two protocols for the 80 mg/mL (multi-dose and single-dose vials) because of concerns about the impact of preservatives on bioavailability of methylprednisolone in the two preparations. The DBE also found the parallel fasting study proposed by (b) (4) acceptable provided the highest strength 80 mg/mL is used and the lower strengths considered for biowaivers. **ANDAs:** 40-557 (Sicor, acceptable, single-dose 2-way crossover study on 80 mg/mL for 40 and 80 mg, single-dose vial). Only one BE study (single-dose crossover fasting study on the 80 mg/mL) was submitted for the approval of the generic Methylprednisolone Acetate Injectable Suspension (ANDA 40-557, Sicor, approved 2/23/05), and is currently on the market. The 40 mg/mL was approved as biowaiver based on the formulation proportionality, dissolution profile comparability and the acceptable biostudy of the 80 mg/mL. There is no FDA-recommended dissolution method and specification for this drug product. Sicor developed an acceptable in vitro testing method (900 mL, Water, Paddle at 50 rpm; 1 – and 4 – hours). The above dissolution method was recommended for this ANDA.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	Yes	1
BCS Waivers	No	
Clinical Endpoints	N/A	
Failed Studies	N/A	
Amendments	Yes	8/9/07 (Potency information)

3.5 Pre-Study Bioanalytical Method Validation

FAST 50534	DATA
Analyte	Methylprednisolone
Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of Methylprednisolone and the internal standard from human EDTA plasma by solid phase extraction. Samples are kept frozen at -20°C prior to analysis and 0.500mL of plasma was used for analysis.
Limit of quantitation (ng/mL)	0.25
Average recovery of drug range (%)	90.69 to 102.48
Average recovery of IS (%)	93.68
Standard curve concentrations range (ng/mL)	0.25 to 24.90
QC concentration (ng/mL)	QC1 0.74 QC2: 7.44 QC3: 17.36
QC Intraday precision range (%)	1.00 to 2.08
QC Intraday accuracy range (%)	104.28 to 108.41
QC Interday precision range (%)	3.20 to 4.75
QC Interday accuracy range (%)	106.08 to 107.89
Bench-top stability (hrs)	24 hours at room temperature
Stock stability (days)	Methylprednisolone: 350 days at -20°C (b) (4) 77 days at -20°C
Processed stability (hrs)	80 hours at room temperature
Freeze-thaw stability (cycles)	4 at -20 °C and -80°C
Long-term storage stability (days)	349 days at -20°C 14 days at -80°C
Dilution integrity	QC3 diluted 1/2: CV (%) 3.78 Nominal (%) 106.99 DQC diluted 1/20: CV (%) 2.29 Nominal (%) 99.60
Selectivity	Human plasma samples (EDTA 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.

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

Pre-study methods validation is **satisfactory.**

3.6 In Vivo Studies

3.6.1 Single-dose Fasting Study:

Table 1. Summary of In Vivo Bioequivalence Study: Single-dose Fasting Study (Firm's Data)

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route)	Subjects (No. M/F) Type, Age and Weight: mean (range)	Mean Parameters (SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf}** (ng·h/mL)	$T_{½}$** (h)	K_{el}** (h^{-1})	
50534	Randomized, Open-Label, Parallel, Bioequivalence Study of Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP and Depo-Medrol (Reference) Following a 1 mL (80 mg) Intramuscular Injection in Healthy Subjects Under Fasting Conditions.	Randomized, single-dose, parallel	Methylprednisolone acetate (1 x 80 mg/mL) injectable suspension IM injection Lot No.: 124943	147 completing (61 males/86 females) Healthy subjects Age (years) = 40 (18-71) Weight (kg) = 70.8 (51.0-104.3) Data set for statistical analysis = 146	7.74 (4.64)	87.9 (231.0) 24.0 (38.0)*	2944.36 (1012.84)	3483.16 (978.70)	400.20 (277.98)	0.0023 (0.0012)	Vol. # p.#
			Depo-Medrol® (1 x 80 mg/mL) injectable suspension IM injection Lot No.: 05MHJ		7.27 (4.08)	48.1 (78.4) 24.0 (38.0)*	3064.81 (897.88)	3646.90 (1024.29)	415.48 (207.31)	0.0021 (0.0011)	

* Median (interquartile range)
** For these parameters, N = 140

Table 2. Statistical Summary of the Comparative BA Data Calculated by the Firm

50534, Fasted Bioequivalence Study

Parameters		Test (A)	Reference (B)	Ratio A/B	90%C.I.
AUC_{0-t}	(ng·h/mL)	-	-	94.06%	86.65% to 102.11%
AUC_{0-inf}*	(ng·h/mL)	-	-	95.43%	88.58% to 102.80%
C_{max}	(ng/mL)	-	-	102.76%	90.45% to 116.73%

* For this parameter, N = 140

Table 3. Statistical Summary of the Comparative BE Data Calculated by the Reviewer

Single-dose Fasting Study – 80 mg/mL

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	2734.35	2922.04	0.94	86.38	101.37
LAUCI	3334.98	3501.77	0.95	88.71	102.24
LCMAX	6.50	6.40	1.02	89.76	115.16

UNIT: AUC=ng HR/ML CMAX=ng/ML TMAX=HR

Table 4. Reanalysis of Study Samples – Fasting study, 80 mg/mL

Study No. 50534
Randomized, Open-Label, Parallel, Bioequivalence Study of Methylprednisolone Acetate 80 mg/mL Injectable Suspension, USP and Depo-Medrol (Reference) Following a 1 mL (80mg) Intramuscular Injection in Healthy Subjects Under Fasting Conditions

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	187	73	5.41	2.12	187	70	5.41	2.03
Poor Chromatography	112	13	3.24	0.38	112	13	3.24	0.38
Unacceptable internal standard response	15	8	0.43	0.23	15	8	0.43	0.23
Incomplete analysis	2	2	0.06	0.06	2	2	0.06	0.06
Sample concentration above upper limit of quantification	57	46	1.65	1.33	57	46	1.65	1.33
Sample reanalyzed to obtain confirming value	0	4	0.0	0.12	0	1	0.0	0.03
Sample repeated or reinjected by error	1	0	0.03	0.0	1	0	0.03	0.0
Total	187	73	5.41	2.12	187	70	5.41	2.03

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[T] Methylprednisolone acetate 80mg/mL injectable suspension USP (Sandoz Cananda Inc., Cananda) Batch No : 124943
[R] Methylprednisolone acetate 80mg/mL injectable suspension, USP (Depo-Medrol) (Pharmacia & Upjohn, USA) Batch No: 05MHJ

Did use of recalculated plasma concentration data change study outcome? There were no PK repeats.

Comments from the Reviewer: The results of plasma sample analyses are **satisfactory**.

3.7 Formulation

Location in appendix	**4.2 Formulation Data**
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
Is the product scored?	Yes
If yes, which strengths are scored?	40 mg/mL and 80 mg/mL
Is scoring of RLD the same as test?	No, only 40 mg/mL strength is scored. The 80 mg/mL strength is not scored.
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

In vitro dissolution testing has previously been reviewed and was found acceptable (see DFS 40794 (Shrivastava): sign off dates 6/6/2007 and 12/4/2006). However, the firm has not accepted the FDA recommended dissolution specifications.

3.9 Waiver Request(s)

Strengths for which waivers are requested	40 mg/mL Injectable Suspension
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Not at this time
If not then why?	The firm has to acknowledge dissolution testing and specification-

3.10 Deficiency/Comments

1. In vitro dissolution testing has previously been reviewed and was found acceptable (see DFS 40794 (Shrivastava): sign off dates 6/6/2007 and 12/4/2006). However, the firm has not accepted the FDA recommended dissolution specifications.

3.11 Recommendations

1. The single-dose, fasting bioequivalence study (50534) conducted by Sandoz Canada on its methylprednisolone acetate table, 80 mg/mL (Lot #124943), comparing it to

Pharmacia and Upjohn's Depo-Medrol, USP (80 mg/mL Lot #05MHJ), is **acceptable**.

2. The dissolution testing conducted by Sandoz on its methylprednisolone acetate table, 80 mg/mL and 40 mg/mL is **incomplete** pending the acceptance of dissolution specifications by the firm.

3. The formulation for methylprednisolone acetate injectable suspension, 40 mg/mL is proportionally similar to the 80 mg/mL strength of the test product, which underwent *in vivo* bioequivalence testing. However, waiver of bioequivalence study for the 40 mg/mL injectable suspensions cannot be granted at this time due to deficiency #1 cited above.

4. The dissolution testing should be conducted as follows:

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading	2 mL for 40 mg/mL; 1 mL for 80 mg/mL

The test product should meet the following specifications:

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

The firm should be informed of the recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	This ANDA is not scheduled for a DSI inspection.

4. APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study – 80 mg/mL

4.1.1.1 Study Design

Table 5. Study Information

Study Number	50534
Study Title	Randomized open-label parallel bioequivalence study of methylprednisolone acetate 80 mg/mL injectable suspension USP and Depo-Medrol (Reference) following a 1 mL (80 mg) intramuscular injection in healthy subjects under fasting conditions
Clinical Site (Name & Address)	SFBC Anapharm, Sainte-Foy, Quebec, Canada
Principal Investigator	Denis Audet, MD
Dosing Dates	Group 1 (Sub #1-40): 2/18/06; Group 2 (#41-80):2/25/06; Group 3 (#81-120):3/4/06; Group 4 (#121-160):3/115/06
Analytical Site (Name & Address)	SFBC Anapharm, Quebec, Canada
Analytical Director	(b) (6), Ph.D.
Analysis Dates	5/18/06-6/21/06
Storage Period of Biostudy Samples	123 days at -20 ^{0}C

Table 6. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Methylprednisolone acetate injectable suspension	Depo-Medrol®
Manufacturer	Sandoz Labs.	Pharmacia and Upjohn
Batch/Lot No.	124943	05MHJ
Manufacture Date	02/10/05	
Expiration Date		09/07
Strength	80 mg/mL	

Dosage Form	Injectable suspensions	
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay), %	101.25	101.875
Content Uniformity (mean, %CV)	101.25 (5.1)	
Dose Administered	1 x 80 mg/mL	
Route of Administration	Intramuscular	

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	160 dosed, 147 completed and 146 analyzed. Test n=70, Ref n=76
No. of Sequences	1
No. of Periods	4
No. of Treatments	2
No. of Groups	4
Washout Period	N/A
Randomization Scheme	**Group 1 A:** 1, 2, 5, 7, 9, 12, 14, 16, 18, 20, 23, 24, 27, 28, 31, 32, 33, 36, 38, 39 **B:** 3, 4, 6, 8, 10, 11, 13, 15, 17, 19, 21, 22, 25, 26, 29, 30, 34, 35, 37, 40 **Group 2 A:** 43, 44, 45, 47, 49, 50, 55, 56, 57, 60, 61, 62, 65, 67, 69, 70, 73, 76, 78, 79 **B:** 41, 42, 46, 48, 51, 52, 53, 54, 58, 59, 63, 64, 66, 68, 71, 72, 74, 75, 77, 80 **Group 3 A:** 82, 84, 86, 88, 89, 91, 93, 96, 98, 99, 101, 104, 105, 107, 111, 112, 114, 116, 119, 120 **B:** 81, 83, 85, 87, 90, 92, 94, 95, 97, 100, 102, 103, 106, 108, 109, 110, 113, 115, 117, 118 **Group 4 A:** 121, 124, 125, 126, 129, 131, 133, 134, 137, 140, 141, 142, 145, 148, 149, 151, 154, 155, 158, 159, **B:** 122, 123, 127, 128, 130, 132, 135, 136, 138, 139, 143, 144, 146, 147, 150, 152, 153, 154, 156, 157, 160
Blood Sampling Times	Pre-dose and 2, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 120, 168, 336, 504, 672, 840, 1008 and 1176 hours post-dose.
Blood Volume Collected/Sample	7-mL in K3-EDTA Vacutainers

Blood Sample Processing/Storage	Samples were centrifuged under refrigeration as soon as possible, and plasma was stored at -20 ^{0}C.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	10 hrs prior to dosing and 4 hrs. post dosing
Length of Confinement	10 Hours prior to dosing and 36 hrs. post-dose
Safety Monitoring	Subjects were monitored throughout the study. Medical tests on subject were run prior to discharging.

Comments on Study Design: Study design is acceptable.

4.1.1.2 Clinical Results

Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study

		Safety population	PK population		
Category		**Total**	**Randomization**		**Total**
			A	**B**	
Age (years)	Mean ± SD	39 ± 13	39 ± 14	40 ± 13	40 ± 14
	Range	18 - 71	18 - 71	20 - 68	18 - 71
	Median	37	37	38	37
	N	160	70	76	146
Age Groups	< 18	0	0	0	0
	18-40	96 (60.0 %)	43 (61.4 %)	42 (55.3 %)	85 (58.2 %)
	41-64	61 (38.1 %)	25 (35.7 %)	33 (43.4 %)	58 (39.7 %)
	65-75	3 (1.9 %)	2 (2.9 %)	1 (1.3 %)	3 (2.1 %)
	> 75	0	0	0	0
Gender	Female	90 (56.3 %)	39 (55.7 %)	46 (60.5 %)	85 (58.2 %)
	Male	70 (43.8 %)	31 (44.3 %)	30 (39.5 %)	61 (41.8 %)
Race	Asian	1 (0.6 %)	0	0	0
	Black	2 (1.3 %)	1 (1.4 %)	1 (1.3 %)	2 (1.4 %)
	Caucasian	141 (88.1 %)	61 (87.1 %)	69 (90.8 %)	130 (89.0 %)
	American Hispanic	13 (8.1 %)	7 (10.0 %)	5 (6.6 %)	12 (8.2 %)
	Oriental	3 (1.9 %)	1 (1.4 %)	1 (1.3 %)	2 (1.4 %)
Height (cm)	Mean ± SD	168.3 ± 9.2	168.3 ± 7.8	167.7 ± 9.9	168.0 ± 8.9
	Range	148.0 - 195.5	150.5 - 185.5	148.0 - 193.0	148.0 - 193.0
	Median	167.0	166.8	166.8	166.8
	N	160	70	76	146
Weight (kg)	Mean ± SD	70.7 ± 10.4	70.4 ± 9.9	71.1 ± 11.0	70.8 ± 10.5
	Range	51.0 - 104.3	51.0 - 89.8	53.6 - 104.3	51.0 - 104.3
	Median	69.6	71.2	69.3	69.9
	N	160	70	76	146
BMI (kg/m^2)	Mean ± SD	24.9 ± 2.7	24.8 ± 2.6	25.2 ± 2.7	25.0 ± 2.7
	Range	19.7 - 29.9	20.2 - 29.9	19.7 - 29.4	19.7 - 29.9
	Median	24.7	24.6	25.2	24.8
	N	160	70	76	146

Table 9. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period/Group	Replaced?
001, 002, 004	Withdrew for personal reasons	1	No
003, 005, 010, 027	Withdrawn due to missed samples	2	No
092, 099, 105, 114, 120	Withdrawn due to missed samples	3	No
028	Withdrawn due to vomiting within 2 times the elimination Thalf	1	No
84	There were no reportable values for all sampling time-points	3	No

Table 10. Study Adverse Events, Fasting and Fed Bioequivalence Studies

System Class	50534	
COSTART	A	B
Eye disorders		
Abnormal sensation in eye		1 (0.4 %)
Dry eye		1 (0.4 %)
Gastrointestinal disorders		
Abdominal pain		3 (1.3 %)
Abdominal pain upper		1 (0.4 %)
Diarrhoea	2 (0.9 %)	
Gingical pain	1 (0.4 %)	
Lip ulceration	1 (0.4 %)	
Nausea	3 (1.3 %)	2 (0.9 %)
Tooth fracture	1 (0.4 %)	
Vomiting	1 (0.4 %)	2 (0.9 %)
General disorders and administration site conditions		
Asthenia		1 (0.4 %)
Chest pain		1 (0.4 %)
Chills		1 (0.4 %)
Fatigue	2 (0.9 %)	
Feeling cold		1 (0.4%)
Oedema peripheral	1 (0.4 %)	
Infections and infestations		
Influenza	1 (0.4 %)	4 (1.8 %)
Pharyngitis	1 (0.4 %)	
Tooth abcess	1 (0.4 %)	
Upper respiratory tract infection	2 (0.9 %)	
Injury, poisoning and procedural complications		
Catheter site erythema	2 (0.9 %)	3 (1.3 %)
Catheter site haemorrhage	1 (0.4 %)	
Catheter site pain		1 (0.4 %)
Contusion	1 (0.4 %)	1 (0.4 %)
Injection site erythema	3 (1.3 %)	4 (1.8 %)
Injection site haemorrhage	7 (3.1 %)	6 (2.6 %)
Injection site induration	3 (1.3 %)	1 (0.4 %)
Injection site irritation	1 (0.4 %)	
Injection site pain	7 (3.1 %)	8 (3.5 %)
Injection site paraesthesia	2 (0.9 %)	4 (1.8 %)
Injection site reaction	2 (0.9 %)	2 (0.9 %)
Post procedural dizziness	1 (0.4 %)	
Scratch		1 (0.4 %)
Vessel puncture site reaction	1 (0.4 %)	1 (0.4 %)
Wrist fracture		1 (0.4 %)
Investigations		
Alanine aminotransferase increased	1 (0.4 %)	2 (0.9 %)
Aspartate aminotransferase		1 (0.4 %)
Blood bilirubin increased	1 (0.4 %)	
Blood glucose decreased	2 (0.9 %)	
Blood glucose increased		3 (1.3 %)
Blood potassium increased	1 (0.4 %)	
Blood alkaline phosphatase increased		1 (0.4 %)
Protein urine present	3 (1.3 %)	2 (0.9 %)
Red blood cells urine positive	3 (1.3 %)	4 (1.8 %)
Metabolism and nutrition disorders		
Anorexia		1 (0.4 %)

Table 11. Study Adverse Events, Fasting and Fed Bioequivalence Studies (Cont'd)

System Class	50534	
COSTART	A	B
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (1.8 %)	
Arthropathy		2 (0.9 %)
Back pain	1 (0.4 %)	4 (1.8 %)
Muscle spasms	2 (0.9 %)	2 (0.9 %)
Musculoskeletal stiffness	1 (0.4 %)	
Myalgia	5 (2.2 %)	7 (3.1 %)
Neck pain	2 (0.9 %)	
Pain in extremity	5 (2.2 %)	8 (3.5 %)
Sensation of heaviness		1 (0.4 %)
Nervous system disorders		
Dizziness	3 (1.3 %)	1 (0.4 %)
Dysaesthesia		1 (0.4 %)
Headache	10 (4.4 %)	16 (7.0 %)
Hypoaesthesia	1 (0.4 %)	
Muscle contractions involuntary	2 (0.9 %)	
Somnolence	2 (0.9 %)	4 (1.8 %)
Syncope		1 (0.4 %)
Tremor		1 (0.4 %)
Pregnancy, puerperium ans perinatal conditions		
Pregnancy		1 (0.4 %)
Psychiatric disorders		
Anxiety		1 (0.4 %)
Reproductive system and breast disorders		
Menstruation irregular	1 (0.4 %)	
Respiratory, thoracic and mediastinal disorders		
Cough	2 (0.9 %)	
Nasal congestion	2 (0.9 %)	
Pharyngolaryngeal pain		2 (0.9 %)
Rhinorrhoea		1 (0.4 %)
Skin and subcutaneous tissue disorders		
Dry skin		1 (0.4 %)
Erythema		1 (0.4 %)
Hyperhidrosis		1 (0.4 %)
Pruritus generalised		1 (0.4 %)
Vascular disorders		
Hot flush	2 (0.9 %)	1 (0.4 %)
Peripheral coldness		1 (0.4 %)
TOTAL	104	124

Table 12. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling deviations	Number of samples	
Concomitant medication prior to and during the study	11	12

Comments on Dropouts/Adverse Events/Protocol Deviations:

The dropouts were appropriate. There were no serious adverse events. Protocol deviations were minor and did not compromise the outcome of the study.

