CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-671

APPROVAL LETTER

ANDA 75-671

JUL 25 2001

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, New York 10977

Dear Madam:

This is in reference to your abbreviated new drug application dated July 14, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Megestrol Acetate Oral Suspension, 40 mg/mL.

Reference is also made to our tentative approval letter dated October 23, 2000, and to your amendments dated August 10, and November 3, 1999; November 1, 2000; and May 4, and July 17, 2001.

The listed drug product referenced in your application, Megace Oral Suspension of Bristol Myers Squibb, is subject to a period of patent protection which expires on August 16, 2011, (U.S. Patent No. 5,338,732 [the '732 patent]). Your application contains a Paragraph IV Certification to the '732 patent under Section 505(j)(2)(A)(vii) (IV) of the Act. This certification states that your manufacture, use, or sale of this drug product will not infringe upon the '732 patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against Par Pharmaceutical, Inc. (Par) for infringement of the patent that is the subject of the certification (the '732 patent). You have notified the agency that Par has complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, Bristol Myers Squibb Company (BMS) initiated a patent infringement suit against Par in the United States District Court for the Southern District of New York involving a challenge to the '732 patent (Bristol-Myers Squibb Company v. Par Pharmaceutical, Inc., Civil Action No. 99 CIV.10822). You have notified the agency that Par prevailed at the district court level and that BMS appealed the decision. Furthermore, you also notified the agency that Par

prevailed in a final appellate ruling issued on July 16, 2001 by the United States Court of Appeals for the Federal Circuit.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Megestrol Acetate Oral Suspension, 40 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Megace® Oral Suspension, 40 mg/mL, of Bristol Myers Squibb). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

In addition, we note that Par was the first ANDA applicant to submit a substantially complete ANDA containing a Paragraph IV Certification to the '732 patent. Therefore, upon this approval Par is eligible for 180-days of generic drug market exclusivity as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the Act. This 180-day exclusivity commenced upon the date of the appellate ruling on July 16, 2001. The agency expects that you will begin commercial marketing of this drug product in a prompt manner.

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

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

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

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

Sincerely yours,

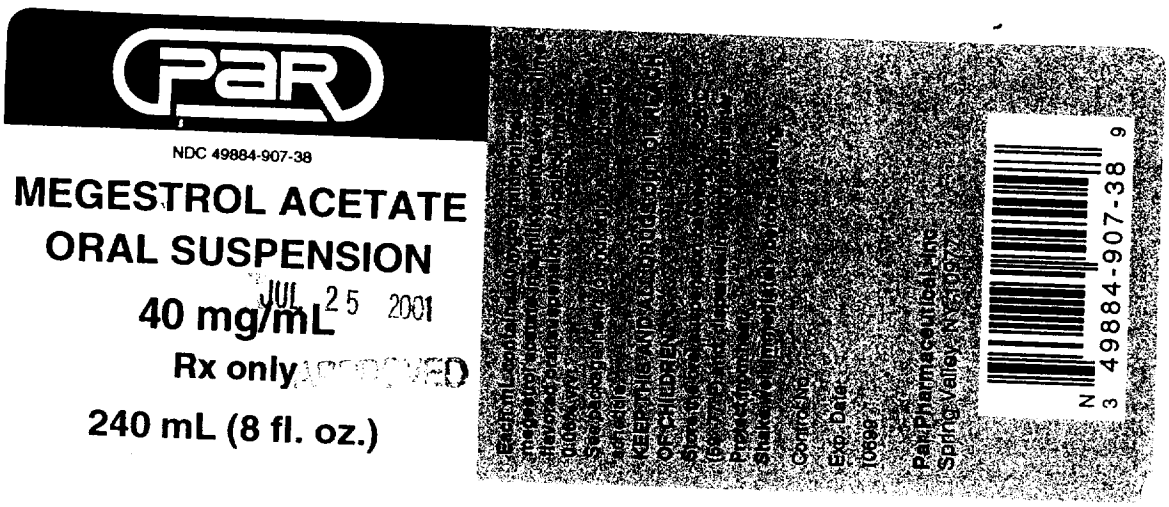
Gary Buehler 7/25/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-671

APPROVED DRAFT LABELING


PAR
NDC 49884-907-38
MEGESTROL ACETATE
ORAL SUSPENSION
40 mg/mL
Rx only
240 mL (8 fl. oz.)
JUL 25 2001
Par Pharmaceutical Inc.
Spring Valley, NY 10977
3 49884-907-38 9

MEGESTROL ACETATE ORAL SUSPENSION

WARNING

THE USE OF MEGESTROL ACETATE ORAL SUSPENSION IS CONTRAINDICATED IN PREGNANCY

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no evidence that the use of a high dose progestational agent such as megestrol acetate oral suspension during any phase of pregnancy is effective for this purpose. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion.

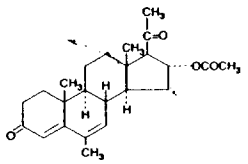
Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses. Because of increased genital abnormalities in male and female fetuses induced by some progestational drugs, it is prudent to avoid the use of megestrol acetate oral suspension during pregnancy.

If the patient is exposed to megestrol acetate oral suspension during pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

DESCRIPTION

Megestrol acetate oral suspension contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol acetate is a white, crystalline solid chemically designated as 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate. Solubility at 37°C in water is 2 µg per mL, solubility in plasma is 24µg per mL. Its molecular weight is 384.52.

The chemical formula is $C_{24}H_{32}O_4$ and the structural formula is represented as follows:



10-206010

MEGESTROL ACETATE ORAL SUSPENSION
101/2000

010907-01

Megestrol acetate oral suspension is supplied as an oral suspension containing 40 mg of micronized megestrol acetate per mL.