4.1.1.3 Bioanalytical Results

Table 13. Assay Validation – Within the Fasting Bioequivalence Study: Methylprednisolone acetate

ANALYTE 1 (Parent)									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.25	0.50	1.25	2.51	5.01	7.52	10.02	12.53	
Inter day Precision (%CV)	9.08	6.45	6.80	6.74	5.73	5.33	6.11	5.56	
Inter day Accuracy (% Bias)	0.48	-0.67	0.16	-1.16	-0.68	0.04	0.05	1.69	
Linearity	(Range of R values) 0.9817-0.9993								
Linearity Range (ng/mL)	0.25-12.53								
Sensitivity/LOQ (ng/mL)	0.25								
Parameter	**Quality Control Samples**								
Concentration (ng/mL)	1.89		3.78		8.82				
Inter day Precision (%CV)	6.28		4.62		5.45				
Inter day Accuracy (% Bias)	3.19		3.40		2.61				

Comments on Chromatograms: Satisfactory.

Table 14. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ANI 157_06	1/9/06	Application of chromatographic methods to routine drug analysis
ANI 156_09	9/23/05	Sample re-assays and reporting of final concentration
ANI 167_05	6/30/05	Chromatographic acceptance criteria and verification of chromatograms

Table 15. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	There were no PK repeats
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Satisfactory

4.1.1.4 Pharmacokinetic Results

Comments on Pharmacokinetic and Statistical Analysis:

- Since studies were carried out in four groups, data were analyzed for any group effects. No group effects were observed (p-values for GRP*TRT interaction were >0.10). Therefore, statistical analyses were conducted using the combined data and without GRP*TRT term in the model.

- The reviewer calculated the 90% confidence intervals for 146 subjects (Test n=70, Ref n=76). The summary of PK data and results for methylprednisolone acetate are presented in **Table 16 - Table 19** and Figure 1.

- The pharmacokinetic parameters and 90% confidence intervals for methylprednisolone acetate calculated by the reviewer agree with firm's calculations.

- The 90% confidence intervals for lnAUC0-t, lnAUC∞, and lnCmax are within the acceptable limits of 80-125%.

Summary and Conclusions: The single-dose fasting BE study on methylprednisolone acetate 80 mg/mL injectable suspensions is **acceptable.**

Table 16. Arithmetic Means for Pharmacokinetic Parameters – Methylprednisolone Acetate (n=146)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCT	2944.36	34.40	3064.81	29.30	0.96
AUCI	3483.16	28.10	3646.90	28.09	0.96
CMAX	7.74	59.93	7.27	56.03	1.06
TMAX	24.00	.	24.00	.	1.00
KE	0.00	50.85	0.00	52.67	1.08
THALF	400.20	69.46	415.48	49.90	0.96

UNIT: AUC=ng Hr/mL CMAX=ng/mL TMAX (Median) =HR

Table 17. Geometric Means and 90% Confidence Intervals – Methylprednisolone Acetate (n=146)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	2734.35	2922.04	0.94	86.38	101.37
LAUCI	3334.98	3501.77	0.95	88.71	102.24
LCMAX	6.50	6.40	1.02	89.76	115.16

Mean1=Test, Mean2=Ref; UNIT: AUC=ng HR/mL CMAX=ng/ML TMAX (Median) =HR

Table 18. Additional Study Information, Fasting Study Methylprednisolone Acetate (n=146)

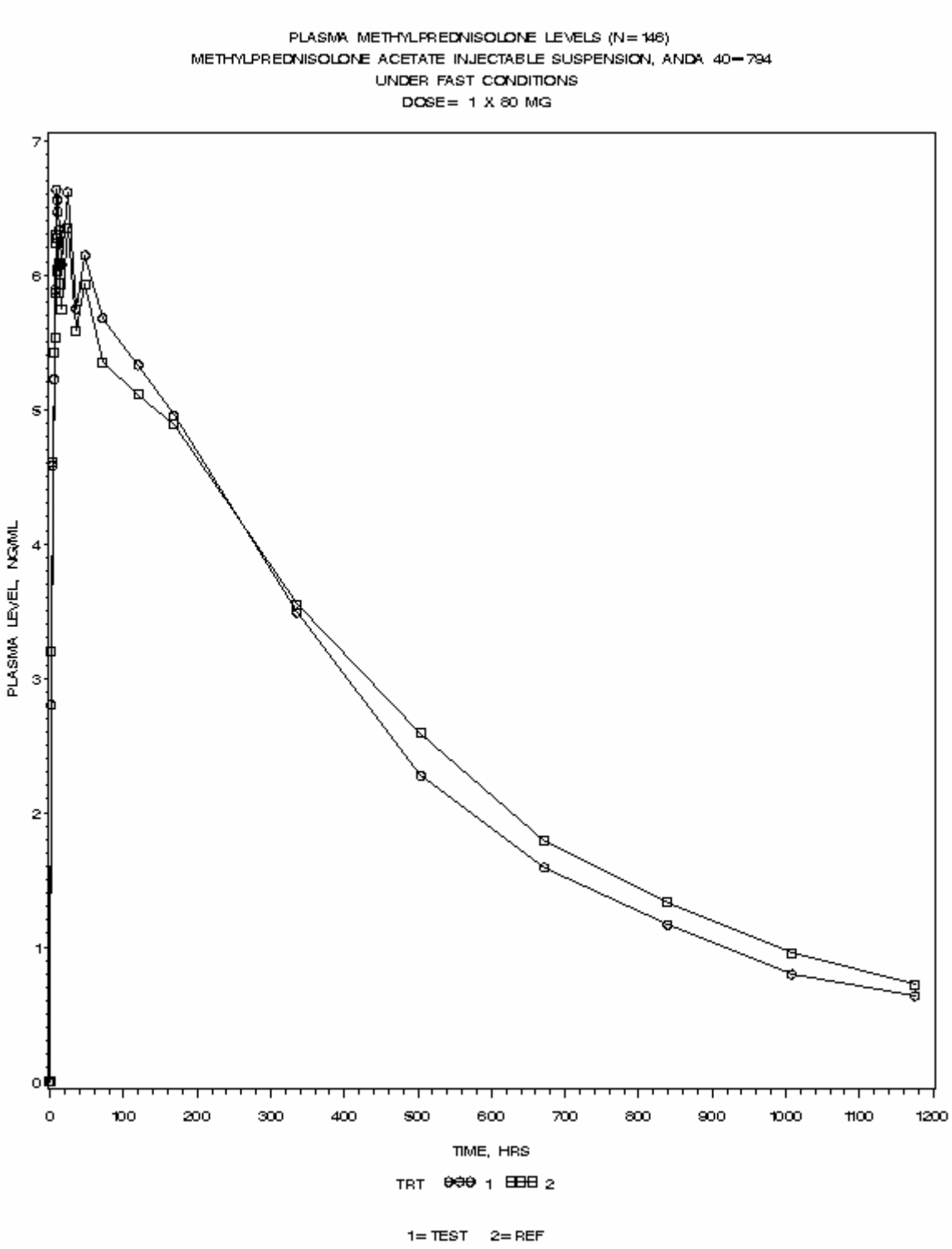
Root mean square error, AUC0-t	0.297496	
Root mean square error, AUC∞	0.261781	
Root mean square error, Cmax	0.463240	
	Test	**Reference**
Ratio of AUC0-t/AUC∞ : Mean (Range)	0.88	0.85
Kel and AUC∞ determined for how many subjects?	65	75
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
Measurable drug concentrations at 0 hr	0	
First measurable drug concentration as Cmax	0	
Were the subjects dosed as more than one group?	Yes	

Table 19. Mean Plasma Concentrations, Single-Dose Fasting BE Study (n=146)
Methylprednisolone Acetate

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME, HR					
0	0.00	.	0.00	.	.
2	2.80	61.46	3.20	102.48	0.87
4	4.58	65.34	4.62	68.82	0.99
6	5.23	56.11	5.42	51.18	0.96
7	5.89	62.90	5.54	46.25	1.06
8	6.31	62.96	5.87	46.37	1.07
9	6.64	63.17	6.24	48.04	1.06
10	6.56	64.23	6.27	45.78	1.05
11	6.47	60.48	6.04	47.16	1.07
12	6.34	62.84	6.09	49.71	1.04
14	6.30	65.20	5.94	52.35	1.06
16	6.08	65.51	5.75	54.68	1.06
24	6.62	61.92	6.35	50.21	1.04
36	5.75	59.22	5.59	50.80	1.03
48	6.15	57.12	5.93	47.50	1.04
72	5.68	56.98	5.35	44.68	1.06
120	5.33	55.80	5.11	39.61	1.04
168	4.95	49.69	4.89	36.68	1.01
336	3.49	40.85	3.55	37.40	0.98
504	2.28	36.31	2.59	36.19	0.88
672	1.59	49.11	1.79	42.21	0.89
840	1.17	46.83	1.33	46.90	0.88
1008	0.80	57.63	0.96	53.67	0.84
1176	0.64	93.34	0.72	66.01	0.89

Mean1=Test, Mean2=Reference, Unit: Plasma Level=ng/mL Time=Hrs

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Methylprednisolone Acetate (n=146)



4.2 Formulation Data

[Not for Release Under FOI]

Components	Amount per unit		Amount (%)	
Methylprednisolone Acetate	40.0 mg	80.0 mg		(b) (4)
Polyethylene Glycol 3350	29.0 mg	28.0 mg		
Myristil-Gamma-Picolinium HCl	0.19 mg	0.19 mg		
Sodium Chloride	(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%

		Methylprednisolone Acetate 40 mg/mL injectable suspension	Depo-Medrol® 40 mg/mL	Methylprednisolone Acetate 80 mg/mL injectable suspension	Depo-Medrol® 80 mg/mL
	Components	Quantity per unit	Quantity per unit	Quantity per unit	Quantity per unit
1	Methylprednisolone Acetate	40.0 mg	40 mg	80.0 mg	80 mg
2	Polyethylene Glycol 3350	29.0 mg	29 mg	28.0 mg	28 mg
3	Myristyl-Gamma-Picolinium Chloride	0.19 mg	(b) (4)	0.19 mg	(b) (4)
4	Sodium Chloride	(b) (4)	*To adjust Tonicity	(b) (4)	*To adjust tonicity
5	Hydrochloric Acid	To adjust pH	To adjust pH	To adjust pH	To adjust pH
6	Sodium Hydroxide	To adjust pH	To adjust pH	To adjust pH	To adjust pH
7	(b) (4)				
8					

4.3 Dissolution Data

Dissolution Review Path	see DFS 40794 (Shrivastava): sign off dates 6/6/2007 and 12/4/2006

Dissolution results: In vitro dissolution testing has previously been reviewed and was found acceptable (see v:\firmsnz\Sandoz\ltrs&rev\40794Cklist0706 and \\40795DA0307). The FDA recommended the following method and specifications:

Medium	0.55% (SDS) at 37 ^{0}C	
Flow rate	8 mL/min.	
Type of Cell	22.6 mm	
Glass beads	1 mm	
Glass beads loading	13 g	
Type of filter	2 filters GF/C (Whatman)	
Sample loading	2 mL for 40 mg/mL; 1 mL for 80 mg/mL	
Specifications:		
40 mg/mL:	30 minutes	(b) (4) %
	90 minutes	NLT (b) (4)
80 mg/mL:	30 minutes	(b) (4) %
	90 minutes	NLT (b) (4)

However, the firm has not accepted the FDA recommended dissolution method and specifications.