Megestrol acetate oral suspension contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial lime flavor, citric acid monohydrate, docusate sodium, glycerin, natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, sucrose and xanthan gum.

CLINICAL PHARMACOLOGY

Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.

There are several analytical methods used to estimate megestrol acetate plasma concentrations, including gas chromatography-mass fragmentography (GC-MF), high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA). The GC-MF and HPLC methods are specific for megestrol acetate and yield equivalent concentrations. The RIA method reacts to megestrol acetate metabolites and is, therefore, nonspecific and indicates higher concentrations than the GC-MF and HPLC methods. Plasma concentrations are dependent, not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet and liver function.

The major route of drug elimination in humans is urine. When radiolabeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5 to 78.4% (mean 66.4%) and fecal excretion ranged from 7.7 to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1 and 94.7% (mean 86.2%). Megestrol acetate metabolites which were identified in urine constituted 5 to 8% of the dose administered. Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in urine and feces.

Plasma steady state pharmacokinetics of megestrol acetate were evaluated in 10 adult, cachectic male patients with acquired immunodeficiency syndrome (AIDS) and an involuntary weight loss greater than 10% of baseline. Patients received single oral doses of 800 mg/day of megestrol acetate oral suspension for 21 days. Plasma concentration data obtained on day 21 were evaluated for up to 48 hours past the last dose.

Mean (±1SD) peak plasma concentration (C_{max}) of megestrol acetate was 753 (±539) ng/mL. Mean area under the concentration time-curve (AUC) was 10476 (±7788) ng x hr/mL. Median T_{max} value was five hours. Seven of 10 patients gained weight in three weeks.

Additionally, 24 adult, asymptomatic HIV seropositive male subjects were dosed once daily with 750 mg of megestrol acetate oral suspension. The treatment was administered for 14 days. Mean C_{max} and AUC values were 490 (±238) ng/mL and 6779 (±3048) hr x ng/mL, respectively. The median T_{max} value was three hours. The mean C_{min} value was 202 (±101) ng/mL. The mean % of fluctuation value was 107 (±40).

The relative bioavailability of megestrol acetate 40 mg tablets and megestrol acetate oral suspension has not been evaluated. The effect of food on the bioavailability of megestrol acetate oral suspension has not been evaluated.

DESCRIPTION OF CLINICAL STUDIES

The clinical efficacy of megestrol acetate oral suspension was assessed in two clinical trials. One was a multicenter, randomized, double-blind, placebo-controlled study comparing megestrol acetate (MA) at doses of 100 mg, 400 mg, and 800 mg per day versus placebo in AIDS patients with anorexia/cachexia and significant weight loss. Of the 270 patients entered on study, 195 met all inclusion/exclusion criteria, had at least two additional post baseline weight measurements over a 12 week period or had one post baseline weight measurement but dropped out for therapeutic failure. The percent of patients gaining five or more pounds at maximum weight gain in 12 study weeks was statistically significantly greater for the 800 mg (64%) and 400 mg (57%) MA-treated groups than for the placebo group (24%). Mean weight increased from baseline to last evaluation in 12 study weeks in the 800 mg MA-treated group by 7.8 pounds, the 400 mg MA group by 4.2 pounds, the 100 mg MA group by 1.9 pounds and decreased in the placebo group by 1.6 pounds. Mean weight changes at 4, 8 and 12 weeks for patients evaluable for efficacy in the two clinical trials are shown graphically. Changes in body composition during the 12 study weeks as measured by bioelectrical impedance analysis showed increases in non-water body weight in the MA-treated groups (See **CLINICAL STUDIES** table). In addition, edema developed or worsened in only 3 patients.

Greater percentages of MA-treated patients in the 800 mg group (89%), the 400 mg group (68%) and the 100 mg group (72%), than in the placebo group (50%), showed an improvement in appetite at last evaluation during the 12 study weeks. A statistically significant difference was observed between the 800 mg MA-treated group and the placebo group in the change in caloric intake from baseline to time of maximum weight change. Patients were asked to assess weight change, appetite, appearance, and overall perception of well-being in a 9 question survey. At maximum weight change only the 800 mg MA-treated group gave responses that were statistically significantly more favorable to all questions when compared to the placebo-treated group. A dose response was noted in the survey with positive responses correlating with higher dose for all questions.

The second trial was a multicenter, randomized, double-blind, placebo-controlled study comparing megestrol acetate 800 mg/day versus placebo in AIDS patients with anorexia/cachexia and significant weight loss. Of the 100 patients entered on study, 65 met all inclusion/exclusion criteria, had at least two additional post baseline weight measurements over a 12 week period or had one post baseline weight measurement but dropped out for therapeutic failure. Patients in the 800 mg MA-treated group had a statistically significantly larger increase in mean maximum weight change than patients in the placebo group. From baseline to study week 12, mean weight increased by 11.2 pounds in the MA-treated group and decreased 2.1 pounds in the placebo group. Changes in body composition as measured by bioelectrical impedance analysis showed increases in non-water weight in the MA-treated group (See **CLINICAL STUDIES** table). No edema was reported in the MA-treated group. A greater percentage of MA-treated patients (67%) than placebo-treated patients (38%) showed an improvement in appetite at last evaluation during the 12 study weeks; this difference was statistically significant. There were no statistically significant differences between treatment groups in mean caloric change or in daily caloric intake at time to maximum weight change. In the same 9 question survey referenced in the first trial, patients' assessments of weight change, appetite, appearance, and overall perception of well-being showed increases in mean scores in MA-treated patients as compared to the placebo group.

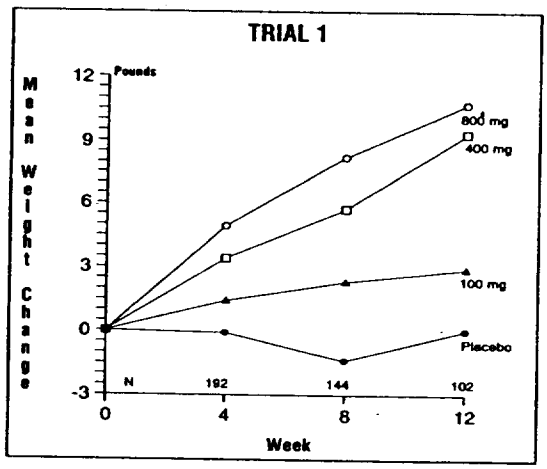
In both trials, patients tolerated the drug well and no statistically significant differences were seen between the treatment groups with regard to laboratory abnormalities, new opportunistic infections, lymphocyte counts, T_4 counts, T_8 counts, or skin reactivity tests (see **ADVERSE REACTIONS** section).

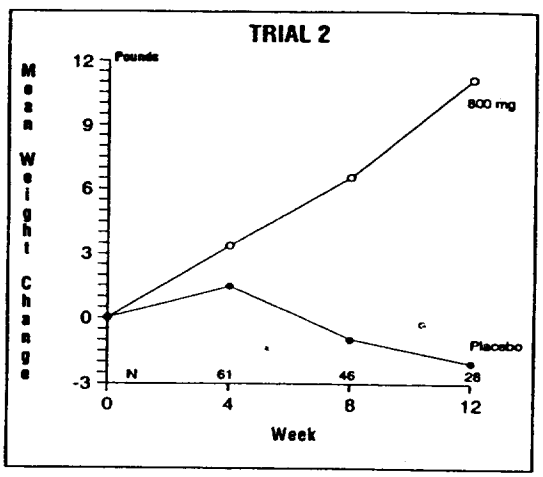
Megestrol Acetate Oral Suspension Clinical Efficacy Trials

	Trial 1 Study Accrual Dates 11/88 to 12/90				Trail 2 Study Accrual Dates 5/89 to 4/91	
Megestrol Acetate, mg/day	0	100	400	800	0	800
Entered Patients	38	82	75	75	48	52
Evaluable Patients	28	61	53	53	29	36
Mean Change in Weight (lb.)						
Baseline to 12 Weeks	0.0	2.9	9.3	10.7	-2.1	11.2
% Patients ≥5 Pound Gain at Last Evaluation in 12 Weeks	21	44	57	64	28	47
Mean Changes in Body Composition*:						
Fat Body Mass (lb.)	0.0	2.2	2.9	5.5	1.5	5.7
Lean Body Mass (lb.)	-1.7	-0.3	1.5	2.5	-1.6	-0.6
Water (liters)	-1.3	-0.3	0.0	0.0	-0.1	-0.1
% Patients With Improved Appetite:						
At Time of Maximum Weight Change	50	72	72	93	48	69
At Last Evaluation in 12 Weeks	50	72	68	89	38	67
Mean Change in Daily Caloric Intake:						
Baseline to Time of Maximum Weight Change	-107	326	308	646	30	464

*Based on bioelectrical impedance analysis determinations at last evaluation in 12 weeks.

The following figures are the results of mean weight changes for patients evaluable for efficacy in trials 1 and 2.





INDICATIONS AND USAGE

Megestrol acetate oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

CONTRAINDICATIONS

History of hypersensitivity to megestrol acetate or any component of the formulation. As a diagnostic test for pregnancy. Known or suspected pregnancy.

WARNINGS

Megestrol acetate may cause fetal harm when administered to a pregnant woman. For animal data on fetal affects, (see **PRECAUTIONS: Impairment of Fertility** section). There are no adequate and well-controlled studies in pregnant women. If this drug is used during preg-

nancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Megestrol acetate is not intended for prophylactic use to avoid weight loss.

(See also **PRECAUTIONS. Carcinogenesis, Mutagenesis, and Impairment of Fertility** sections).

Although the glucocorticoid activity of megestrol acetate oral suspension has not been fully evaluated, laboratory evidence of adrenal suppression has been observed. Clinical cases of new onset diabetes, exacerbation of preexisting diabetes, and Cushing's syndrome have been reported in association with the use of megestrol acetate. Rare cases of clinically apparent adrenal insufficiency have also been reported in association with megestrol acetate. The possibility of adrenal suppression should be considered in any patient taking or withdrawing from chronic megestrol acetate therapy who presents with symptoms of adrenal insufficiency such as hypotension, nausea, vomiting, dizziness or weakness. Laboratory evaluation for adrenal insufficiency and replacement stress doses of a rapidly acting glucocorticoid may be indicated for such patients.

PRECAUTIONS

General: Therapy with megestrol acetate oral suspension for weight loss should only be instituted after treatable causes of weight loss are sought and addressed. These treatable causes include possible malignancies, systemic infections, gastrointestinal disorders affecting absorption, endocrine disease and renal or psychiatric diseases.

Effects on HIV viral replication have not been determined.

Use with caution in patients with a history of thromboembolic disease.

Use in Diabetics: Exacerbation of pre-existing diabetes with increased insulin requirements have been reported in association with the use of megestrol acetate.