Following this page, 26 pages withheld in full - (b)(4) SAS data

BIOEQUIVALENCE DEFICIENCIES

ANDA/AADA: 40-794

APPLICANT: Sandoz Canada, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP, Single-dose vial Formulation, 40 mg and 80 mg

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

1. Please acknowledge your acceptance of the following dissolution testing method and specifications:

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading:	2 mL for 40 mg/mL; 1 mL for 80 mg/mL

Specifications:

40 mg/mL:	30 minutes	(b) (4) 0%
	90 minutes	NLT (b) (4) %
80 mg/mL:	30 minutes	(b) (4) %
	90 minutes	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

ANDA: 40-794

1.	**Fasting Study**	Strength:	80 mg/mL
	(STF)	Outcome:	**AC**
	Submission Date(s)	**October 18, 2006**	
	Clinical Site:	SFBC Anapharm, Quebec, Canada	
	Analytical Site:	SFBC Anapharm, Quebec, Canada	
2.	**Dissolution waiver**	Strength:	40 mg/mL
	(DIW)	Outcome:	**IC**
	Submission Date(s)	**October 18, 2006**	

3	**Study Amendment**	Strength:	40 mg/mL and 80 mg/mL		
	(STA)	Outcome:	**IC**	**WC**	
	Submission Date(s)	**August 9, 2007 (Potency Data)**			
	Clinical Site:				
	Analytical Site:				

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/s/

Surendra P. Shrivastava
8/30/2007 11:02:45 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
8/30/2007 11:14:42 AM
BIOPHARMACEUTICS

Dale Conner
8/30/2007 11:31:03 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	40-794
Drug Product Name	Methylprednisolone Acetate Injectable Suspension
Strength	40 mg/mL and 80 mg/mL
Applicant Name	Sandoz, Inc.
Submission Date	September 5, 2007
Reviewer	Keri Suh, Pharm.D.

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.

ANDA 40-794

BIOEQUIVALENCE - ACCEPTABLE

Submission date: September 5, 2007

1. Study Amendment (STA) Strengths: All
Outcome: AC

Outcome Decisions: **AC** - Acceptable

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

/s/

Keri Suh
9/17/2007 01:16:12 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

June 19, 2008

ANDA: 40-794

Drug Product Name
Proprietary: N/A
Non-proprietary: Methylprednisolone Acetate Injectable Suspension, USP (single-dose)
Drug Product Classification: N/A
Review Number: #1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
July 21, 2006	July 21, 2006	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) (single-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 40-719 - Sandoz Canada Inc. Multi-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 40-794 and 40-719 are similar.

C. **REMARKS:** None

filename: 40-794.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

Data for (b) (4) data were incomplete. Data are required for (b) (4). Data for the (b) (4) were 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

Following this page, 20 pages withheld in full - (b)(4)

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

(1.14.1.3, Vol. 1.1, pages 2-14)

The drug product is a sterile solution available in 2 strengths (40 mg/ml, 1 ml fill volume, single dose) and 80 mg/ml, 1 ml fill volume, single dose) given by intramuscular, intrasynovial, soft tissue or intralesional injection. The drug product is stored at 20-25^{o}C (68-77^{o}F).

Acceptable

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 40-794 APPLICANT: Sandoz Canada Inc

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP (single-dose)

A. Microbiology Deficiencies:

1. (b) (4)

2.

3.

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 12:23:38 PM
MICROBIOLOGIST

Kun Shen
7/21/2008 12:34:04 PM
MICROBIOLOGIST

Neal Sweeney
7/21/2008 01:08:43 PM
MICROBIOLOGIST

Brenda Pillari
7/21/2008 01:11:31 PM
MICROBIOLOGIST

Product Quality Microbiology Review

January 12, 2009

ANDA: 40-794

Drug Product Name
Proprietary: N/A
Non-proprietary: Methylprednisolone Acetate Injectable Suspension, USP (single-dose)
Drug Product Classification: N/A
Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
August 22, 2008	August 25, 2008	N/A	January 7, 2009

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Microbiology Review Date
July 21, 2006	1	June 19, 2008
December 10, 2007*	1	June 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) (single-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: 40-794a1.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)

[redacted]

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

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

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
1/14/2009 08:21:12 AM
MICROBIOLOGIST

Kun Shen
1/14/2009 12:42:39 PM
MICROBIOLOGIST

checked for correct file and linking

Neal Sweeney
2/12/2009 10:48:40 AM
MICROBIOLOGIST

Brenda Pillari
2/12/2009 04:54:39 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-794

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

SANDOZ

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

JUL 2 1 2006

40-794

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 (Single 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 (Single Dose Vials) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA in CTD format consists of 22 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 (white jackets) 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).

Electronic Media: Sandoz is providing the following electronic media:

- MODULE 2- Quality Overall Summary: contains the QOS in MS Word Format
- BIO SUMMARY TABLES 1-8: contains MS Word and pdf Format
- BIO SAS Transport Files

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 LABELING SUBMISSION contains draft physician insert and draft container labels in pdf format

If there are any comments or questions about this application, please contact me at 303-438-4237.

Sincerely,

Sandoz Inc.

A Sherwood for

Beth Brannan, Director
Regulatory Affairs

cc: Peggy Levy (Module 1)

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

****For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www.fda.gov/cder/regulatory/ersr/ectd.htm**
*****For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
** For more CTD and eCTD informational links see the final page of the ANDA Checklist
*** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage **http://www.fda.gov/cder/ogd/** ***

ANDA #: 40-794 **FIRM NAME:** SANDOZ INC.

PIV: NO **Electronic or Paper Submission:** PAPER

RELATED APPLICATION(S): 40-719 FROM SANDOZ INC. FOR METHYLPREDNISOLONE ACETATE INJECTION FOR 40 MG/ML AND 80 MG/ML (MULTIPLE DOSE VIALS) PN 3/9/06

First Generic Product Received? NO

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☒ **Micro Review !!!Yes, MICRO Review NEEDED!!!**
☐ **BST**	☒ **BDI**	

DRUG NAME: METHYLPREDNISOLONE ACETATE
DOSAGE FORM: INJECTABLE SUSPENSION USP, 40 MG/ML AND 80 MG/ML (SINGLE DOSE)

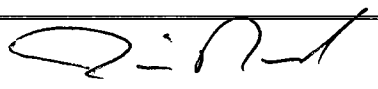
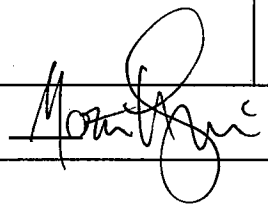
Random Queue: 5
Chem Team Leader: Bykadi, Raj PM: Ben Danso Labeling Reviewer: Ruby Wu

Letter Date: JULY 21, 2006 **Received Date:** JULY 24, 2006

Comments: **EC-1 YES** **On Cards:** YES
Therapeutic Code: 5030100 CORTICOSTEROIDS

Archival copy: PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand  **Date 9/25/06**	**Recommendation:** ☐ **FILE** ☒ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: 	**Date:** 26 Sept 2006

ADDITIONAL COMMENTS REGARDING THE ANDA:

Incomplete dissolution. The applicant has not provided a comparison of their product verses the RLD product.

Need to revise patent certification by removing reference to the (b) (4) and adding the 80 mg/mL strength.

Need to provide a DMF letter of authorization from (b) (4) allowing FDA to access the DMF # (b) (4)

Contact: Beth Brannan 303-438-4237

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JULY 21, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations NO **1.3.5.2** **Patent Certification** 1. Patent number(s) N/A 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES no unexpired exclusivities	☐

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y (b) (4) b. Type III DMF authorization letter(s) for container closure Y **DMF letter from (b) (4) needs to be revised to allow FDA to review the DMF.** 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Y	☐
1.12.11	**Basis for Submission** NDA# : 11-757 Ref Listed Drug: DEPO MEDROL Firm: PHARMACIA AND UPJOHN ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

		ACCEPTABLE
1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Methylprednisolone acetate 3. Inactive ingredients Same 4. Route of administration Intramuscular 5. Dosage Form Injectable suspension 6. Strength 40 mg/mL, 80 mg/mL	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** For 40 mg/mL strength Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES	☒
1.14.1	**Draft Labeling** **(Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y single copy paper and electronic **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** Y **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** Y **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** Y **3.2.S.1.2** **Structure** Y **3.2.S.1.3** **General Properties** Y	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API DMF# (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5** **Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition Y 2) Inactive ingredients are appropriate per IIG Q1/Q2 per RLD labeling	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report Y	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation Y **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 40mg/mL – (b) (4) 80mg/mL – (b) (4) 3. If sterile product: (b) (4) 4. Reprocessing Statement Y **3.2.P.3.4** **Controls of Critical Steps and Intermediates** **3.2.P.3.5** **Process Validation and/or Evaluation** OK for filing per Lynn E. (b) (4)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** Y **3.2.P.4.3** **Validation of Analytical Procedures** Y **3.2.P.4.4** **Justification of Sepcifications** Applicant COA Y	☒