Information for Patients: Patients using megestrol acetate should receive the following instructions:

1. This medication is to be used as directed by the physician.
2. Report any adverse reaction experiences while taking this medication.
3. Use contraception while taking this medication if you are a woman capable of becoming pregnant.
4. Notify your physician if you become pregnant while taking this medication.

Drug Interactions: Pharmacokinetic studies show that there are no significant alterations in pharmacokinetic parameters of zidovudine or rifabutin to warrant dosage adjustment when megestrol acetate is administered with these drugs. The effects of zidovudine or rifabutin on the pharmacokinetics of megestrol acetate were not studied.

Animal Toxicology: Long-term treatment with megestrol acetate may increase the risk of respiratory infections. A trend toward increased frequency of respiratory infections, decreased lymphocyte counts and increased neutrophil counts was observed in a two-year chronic toxicity/carcinogenicity study of megestrol acetate conducted in rats.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis - Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at doses 53.2, 26.6 and 1.3 times *lower* than the proposed dose (13.3 mg/kg/day) for humans. No males were used in the dog and monkey studies. In female beagles, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk-to-benefit ratio when prescribing megestrol acetate oral suspension and in surveillance of patients on therapy. (See **WARNINGS** section).

Mutagenesis - No mutagenesis data are currently available.

Impairment of Fertility - Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses (0.05 to 12.5 mg/kg) *less* than that indicated for humans (13.3 mg/kg); in these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live births, and feminization of male fetuses. No toxicity data are currently available on male reproduction (spermatogenesis).

Pregnancy: ***Pregnancy Category X.*** (See **WARNINGS** and **PRECAUTIONS: Impairment of Fertility** sections). No adequate animal teratology information is available at clinically relevant doses.

Nursing Mothers: Because of the potential for adverse effects on the newborn, nursing should be discontinued if megestrol acetate oral suspension is required.

Use in HIV Infected Women: Although megestrol acetate has been used extensively in women for the treatment of endometrial and breast cancers, its use in HIV infected women has been limited.

All 10 women in the clinical trials reported breakthrough bleeding.

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

ADVERSE REACTIONS

Clinical Adverse Events: Adverse events which occurred in at least 5% of patients in any arm of the two clinical efficacy trials and the open trial are listed below by treatment group. All patients listed had at least one post baseline visit during the 12 study weeks. These adverse events should be considered by the physician when prescribing megestrol acetate oral suspension.

ADVERSE EVENTS
% of Patients Reporting

	Trial 1 (N=236)				Trial 2 (N=87)		Open Label Trial
Megestrol Acetate	Placebo				Placebo		
mg/day	0	100	400	800	0	800	1200
No. of Patients	N=34	N=68	N=69	N=65	N=38	N=49	N=176
Diarrhea	15	13	8	15	8	6	10
Impotence	3	4	6	14	0	4	7
Rash	9	9	4	12	3	2	6
Flatulence	9	0	1	9	3	10	6
Hypertension	0	0	0	8	0	0	4
Asthenia	3	2	3	6	8	4	5
Insomnia	0	3	4	6	0	0	1
Nausea	9	4	0	5	3	4	5
Anemia	6	3	3	5	0	0	0
Fever	3	6	4	5	3	2	1
Libido Decreased	3	4	0	5	0	2	1
Dyspepsia	0	0	3	3	5	4	2
Hyperglycemia	3	0	6	3	0	0	3
Headache	6	10	1	3	3	0	3
Pain	6	0	0	2	5	6	4
Vomiting	9	3	0	2	3	6	4
Pneumonia	6	2	0	2	3	0	1
Urinary Frequency	0	0	1	2	5	2	1

Adverse events which occurred in 1 to 3% of all patients enrolled in the two clinical efficacy trials with at least one follow-up visit during the first 12 weeks of the study are listed below by body system. Adverse events occurring less than 1% are not included. There were no significant differences between incidence of these events in patients treated with megestrol acetate and patients treated with placebo.

Body as a Whole - abdominal pain, chest pain, infection, moniliasis and sarcoma

Cardiovascular System - cardiomyopathy and palpitation

Digestive System - constipation, dry mouth, hepatomegaly, increased salivation and oral moniliasis

Hemic and Lymphatic System - leukopenia

Metabolic and Nutritional - LDH increased, edema and peripheral edema

Nervous System - paresthesia, confusion, convulsion, depression, neuropathy, hypesthesia and abnormal thinking

Respiratory System - dyspnea, cough, pharyngitis and lung disorder

Skin and Appendages - alopecia, herpes, pruritus, vesiculobullous rash, sweating and skin disorder

Special Senses - amblyopia

Urogenital System - albuminuria, urinary incontinence, urinary tract infection and gynecomastia

Postmarketing - Postmarketing reports associated with megestrol acetate oral suspension included thromboembolic phenomena including thrombophlebitis and pulmonary embolism and glucose intolerance (see **WARNINGS** and **PRECAUTIONS** sections).

OVERDOSAGE

No serious unexpected side effects have resulted from studies involving megestrol acetate oral suspension administered in dosages as high as 1200 mg/day. Megestrol acetate has not been tested for dialyzability, however, due to its low solubility it is postulated that dialysis would not be an effective means of treating overdose.

DOSAGE AND ADMINISTRATION

The recommended adult initial dosage of megestrol acetate oral suspension is 800 mg/day (20 mL/day). Shake container well before using.

In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day were found to be clinically effective.

A plastic dosage cup with 10 mL and 20 mL markings is provided for convenience.

HOW SUPPLIED

Megestrol acetate oral suspension is available as a milky white, lemon-lime flavored oral suspension containing 40 mg of micronized megestrol acetate per mL.

NDC 49884-907-38 Bottles of 240 mL (8 fl. oz.)

STORAGE

Store megestrol acetate oral suspension between 15°-25°C (59°-77°F) and dispense in a tight container. Protect from heat.

SPECIAL HANDLING

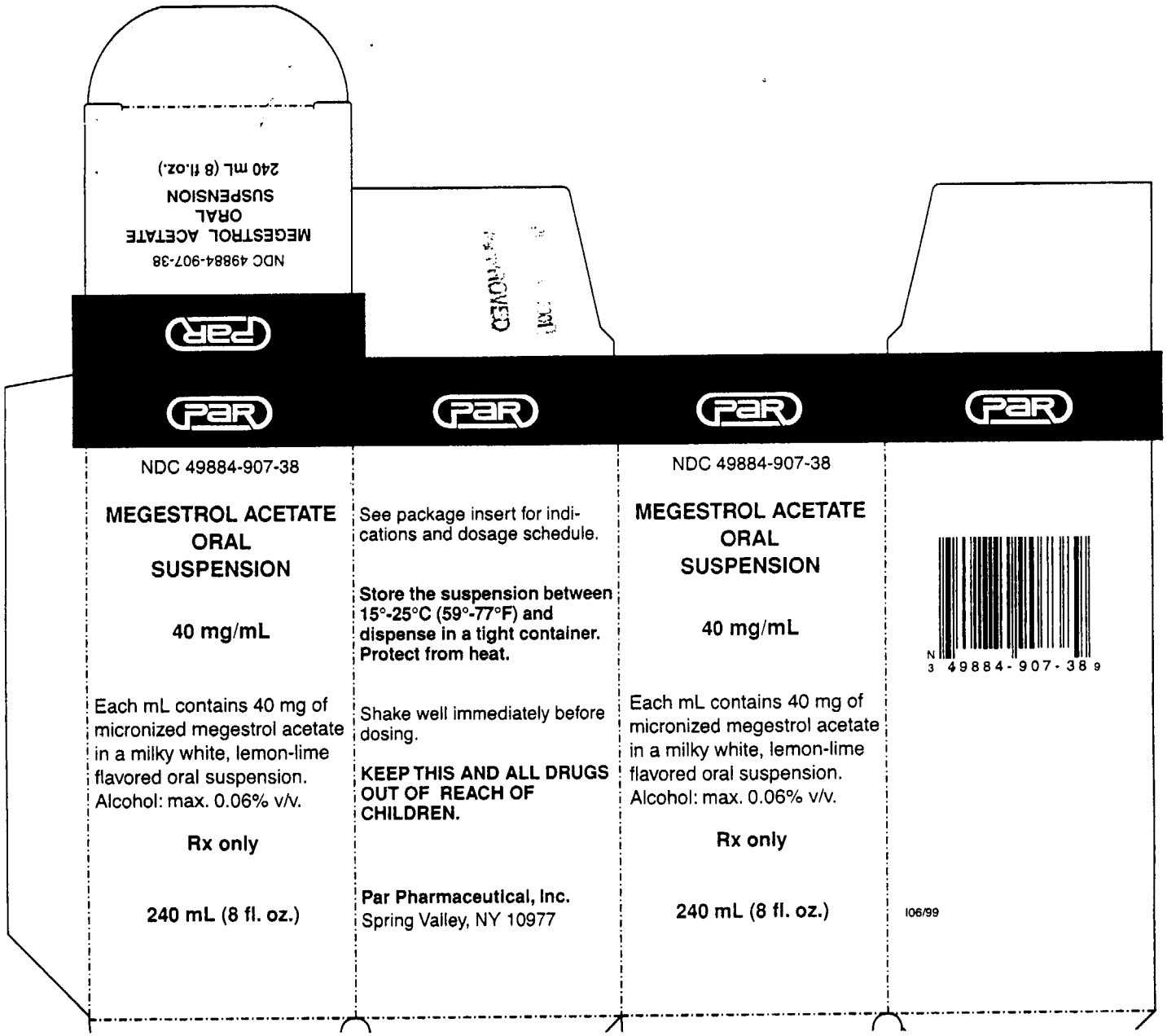
Health Hazard Data: There is no threshold limit value established by OSHA, NIOSH, or ACGIH.

Exposure or "overdose" at levels approaching recommended dosing levels could result in side effects described above (see **WARNINGS** and **ADVERSE REACTIONS** sections). Women at risk of pregnancy should avoid such exposure.

Manufactured by:
PAR PHARMACEUTICAL, INC.
Spring Valley, New York 10977

Issued: 01/2000

MEGESTROL ACETATE
ORAL
SUSPENSION



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-671

CHEMISTRY REVIEW(S)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-671 APPLICANT: Par Pharmaceuticals

DRUG PRODUCT: Megestrol Acetate Oral Suspension, 40 mg/mL

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. Your proposed range for Specific Gravity for in-process control, release and stability of the drug product is still too wide. We request a narrower range based on the data obtained for the bio/stability batch.

2. We note a large difference in particle size limits for the drug product versus the drug substance. Please clarify if this difference is based on the formation of larger particles during formulation of the suspension or a difference in your analytical methodology? Please further tighten the particle size specifications for both drug substance and drug product based on the actual analytical data for the lot of drug substance used in the biobatch and the biobatch for the drug product. Your proposed limits are still not reflective of the data.

3. Please submit stability data for samples stored in the upright orientation under 3 months accelerated conditions or full term long term conditions.