MODULE 3
3.2.P DRUG PRODUCT

		ACCEPTABLE
3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form 2. Same lot numbers see sec. 3.2.R.3.P **3.2.P.5.4** **Batch Analysis** 40 mg/mL - 1100402 Certificate of Analysis for Finished Dosage Form 80 mg/mL - 124943 **3.2.P.5.5** **Characterization of Impurities** Y **3.2.P.5.6** **Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes 2 mL glass vial 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period (b) (4) months **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data Y 40mg/mL-1100402 2. Batch numbers on stability records the same as the test batch 80mg/mL-124943	☒

MODULE 3
3.2.R Regional Information

		ACCEPTABLE
3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) N/A** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 40mg/mL 80mg/mL Theoretical Yield (b) (4) Actual Yield Packaged Yield **3.2.R.1.P.2** **Information on Components** N **3.2.R.2.P** **Comparability Protocols** Y **3.2.R.3.P** **Methods Validation Package** N- USP drug product Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) Q1/Q2 per RLD labeling **2. Lot Numbers of Products used in BE Study(ies):** 80mg/mL-124943 40mg/mL-1100402 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 **Comparative BA/BE Study Reports** Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** In-Vitro Dissolution: Did not provide comparative dissolution, only the applicant product **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** Bioanalytical validation report N **5.3.7** **Case Report Forms and Individual Patient Listing** N	☐
5.4	**Literature References** N/A	
	Possible Study Types:	

Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING 80MG/ML 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) AUCt 86.65 – 102.11 2. EDR Email: Data Files Submitted: YES SENT TO EDR AUC∞ 88.58 – 102.80 3. In-Vitro Dissolution: YES – not comparative Cmax 90.45 – 116.73	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 4/18/2006 C. Bina

****CTD and eCTD Informational Links**

ANDA 40-794 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

RTR 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD.

✓ 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. Depo-Medrol 11-757

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

RTR 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ✓ yes ____ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

____ 22) Document in record book.

Signature Martin A Green date 26 Sept 2006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 40-794

Sandoz Inc.
U.S. Agent for: Sandoz Canada Inc.
Attention: Beth Brannan
2555 West Midway Boulevard,
P.O. Box 446
Broomfield, CO 80038

SEP 28 2006

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated July 21, 2006, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL single dose 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 submit *in vitro* comparative dissolution profiles comparing your proposed drug product to the reference listed drug. A complete dissolution report should contain the individual data for twelve dosage units (for both the proposed product and the reference listed product), 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.

In addition, please provide the following:

Please revise the Patent Certification Statement by removing reference to the [redacted] (b) (4) of the drug product and including reference to the 80 mg/mL strength of the proposed drug product.

Pleas provide a Drug Master File (DMF) letter of authorization from [redacted] (b) (4) authorizing the FDA to access the DMF information.

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:

Iain Margand
Project Manager
(301)827-5835

Sincerely yours,

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

cc: ANDA 40-794
DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610
HFD-143/OIM/DRM

Endorsement:
HFD-615/M.Shimer, Chief, RSB _____ date 26 Sept 06
HFD-615/I.Margand, CSO _____ date 9/26/06

Word File \\CDSNAS\OGDS11\FIRMSNZ\Sandoz\Ltrs&rev\0794.rtr
F/T 9/25/06
Refuse to Receive 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

SANDOZ

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

505(j)(2)(a) OK
9 Nov 2006
AMENDMENT
N/A c

October 18, 2006

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 September 28, 2006. Provided in this amendment is a complete response to FDA's request.

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.

Aherwood for
Beth Brannan, Director
Regulatory Affairs

Enclosures

BB/ags
Cc: Peggy Levy (submission)

RECEIVED
OCT 19 2006
OGD / 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

SANDOZ

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

N/AC

NOV 6 2006

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Minor Amendment – Telephone Amendment to October 18, 2006 Submission

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 telephone request on October 30, 2006 from Ian Margand, requesting a revised DMF Letter of Authorization from (b) (4) previously filed on October 18, 2006. Provided in this amendment is the requested information.

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

RECEIVED
NOV 0 8 2006
OGD / CDER

Enclosures

BB/lah
Cc: Peggy Levy (submission)

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

****For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm**
*****For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
** For more CTD and eCTD informational links see the final page of the ANDA Checklist
*** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ ***

ANDA #: 40-794 **FIRM NAME**: SANDOZ INC.

PIV: NO **Electronic or Paper Submission:** PAPER

RELATED APPLICATION(S): 40-719 FROM SANDOZ INC. FOR METHYLPREDNISOLONE ACETATE INJECTION FOR 40 MG/ML AND 80 MG/ML (MULTIPLE DOSE VIALS) PN 3/9/06

First Generic Product Received? NO

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☒ **Micro Review !!!Yes, MICRO Review NEEDED!!!**
☐ **BST**	☒ **BDI**	

DRUG NAME: METHYLPREDNISOLONE ACETATE
DOSAGE FORM: INJECTABLE SUSPENSION USP, 40 MG/ML AND 80 MG/ML (SINGLE DOSE)

Random Queue: 5
Chem Team Leader: Bykadi, Raj PM: Ben Danso Labeling Reviewer: Ruby Wu

Letter Date: JULY 21, 2006 **Received Date**: JULY 24, 2006

Comments: EC-1 YES **On Cards:** YES
Therapeutic Code: 5030100 CORTICOSTEROIDS

Archival copy: PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand **Date 11/7/06**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Incomplete dissolution. The applicant has not provided a comparison of their product verses the RLD product.

Need to revise patent certification by removing reference to the (b) (4) and adding the 80 mg/mL strength.

Need to provide a DMF letter of authorization from (b) (4) allowing FDA to access the DMF # (b) (4)

Dissolution information provided in amendment dated 10/18/06 along with revision of patent information. DMF letter for (b) (4) was provided in a telephone amendment dated 11/6/06.

Contact: Beth Brannan 303-438-4237

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JULY 21, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations NO **1.3.5.2** **Patent Certification** 1. Patent number(s) N/A 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES no unexpired exclusivities	☐

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y (b) (4) b. Type III DMF authorization letter(s) for container closure Y **DMF letter from (b) (4) needs to be revised to allow FDA to review the DMF.** 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Y	☐
1.12.11	**Basis for Submission** NDA# : 11-757 Ref Listed Drug: DEPO MEDROL Firm: PHARMACIA AND UPJOHN ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Methylprednisolone acetate 3. Inactive ingredients Same 4. Route of administration Intramuscular 5. Dosage Form Injectable suspension 6. Strength 40 mg/mL, 80 mg/mL	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** For 40 mg/mL strength Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y single copy paper and electronic **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** Y **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** Y **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** Y **3.2.S.1.2** **Structure** Y **3.2.S.1.3** **General Properties** Y	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API DMF# (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5** **Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition Y 2) Inactive ingredients are appropriate per IIG Q1/Q2 per RLD labeling	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report Y	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation Y **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 40mg/mL (b) (4) 80mg/mL – (b) (4) 3. If sterile product: (b) (4) 4. Reprocessing Statement Y **3.2.P.3.4** **Controls of Critical Steps and Intermediates** **3.2.P.3.5** **Process Validation and/or Evaluation** OK for filing per Lynn E. (b) (4)	☒

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** Y **3.2.P.4.3** **Validation of Analytical Procedures** Y **3.2.P.4.4** **Justification of Sepcifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form 2. Same lot numbers see sec. 3.2.R.3.P **3.2.P.5.4** **Batch Analysis** 40 mg/mL - 1100402 Certificate of Analysis for Finished Dosage Form 80 mg/mL - 124943 **3.2.P.5.5** **Characterization of Impurities** Y **3.2.P.5.6** **Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes 2 mL glass vial 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period (b) (4) months **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data Y 40mg/mL-1100402 2. Batch numbers on stability records the same as the test batch 80mg/mL-124943	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) N/A** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 40mg/mL 80mg/mL Theoretical Yield (b) (4) Actual Yield Packaged Yield **3.2.R.1.P.2** **Information on Components** N **3.2.R.2.P** **Comparability Protocols** Y **3.2.R.3.P** **Methods Validation Package** N- USP drug product Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

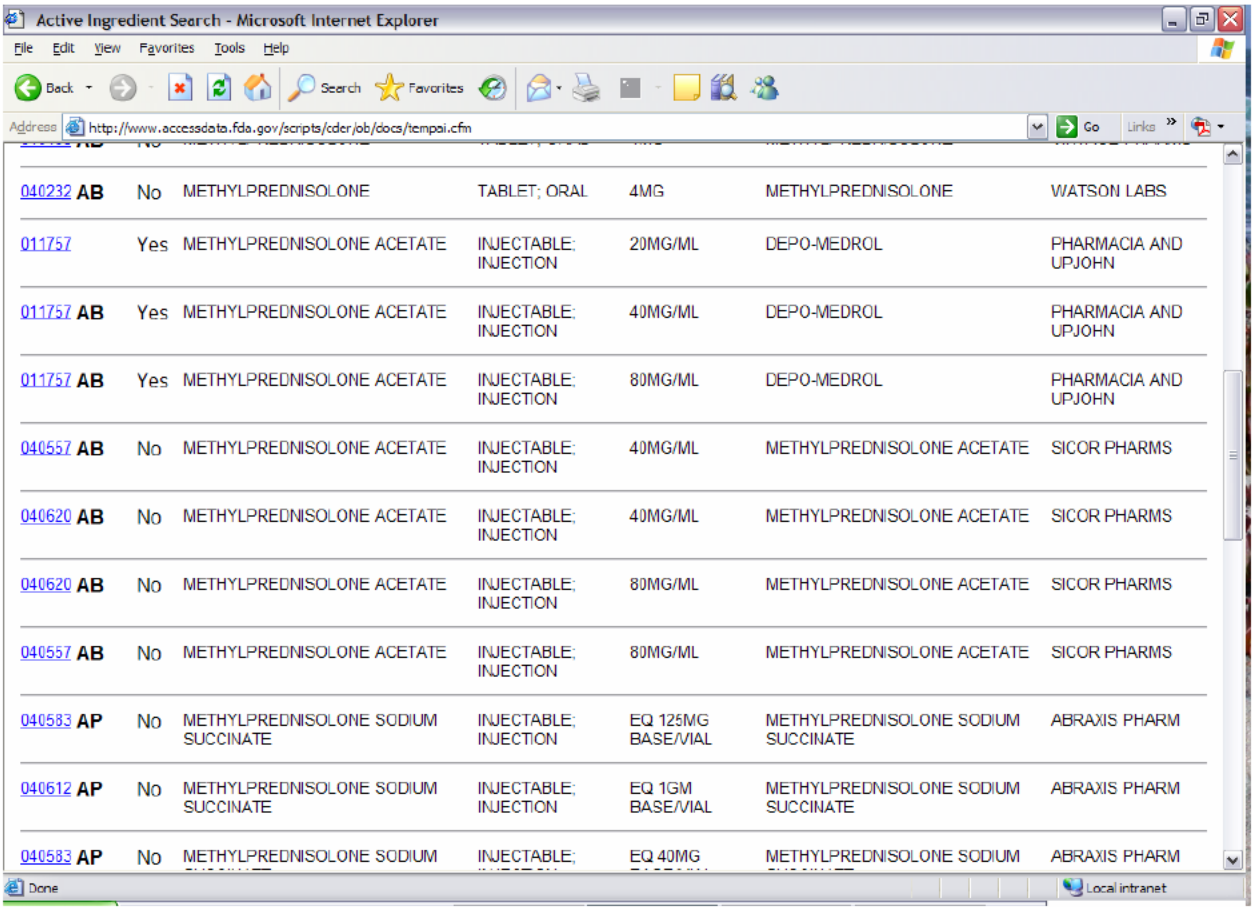
5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) Q1/Q2 per RLD labeling **2. Lot Numbers of Products used in BE Study(ies):** 80mg/mL-124943 40mg/mL-1100402 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 **Comparative BA/BE Study Reports** Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** In-Vitro Dissolution: Did not provide comparative dissolution, only the applicant product See amendment dated 10/18/06. **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** Bioanalytical validation report N **5.3.7** **Case Report Forms and Individual Patient Listing** N	☐
5.4	**Literature References** N/A	

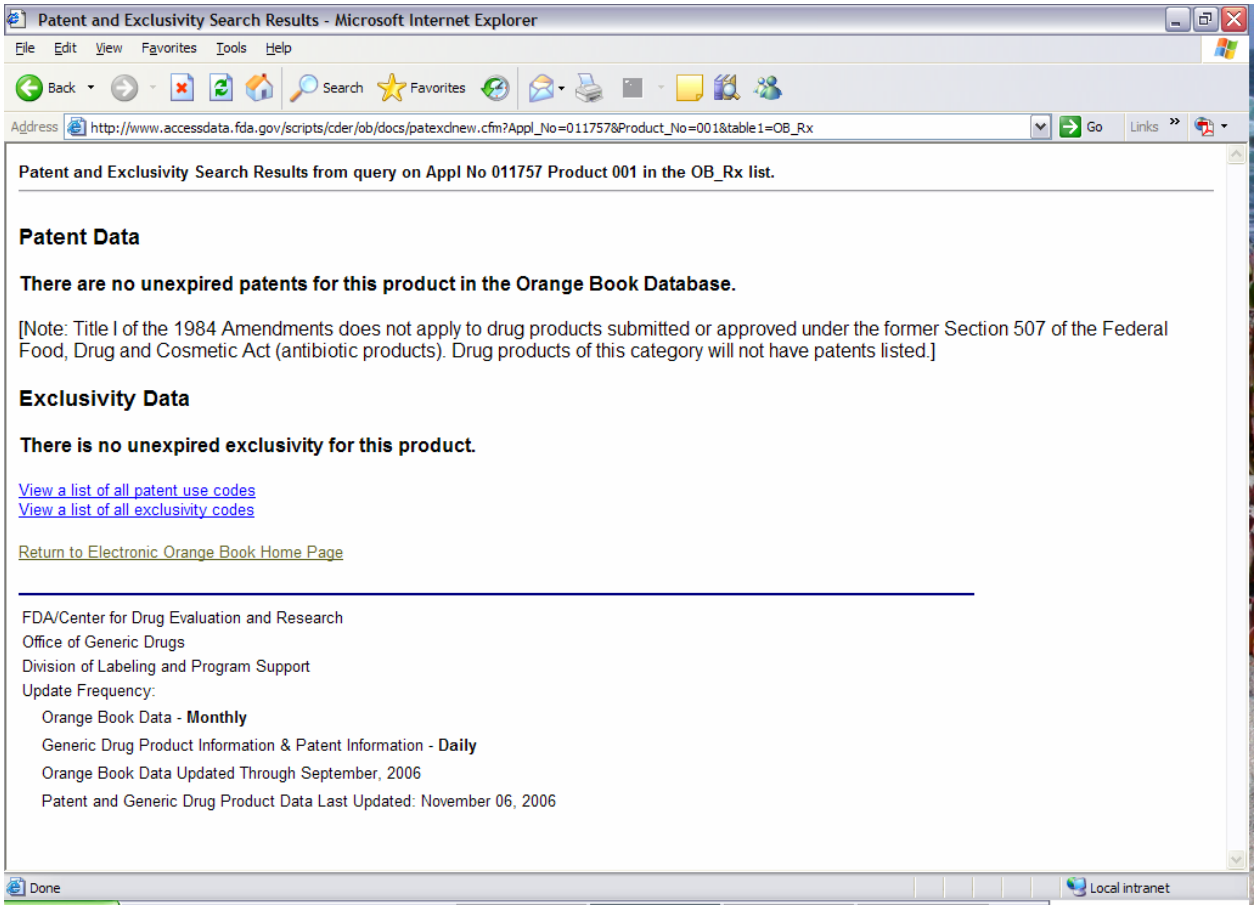
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING 80MG/ML 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) AUCt 86.65 – 102.11 2. EDR Email: Data Files Submitted: YES SENT TO EDR AUC∞ 88.58 – 102.80 3. In-Vitro Dissolution: YES – not comparative Cmax 90.45 – 116.73	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐

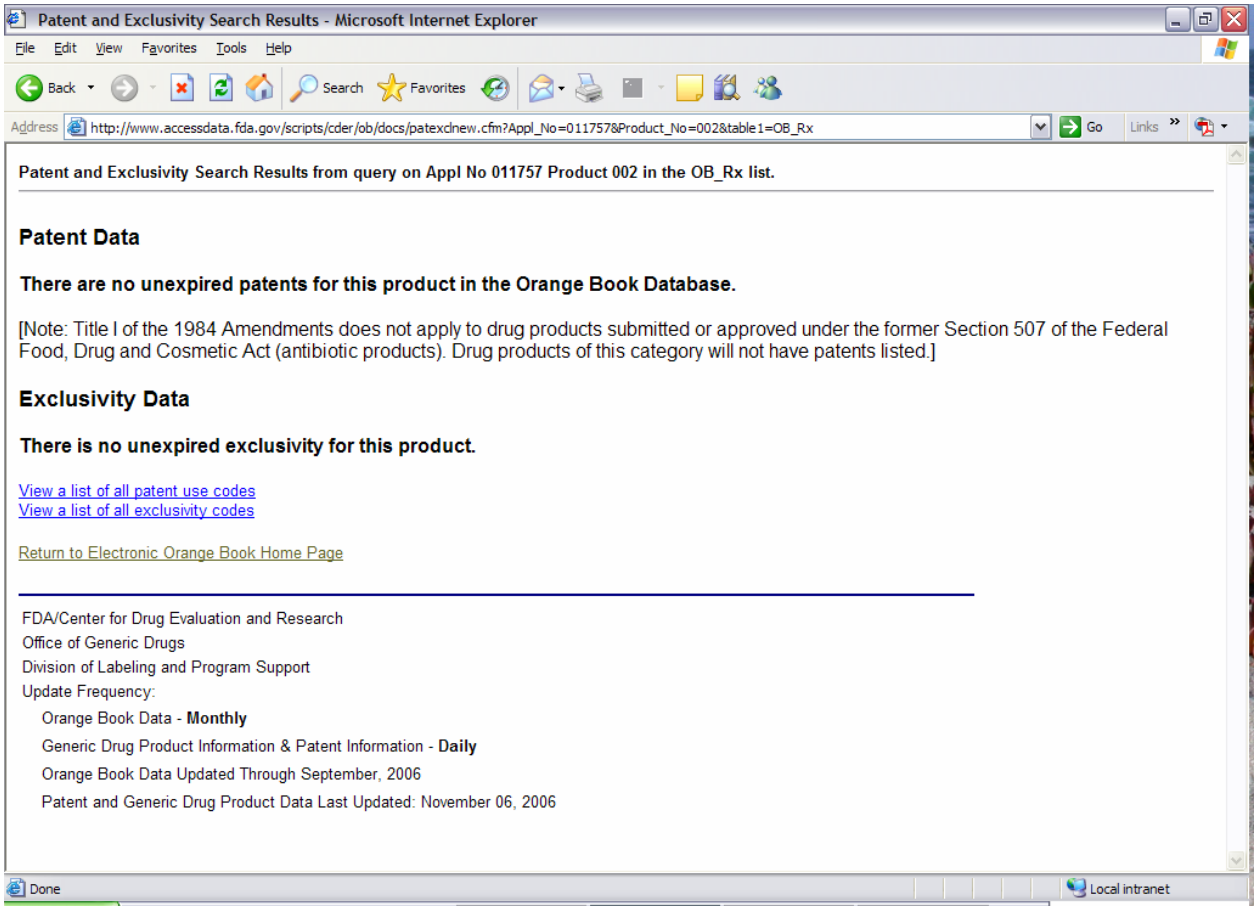
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 4/18/2006 C. Bina

**CTD and eCTD Informational Links







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

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/s/

Martin Shimer

11/17/2006 11:24:40 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 40-794

Sandoz Inc.
U.S. Agent for: Sandoz Canada Inc.
Attention: Beth Brannan
2555 West Midway Boulevard
P.O. Box 446
Broomfield, CO 80038

Dear Madam:

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

Reference is made to our "Refuse to Receive" letter dated September 28, 2006 and your amendment dated October 18, 2006.

Reference is also made to the telephone conversation dated October 30, 2006 and your correspondence dated November 6, 2006.