4. Based on the revised dissolution method approved by the Division of Bioequivalence, please submit stability data with the revised dissolution test at the next stability station. Your release and stability dissolution method should also be updated to reflect the change. The stability data provided in response to item 3 should also use the new method.

5. Please describe your test method for Resuspendability.

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

A satisfactory Methods Validation is needed to support the ANDA. We will schedule the validation after the testing issues are resolved.

Sincerely yours,

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

1. CHEMISTRY REVIEW NO.4

2. ANDA # 75-671

3. NAME AND ADDRESS OF APPLICANT
Par Pharmaceuticals (PP)
One Ram Ridge Road
Spring Valley, NY 10977

4. BASIS OF SUBMISSION
Listed drug product: Megace 40 mg/mL by Bristol-Myers Squibb (BMS) approved under NDA 16-979.

U.S. Patent no. 5,338,732 will expire on 9-10-2000 and no extension has been registered per their best knowledge.

On 10-6-99, BMS filed a lawsuit against Par in Federal district court in New York, NY alleging infringement of a U.S. patent with expiry date in 2011. On July 16, 2001, U.S. Court issued a final ruling in which the court affirmed the judgement that was appealed by Bristol. Based on this, Par has requested for full approval.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Megestrol Acetate Oral Suspension

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 7-14-99
Tentative Approval: 10-23-00
* NC: 11-1-00 (Patent issues)
* Minor Amendment: 5-4-01
* Amendment: 7-17-01 (Patent issues)

10. PHARMACOLOGICAL CATEGORY
For treatment of anorexia, cachexia, or weight loss in AIDS patients.

11. Rx or OTC
Rx

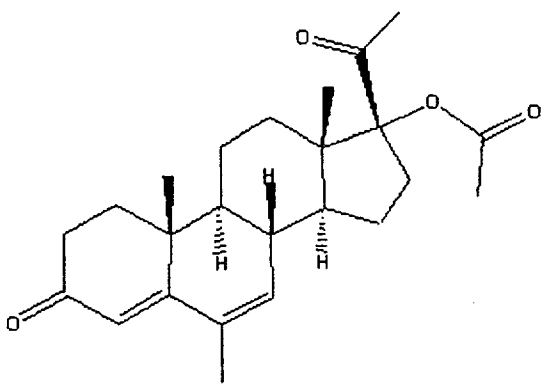
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Suspension

14. POTENCY
40 mg/mL

15. CHEMICAL NAME AND STRUCTURE
Name: 17-Hydroxy-6-methylpregna-4,6-diene-3,20,dione acetate

Structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. for Pharmacia & Upjohn - the manufacturer of Megestrol Acetate is adequate per review conducted by this reviewer on 12-20-99. It remains adequate per review completed on 2-20-01
2. Megestrol Acetate Oral suspension is not USP 24 material. Therefore, MVP was submitted to FDA Northeast District Laboratory. This was completed on 12-20-00 and it is suitable for regulatory analysis of the product per recommendation made by District.
3. EER: Acceptable on 4-26-00.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 7-18-01

cc:

Endorsements:

7/23/01

7/24/01

Page(s) 9

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Rev 4

7/18/01

JAN 14 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-671 APPLICANT: Par Pharmaceuticals

DRUG PRODUCT: Megestrol Acetate Oral Suspension, 40 mg/mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. We have following comments regarding raw materials:

   a. Your proposed tentative particle size specifications for Megestrol Sulfate drug substance are not acceptable. Please establish final specifications based on the lot of Megestrol Acetate used in manufacture of the biobatch. Your current specifications are not reflective of your data.

   b. Please submit the exact quantitative composition with all artificial ingredients stating exact chemical names and safety references for each ingredient (e.g. USP, NF, FCC, GRAS, FEMA #) for both Flavor and Natural and Artificial Flavors. Alternatively, you may provide this information by reference to a DMF.

2. Please provide a time limit for packaging the bulk suspension. If the suspension is not stirred during packaging, please demonstrate that the suspension is physically stable for the maximum length of time it takes to package.

3. We have the following comments regarding the dosage form controls:

   a. You failed to provide your specifications for the proposed in-process controls.

   b. Please include pH as an in-process control.

   c. Please tighten your particle size specification based on the actual data for the biobatch. Please be advised that tentative limits are not acceptable.

d. Your proposed range for Specific Gravity for release of the drug product is too wide. We request a narrower range based on the results obtained for the bio/stability batch.

e. Your Identification test (i.e., retention time) for the drug product is non-specific. Please use a specific ID test (e.g. IR) or add a second non-specific test.

4. On page 2838, you have stated name of as the alternate manufacturer of Megestrol Acetate drug substance. Please clarify this statement as you have submitted no data for this source.

5. We have the following comments regarding the stability of the drug product:

a. Your proposed limit for Total Impurities of is excessive. Please tighten slightly.

b. Your proposed range for Specific Gravity is too wide. We request a narrower range.

c. Please change your particle size specification to be the same as the release specification (comment 3c of this letter).

d. Please include a Resuspendability test for stability monitoring of the drug product. In addition, please include Description of the drug product for stability testing.

e. Please provide data to support your proposed lower limit of for Sodium Benzoate.

f. Please revise your post-approval stability commitment as recommended below:

i. Stability testing for the smallest and largest size containers is not acceptable. It should be <u>all</u> sizes for liquids.

ii. Stability samples should be stored in both upright and inverted orientations. The samples stored in the upright position may be tested at annual intervals.

iii. At least three batches are required to extend the expiration date for the drug product.

g. Please provide upright orientation stability data for the exhibit batch.