NAME OF DRUG: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL and 80 mg/mL single dose vials

DATE OF APPLICATION: July 21, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 19, 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:

Benjamin Danso
Project Manager
301-827-5763

Sincerely yours,

{See appended electronic signature page}
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Martin Shimer

11/17/2006 01:30:18 PM

BIOEQUIVALENCY AMENDMENT

ANDA 40-794

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 FAX: 303-438-4600

FROM: Keri Suh PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 18, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 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 **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA:40-794 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP, 40 mg/mL and 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 deficiencies have been identified:

1. You have proposed a dissolution method using USP Apparatus IV (flow-through cell) and 0.55% SDS. However, you have provided data for test products only. Complete comparative dissolution data for 40 and 80 mg/mL test and reference products are requested.

2. Additionally, please conduct comparative dissolution testing on 40 and 80 mg/mL test and reference products using the following FDA-recommended method:

Medium:	Water
Volume (mL):	900 mL
USP Apparatus:	II (Paddle) at 50 rpm
Sampling Times:	15, 30, 45, 60, 120 and 240 minutes
Dosage Units:	12 each for the test and reference

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Barbara Davit
12/5/2006 12:49:46 PM
Signing for Dale P Conner

Telephone Fax

ANDA 40-794

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 (1 mL single-dose vials) and 80 mg/mL (1 mL single-dose vials).

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling comments

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

ANDA Number: 40-794

Date of Submission: October 18, 2006

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (1 mL single-dose vials) and 80 mg/mL (1 mL single-dose vials)

Labeling Deficiencies (based on labeling submitted July 21, 2006)

1. CONTAINER –(1 mL single-dose vial)
   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. Ensure that "NOT" appears on the same line as "FOR INTRAVENOUS USE."

2. CARTON- (1 x 1 mL vial and 10 x 1 mL vials)
   a. Refer to CONTAINER comment 1.a.
   b. Please add the statement "Sterile"
   c. 40 mg/mL 1 x 1 mL vial only: '(b) (4)" is listed in the "Each mL contains" statement. However, this ingredient is not found in your composition statement. Please comment.

3. PACKAGE INSERT
   a. CONTRAINDICATIONS: Revise this section to read as "Methylprednisolone acetate injectable suspension is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents."
   b. WARNINGS:
      i. Add "**Methylprednisolone acetate injectable suspension, USP is Not Recommended For Intrathecal Administration**." after "It is critical that…" paragraph.
      ii. Delete '(b) (4)"
      iii. Replace (b) (4) with "**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."**
      iv. Replace (b) (4) ." with "Allergic skin reactions have been reported apparently related to the excipients in the formulation (see DESCRIPTION). Rarely has skin testing demonstrated a reaction to methylprednisolone acetate, per se."
   c. PRECAUTIONS
      i. Delete (b) (4)
      ii. Add "Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia." after "Psychic derangements…" paragraph.
      iii. Delete the '(b) (4)" and '(b) (4)" subsections.

d. ADVERSE REACTIONS
   i. Delete "(b) (4)"
   ii. Delete (b) (4) ."

e. (b) (4) delete this section.

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
1/3/2007 10:53:01 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

SANDOZ

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)

ORIG AMENDMENT
N/AF

FEB 1 2 2007

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Amendment – Labeling – Response to January 3, 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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 January 3, 2007. The following is provided in response to the FDA comments (*in italics*):

1. CONTAINER –(1 mL single-dose vial)

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.*

Sandoz Response: Sandoz has revised the established name to use the recommended "Tall Man" lettering in accordance with this request.

B. Ensure that "NOT" appears on the same line as "FOR INTRAVENOUS USE."

Sandoz Response: The vial labels have been revised so that "NOT FOR INTRAVENOUS USE" appears on one line.

RECEIVED
FEB 1 3 2007
OGD / CDER

2. CARTON (1 x 1 mL vial and 10 x 1 mL vial)
A. *Refer to CONTAINER comment 1.a.*

Sandoz Response: The cartons have all been revised to include the Tall Man lettering of "MethylPREDNISolone".

B.Please add the statement "Sterile".

Sandoz Response: The cartons have all been revised to include the word "Sterile" on the principal display panel.

C. 40 mg/mL 1 x 1 mL vial only: " (b) (4) *" is listed in the "Each mL contains" statement. However, this ingredient is not found in your composition statement. Please comment.*

Sandoz Response: The (b) (4) was included in error on the 40 mg/mL 1 x 1 mL carton. It has been removed as this ingredient does not appear in the formulation/composition of the drug product.

3. PACKAGE INSERT
A. *CONTRAINDICATIONS: Revise this section to read as "Methylprednisolone acetate injectable suspension is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents."*

Sandoz Response: The CONTRAINDICATIONS section has been revised accordingly.

B. *WARNINGS:*
*i. Add "**Methylprednisolone acetate injectable suspension, USP is Not Recommended For Intrathecal Administration.**" After "It is critical that…" paragraph.*
ii. Delete " (b) (4) *"*
iii. Replace " (b) (4) *" with "* ***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."***

iv. Replace ' [redacted] *" With "Allergic skin reactions have been reported apparently related to the excipients in the formulation (see DESCRIPTION). Rarely has skin testing demonstrated a reaction to methylprednisolone acetate, per se."*

Sandoz Response: Sandoz has incorporated all WARNINGS section changes as described above.

C. PRECAUTIONS:
i. Delete " [redacted] *"*

ii. Add "Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia."
iii. Delete the " [redacted] *" and "* [redacted] *" subsections.*

Sandoz Response: Sandoz has incorporated all PRECAUTIONS section changes as described above.

D. ADVERSE REACTIONS:
i. Delete ' [redacted] *"*
ii. Delete " [redacted] *"*
iii. Delete the " [redacted] *" and "* [redacted] *" subsections.*

Sandoz Response: Sandoz has incorporated all ADVERSE REACTIONS section changes as described above.

E. [redacted] *delete this section*

Sandoz Response: Sandoz has deleted the [redacted] section as described above.

The revised labeling is attached electronically. The DRAFT package insert is provided in both pfd and word. Additionally, a side-by-side comparison of the proposed labeling with the last submission is provided electronically. The revised vial and carton labels are also provided.

Included on the CD are the following files:

Document	File Name on CD
Draft Physician Insert in MSWord format	PI_12pt.pdf
Draft Physician Insert in pdf format	PI_12pt.doc
Side by Side Comparison of previous filed and current proposed Physician Insert	Comparison_PI_previous vs current revised.doc
40 mg/mL -1 mL single dose vial label	Methylpred 3131-71 v.pdf
40 mg/mL – 1 x 1 mL carton label	Methylpred 3131-71 c.pdf
40 mg/mL – 10 x 1 mL carton label	Methylpred 3131-95 c.pdf
80 mg/mL – 1mL single dose vial label	Methylpred 3132-71 v.pdf
80 mg/mL – 1 x 1 mL carton label	Methylpred 3132-71 c.pdf
80 mg/mL – 10 x 1 mL carton label	Methylpred 3132-95 c.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 40-794

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
(301-827-7351 or 240-276-8952)

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 (1 mL single-dose vials) and 80 mg/mL (1 mL single-dose vials).

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling comments

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

ANDA Number: 40-794

Date of Submission: February 12, 2007 (amendment)

Applicant's Name: Sandoz Canada Inc.

Established Name: Methylprednisolone Acetate Injectable Suspension USP, 40 mg/mL (1 mL single-dose vials) and 80 mg/mL (1 mL single-dose vials)

Labeling Deficiencies

1. CONTAINER –(1 mL single-dose vial)
   Satisfactory in final print as submitted in the February 12, 2007 e-amendment.

2. CARTON- (1 x 1 mL vial and 10 x 1 mL vials)
   Satisfactory in final print as submitted in the February 12, 2007 e-amendment.

3. PACKAGE INSERT
   Satisfactory in draft.

Please submit final printed insert 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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/s/

John Grace
2/23/2007 06:59:46 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

SANDOZ

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

MAR 9 2007

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 December 5, 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.

A Sherwood for
Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/ags
cc. Peggy Levy (CL)

RECEIVED
MAR 12 2007
OGD / 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
Email:
Beth.Brannan@sandoz.com

SANDOZ

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

AMENDMENT
(including electronic labeling)

MAR 2 8 2007

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Amendment – Labeling – Response to February 23 and March 5, 2007 Deficiency Letters

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 dated February 23 and March 5, 2007. The following is provided in response to the FDA comments (*in italics*):

1. *CONTAINER –(1 mL single-dose vial)*
   Satisfactory in final print as submitted in the February 12, 2007 e-amendment.

Sandoz Response: Sandoz is providing final print container labels again. The label is now prepared for printing, the layout has not changed. The "manufactured by" statement has been revised, the (b) (4) distribution channel has been removed:

(b) (4)

MAR 2 8 2007

2. CARTON (1 x 1 mL vial and 10 x 1 mL vial)

Satisfactory in final print as submitted in the February 12, 2007 e-amendment.

Sandoz Response: Sandoz is providing the final print carton labels again. The cartons have been formatted for printing which includes a relocation of the bar code. The "manufactured by" statement has been revised, the (b) (4) distribution channel has been removed:

3. PACKAGE INSERT

Satisfactory in draft.

March 5, 2007 deficiency letter: In addition to addressing the labeling deficiency dated 2/23/07, please respond to the following request-
INSERT, DESCRIPTION: Please update the pH range of the drug product to be in accord with the USP. Methylprednisolone Acetate Injectable Suspension pH <791>: between 3.0 and 7.0.

Sandoz Response: Sandoz is providing the final print Physician Insert. The PI is provided in SPL, MS word, and final print artwork pdf. The "manufactured by" statement has been revised, the (b) (4) distribution channel has been removed as indicated for the carton. Additionally, the pH range has been revised to reflect the range of 3.0 to 7.0 as requested.

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 previous filed vs current.doc
Final Print Insert – actual size	M-1003052 136x296mm 03-2007.pdf

Document	File Name on CD
40 mg/mL -1 mL single dose vial label	Methylpred Inj 3131-71.pdf
40 mg/mL – 1 x 1 mL carton label	Methylpred Inj 3131-71 Carton.pdf
40 mg/mL – 10 x 1 mL carton label	Methylpred Inj 3131-95 Carton.pdf
80 mg/mL – 1mL single dose vial label	Methylpred Inj 3132-71.pdf
80 mg/mL – 1 x 1 mL carton label	Methylpred Inj 3132-71 Carton.pdf
80 mg/mL – 10 x 1 mL carton label	Methylpred Inj 3132-95 Carton.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)

MINOR AMENDMENT

ANDA 40-794

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 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 October 18, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__4__ 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.

Following this page, 3 pages withheld in full - (b)(4)

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/s/

Gururaj Bykadi
5/31/2007 11:39:17 AM

BIOEQUIVALENCY AMENDMENT

ANDA 40-794

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 FAX: 303-438-4600

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 18, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 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 **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA:40-794 APPLICANT: Sandoz, Inc.

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

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence study and the waiver request will be conducted later. The following comments/deficiency has been identified:

1. Your request to use the following dissolution method is acceptable:

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading	2 mL for 40 mg/mL; 1 mL for 80 mg/mL

2. You have not proposed any dissolution specifications for your products. Please acknowledge your acceptance of the following dissolution specifications:

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

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
6/7/2007 05:56:14 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

SANDOZ

ORIG AMENDMENT
N/AB

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 TELEPHONE AMENDMENT

AUG 9 2007

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Bioequivalence Telephone Amendment – Response to Telephone Request

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 telephone request from Keri Suh in the Division of Bioequivalence on August 1, 2007. Ms. Suh requested the potency results for our Reference Product Depo-Medrol 80mg/mL lot # 05MHJ. Attached, please find a COA for lot 05MHJ including results for Assay of Methylprednisolone Acetate.

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 10 2007
OGD

BIOEQUIVALENCY AMENDMENT

ANDA 40-794

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 FAX: 303-438-4600

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 18, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 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 **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA/AADA: 40-794

APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP, Single-dose vial Formulation, 40 mg and 80 mg

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

Please acknowledge your acceptance of the following dissolution testing method and specifications:

Medium	0.55% (SDS) at 37 ^{0}C
Flow rate	8 mL/min.
Type of Cell	22.6 mm
Glass beads	1 mm
Glass beads loading	13 g
Type of filter	2 filters GF/C (Whatman)
Sample loading:	2 mL for 40 mg/mL; 1 mL for 80 mg/mL
Specifications:	

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

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

9/4/2007 11:33:43 AM

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

ORIG AMENDMENT

SANDOZ

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

N 0794 /A B

SEP 5 2007

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Bioequivalence Amendment – Response to June 7 and September 4, 2007 Deficiencies

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 FDA deficiency letters dated June 7 and September 4, 2007. Please note both letters requested the same information. Attached, please find a complete response to the comments provided.

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.

BBran

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/ags
cc. Peggy Levy (CL)

RECEIVED
SEP 06 2007
OGD/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

SANDOZ

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

NOV 8 2007

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Minor Amendment – Response to May 31, 2007 Chemistry Deficiencies

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 FDA communication dated May 31, 2007. Provided in this amendment is a complete response to the deficiencies and comments.

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

RECEIVED
NOV 13 2007
OGD

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

SANDOZ

OVERNIGHT DELIVERY

ORIG AMENDMENT
N/AP

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
(Microbiology)

DEC 10 2007

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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

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/acs
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

SANDOZ

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)

FEB 8 2008

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Telephone Amendment – Chemistry

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 phone request made by Aijin Shen of FDA on January 28, 2008. Provided in this amendment is a complete response to her 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	**ANDA 40-794**
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
telephone amendment	**cmc** folder telephoneamendment.pdf (bookmarked)

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 (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

TELEPHONE AMENDMENT
(electronic)

FEB 28 2008

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Telephone Amendment – Chemistry – Response to 2-12-08 Request

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 phone request made by Aijin Shen of FDA on February 12, 2008. Provided in this amendment is a complete response to her 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	**ANDA 40-794**
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
telephone amendment	**cmc** folder telephone amendment.pdf (bookmarked)

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 (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 40-794, Methylprednisolone Acetate Injectable Suspension USP (single-dose)**. The submissions reviewed were submitted on 7/21/2006 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.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 40-794 APPLICANT: Sandoz Canada Inc

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension USP (single-dose)

A. Microbiology Deficiencies:

1. (b) (4)

2.

3.

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 01:57:21 PM

MINOR AMENDMENT

ANDA 40-794

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sandoz Inc. TEL: 303-438-4237

ATTN: Beth Brannan 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 October 18, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Acetate Injectable Suspension, 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.

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.

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

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

1 Please follow ICH guideline for method precision validation.

2 Please be diligent in generating various data, specifically stability data for FDA submission and reduce any human error during data generation.

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
7/25/2008 08:11:06 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
(electronic)

AUG 2 2 2008

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 40-794**
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Response to deficiencies	**cmc** folder micro amendment.pdf (bookmarked)

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 (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

SANDOZ

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)

OCT 7 2008

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Minor Amendment – Response to Chemistry Deficiency Letter dated July 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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 letter dated July 25, 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 40-794**
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Response to deficiencies	**cmc** folder minor amendment.pdf (bookmarked)

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 (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

CMC
TELEPHONE AMENDMENT
(electronic)

December 24, 2008

RE: ANDA 40-794 Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single Dose Vials)
Telephone Amendment – Chemistry – Response to 12-22-08 Request

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 40-794 for Methylprednisolone Acetate Injectable Suspension USP 40 mg/mL and 80 mg/mL (Single 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 phone request made by Aijin Shen of FDA on December 22, 2008. Below is summary of the telephone conversation between Aijin Shen and Alison Sherwood of Sandoz:

FDA Comment:

- Aijin Shen requested further clarification of our proposed drug substance specifications (b) (4) (ver 3, issue date 08-02-21) are acceptable.
- Also she would like us to submit the revised drug product specifications with the USP <467> statement included.

Sandoz Response:

- As requested, Sandoz has reviewed the submission history for this ANDA. In our telephone amendment submitted on February 28, 2008, we provided the current drug substance specification (version 3, issue date 08-02-21) and noted that the (b) (4)

SANDOZ

(b) (4)

- Also provided are updated drug product specifications which include a footnote indicating compliance to USP <467> (b) (4) requirements as demonstrated by the certification statement submitted on October 7, 2008.

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 40-794**
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
telephone amendment	**cmc** folder telephone 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.

Alison Sherwood, Manager
Regulatory Affairs

Enclosures

Cc: Daniel Abran (CL)

Alison Sherwood, Manager
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4513
Fax +1 303 438-4600
Email:
alison.sherwood@sandoz.com

SANDOZ

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

Ume

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.

ASherwood

Alison Sherwood, Manager
Regulatory Affairs

Enclosures: List of Applications

AS/sc

OGD APPROVAL ROUTING SUMMARY

ANDA # 40-794 Applicant SANDOZ Inc
Drug Methyprednisolone Acetate Inj. Susp. USP Strength(s) 40 mg/mL and 80 mg/mL

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

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 2/25/2009 Date 3/5/09
Chief, Reg. Support Branch Initials P.Chen for Initials rlw
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: Full Approval.
Comments: Letter date=7/21/2006; RTR date=9/28/2006. AC date=10/18/2006; Stamp date 10/19/2006. ACK on 11/17/2006. BOS=NDA 11-757 Depo-Medrol. "No relevant patents" certification. There are no patents/exclusivities listed in the OB for the RLD. This ANDA is eligible for full approval

2. Project Manager, Benjamin Danso Team 5 Date 2-20-09 Date _____
Review Support Branch Initials bd Initials _____

Original Rec'd date 7-21-06 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 10-19-06 Date of EER Status 11-20-06
Patent Certification (type) P2 Date of Office Bio Review 9-17-07
Date Patent/Exclus.expires Date of Labeling Approv. Sum 4-15-07
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App. 2-12-09
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☐
First Generic Yes ☐ No ☒ MV Commitment Rcd. from Firm Yes ☐ No ☐
Priority Approval Yes ☐ No ☒ Modified-release dosage form: Yes ☐ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) Interim Dissol. Specs in AP Ltr: Yes ☒
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date _____ Date 3/5/09
Name/Initials _____ Name/Initials rlw/for

Comments:
Final-printed labeling found acceptable for approval 4/15/07.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 3/5/09
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. Date 3/3/09
Chemistry Div. I Initials RMP

Comments:CMC is satisfactory for AP.

6. Frank Holcombe **First Generics Only** Date 3/5/09
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. TEVA Parenteral's ANDA 40-557 and 40-620 for this drug product were approved on February 23, 2005 and October 27, 2006.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Depo-Medrol Injectable Suspension, 40 mg/mL and 80 mg/mL; SDVs
Pharmacia & Upjohn Co. NDA 11-757 (001, 004)

8. Peter Rickman Date 3/5/09
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments:Bioequivalence study (single-dose, 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 8/30/07 and 9/17/07.

Final-printed labeling (FPL) found acceptable for approval 4/15/07.

Microbiology/Sterility Assurance found acceptable for approval (Micro Review #2) 2/12/09.

CMC found acceptable for approval (Chemistry Review #3).

OR

8. Robert L. West Date 3/5/09
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 11/20/06 (Verified 3/5/09). No "OAI" Alerts noted. Facilities are the same as those approved for Sandoz Canada's ANDA 40-719 approved on 1/29/09 for the multiple-dose presentation of this drug product.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for approval. Note: This is the "sister" ANDA to Sandoz Canada's ANDA 40-719 for this drug product packaged in multiple-dose vials.

9. Gary Buehler Date 3/5/09
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.

EES Data for: 040794

*** Compliance Recommendations ***

App No	Doc Seq No	Date	OC Recommendation
040794	000	11/20/2006	ACCEPTABLE

*** EER Table ***

(b) (4)

[redacted]

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 011757 Product 001 in the OB_Rx list.

Patent Data

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

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

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through January, 2009
Patent and Generic Drug Product Data Last Updated: March 04, 2009

Patent and Exclusivity Search Results from query on Appl No 011757 Product 004 in the OB_Rx list.

Patent Data

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

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

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Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through January, 2009
Patent and Generic Drug Product Data Last Updated: March 04, 2009

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/s/

Benjamin Danso
3/5/2009 01:22:39 PM