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

1. Labeling deficiencies will also need to be addressed in your reply.

2. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

3. Please submit additional stability data for the exhibit batch, if available.

4. You response dated November 3, 1999 regarding bioequivalence issues is pending review.

5. A satisfactory Methods Validation is needed to support the ANDA. We will schedule the validation after the testing issues are resolved.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-671

Bioequivalence Review(s)

2.1

Megestrol Acetate
40 mg/mL Oral Suspension
ANDA 75-671
Reviewer: Lin-Whei Chuang
V:\FIRMSNZ\PAR\LTRS&REV\75671AM.N99

Par Pharmaceutical Inc.
Spring Valley, NY
Submission Date:
November 3, 1999

Review of an Amendment to a Bioequivalence Study and Dissolution Data

Background:

Results of an *in vivo* bioequivalence study and dissolution data submitted on 7/14/99 and 8/10/99 were found to be incomplete due to the following deficiencies:

1. *The firm should provide the potency of the reference drug used in the fasting in vivo bioequivalence study.*

2. *The firm should explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.*

3. *The dissolution method conducted by the firm is unacceptable. The following dissolution method is recommended:*

   Medium: 0.5% sodium lauryl sulfate; 900 mL
   Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Firm's Response:

1. *The firm should provide the potency of the reference drug used in the fasting in vivo bioequivalence study.*

   Response: The potency of the reference drug used in the fasting *in vivo* bioequivalence study was reported by the firm as 99.9%.

2. *The firm should explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.*

Response: The actual sampling time of these 4 plasma samples were deviated from the scheduled sampling time by an inconclusive amount of time and therefore were not reportable.

3. *The dissolution method conducted by the firm is unacceptable. The following dissolution method is recommended:*

Medium: 0.5% sodium lauryl sulfate; 900 mL
Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Response: *In vitro* dissolution tests were conducted by the firm according to Agency's recommendation. The dissolution method and results are presented in Table 1.

Table 1: In Vitro Dissolution Tests Conducted by Par Pharmaceutical Inc.

Drug (Generic Name): Megestrol Acetate
Dosage Form: Oral Suspension
Dose Strength: 40 mg/mL
ANDA No.: 75-671
Firm: Par Pharmaceutical, Inc.
Submission Date: 11/3/99

Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 25 No. Units Tested: 12
Medium: 0.5% sodium lauryl sulfate in water Volume: 900 mL
Tolerance: in 20 minutes
Reference Drug: Megace Oral Suspension (Bristol-Myers Squibb)
Assay Methodology:

Results of In Vitro Dissolution Testing:

Sampling Times (minute)	**Test Product** Lot #22618 Strength (mg/mL): 40			**Reference Product** Lot #MDN51 Strength (mg/mL): 40		
	Mean %	Range	%CV	Mean %	Range	%CV
5	77.5		10.3	43.3		16.0
10	86.6		6.7	50.5		3.3
15	89.7		4.7	52.6		3.2
30	92.8		2.1	55.8		2.8
60	94.7		3.0	56.6		3.8

Reviewer's Comments:

1. The firm's responses to all 3 deficiencies are acceptable.

2. -- **NOT FOR RELEASE THROUGH FOI** -

   Presented in Table 2 are the dissolution data conducted by the innovator firm, Bristol-Myers Squibb, on two lots of its Megace oral suspension. The amount dissolved at various time points (75-94%) are much higher than those conducted and submitted by the firm as shown in Table 1 (29.2-59.6%) on the same product with the same dissolution method.

Table 2: In Vitro Dissolution Tests Conducted by Bristol-Myers Squibb

Drug (Generic Name): Megestrol Acetate
Dosage Form: Oral Suspension
Dose Strength: 40 mg/mL
NDA No.: 20-264 & 20-296
Firm: Bristol-Myers Squibb
Submission Date: 4/1/92 & 8/13/92

Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 25 No. Units Tested: 6
Medium: 0.5% sodium lauryl sulfate in water Volume: 900 mL

Results of In Vitro Dissolution Testing:

Sampling Times (minute)	**Reference Product Lot #E89G309** Strength (mg/mL): 40		**Reference Product Lot #E90K567** Strength (mg/mL): 40	
	Mean %	%CV	Mean %	%CV
5	75	1	77	1
15	88	1	90	1
30	92	0.4	91	1
60	94	0.4	92	0.4

Recommendation:

1. The bioequivalence study conducted by Par Pharmaceutical Inc. on its megestrol acetate 40 mg/mL oral suspension, batch #22618, comparing it to Megace^{R} 40 mg/mL oral suspension, lot #MDN51, manufactured by Bristol Myers Squibb, has been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Par Pharmaceutical Inc. on its megestrol acetate 40 mg/mL oral suspension, batch #22618,

comparing it to Megace[R] 40 mg/mL oral suspension, lot #MDN51, has been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of 0.5% sodium lauryl sulfate in water at 37° C using USP 23 apparatus 2 (paddle) at 25 rpm. The test products should meet the following specifications:

Not less than of the labeled amount of megestrol acetate in the dosage form is dissolved in 20 minutes.

Lin-Whei Chuang 11/17/99

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG 11/29/99

Concur Date: 12/2/99
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-671 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Megestrol Acetate Oral Suspension 40 mg/mL

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water, at 37° C using USP Apparatus 2 at 25 rpm. The test product should meet the following specifications:
>
> Not less than f the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

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

Sincerely yours,

Dale P. Conner

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

Megestrol Acetate	Par Pharmaceutical Inc.
40 mg/mL Oral Suspension	Spring Valley, NY
ANDA 75-671	Submission Date:
Reviewer: Lin-Whei Chuang	July 14, 1999
V:\FIRMSNZ\PAR\LTRS&REV\75671SD.799	August 10, 1999

Review of a Bioequivalence Study and Dissolution Data

Background:

Chemical Nature:
A synthetic derivative of the naturally occurring steroid hormone, progesterone. Solubility in water at 37° C is 2 ug/mL, and in plasma is 24 ug/mL.

Reference Listed Drug (RLD):
Megace oral suspension of Bristol-Myers Squibb (NDA #20264 approved on 9/10/1993).

Pharmacology:
The appetite enhancing property of megestrol acetate has been reported by investigators but the precise mechanism is unknown at present. Megace oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of AIDS. The recommended adult initial dose is 800 mg/day.

Pharmacokinetics:
In normal subjects who received 160 mg of megestrol acetate given as 40 mg q.i.d., the Cmax ranged 10-56 ng/mL and Tmax 1-3 hours after the first dose. Plasma elimination half-life ranged 13-105 hours. The effect of food on the bioavailability of Megace oral suspension has not been evaluated as indicated in the labeling.

Comparative Formulations - *Not For Release through FOI*:

	Megace Oral Suspension (Bristol-Myers Squibb)	Megestrol Acetate Oral Suspension (Par)
Megestrol Acetate	40 mg /mL	40 mg/mL
Xanthan Gum		
Polysorbate		
Citric Acid		
Sucrose		
Sodium Benzoate		
Sodium Citrate		
Polyethylene Glycol		
Purified Water		
Flavor		
Docusate Sodium		
Glycerin		

Submission History:
The original submission of 7/14/99 was found to be incomplete due to lack of the data diskette. The firm was notified by telephone and subsequently submitted on 8/10/99 the data diskette.

***In Vivo* Bioequivalence Study -- Fasting Subjects -- 2 x 40 mg/mL:**

Objective:
To compare the rate and extent of absorption of megestrol acetate in the test and reference drug products administered as 2 mL (80 mg) oral suspension to fasting male subjects.

Sites, Dates, and Investigators:
The clinical portion of this study was conducted at Anapharm Inc. in Saint-Foy, QC, Canada during 4/2-6/99 (period 1) and 4/16-20/99 (period 2) with E. Masson, Pharm.D. as the principal investigator. The analytical part was performed at the same site as the clinical study by during 4/22-5/18/99. Maximal storage period for study samples was 46 days. The pharmacokinetic and statistical analyses were performed by at Anapharm Inc..

Design and IRB:
A single-dose, randomized, 2-way crossover of the test drug and the reference product in fasting volunteers. The protocol

dated 10/8/98) and informed consent form were approved by the Ethics Review Committee of Integrated Research Inc. in Montreal, Quebec, Canada on 10/23/98.

Subject Inclusion:
Thirty-eight (38) men (37 Caucasian and 1 Black) with 18-45 years of age, weighed within ± 15% of the ideal weight for their height and frame were recruited. They were screened within 28 days prior to study drug administration and were found to be healthy according to their medical history, clinical laboratory tests, ECG, hepatitis, HIV and urine drug screen tests.

Subject Exclusion:
Subjects who were allergic to progestational drugs, participated in another clinical trial within 30 days, gave blood within 56 days, had taken drugs known to affect hepatic drug metabolism within 30 days, had been treated with drugs known to be toxic to major organs such as chloramphenicol within 3 months, or had abnormal diet within 4 weeks preceding the study were excluded from the study.

Restrictions:
Subjects were instructed not to take any prescription drugs for 14 days, to report any OTC drugs taken within 14 days, to abstain from xanthine-product, grapefruit-product, and alcohol within 48 hours, prior to study start.

Treatments:
Subjects fasted overnight before receiving one of the following drug treatments randomly assigned in the morning of 4/3/99:

Treatment A - Test Drug: Megestrol acetate oral suspension, 2 mL of 40 mg/mL, Par bulk batch #22618, bulk control #017061, and control #017178, potency 98.8%, lot size of Liters.

Treatment B - Reference Drug: Megace^{R} oral suspension, 2 mL of 40 mg/mL, Bristol-Myers Squibb-Mead Johnson, lot #MDN51, potency not given, expires 4/2000.

Post-dose Procedure:
Each treatment was taken with 240 mL of water. Subjects continued to fast until 4 hours post-dose. Blood samples (10 mL each) were drawn into collection tubes with EDTA at pre-dose, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, and 72 hours after dosing. Plasma samples were prepared and stored at -20°C. After a washout period of 14 days, in the morning of 4/17/99, subjects received the alternate treatment. It was stated in the protocol that, at the conclusion of the study, inventory and remaining of drug supply would be retained securely at Anapharm Inc. for appropriate amount of time per federal requirements.

Subjects were confined to the clinical facility from 9 PM of the night before dosing to 24 after dosing. They engaged in normal activities and were not allowed to rest for the first 4 hours after dosing. All meals were standardized and no xanthine- or grapefruit-product were included. At the end of the study, all subjects underwent a procedure which included laboratory tests and physical examination.

Analytical Method:

A total of 1437 plasma samples were received at the analytical site on 4/6, 20 & 22/99. Plasma megestrol acetate and added internal standard) were extracted using a followed by a procedure, then injected onto a

Pre-Study Validation:
Data presented below in Table 1 are from 9 standard curves, each with duplicates of 3 levels of QC samples.

Table 1: Pre-Study Validation			
Sensitivity/LLOQ (ng/mL)	1.96		
Quality Control Conc.(ng/mL)	5.91, 68.9, 148		
Linear Range (ng/mL)	1.96 - 196		
Correlation Coefficient	≥0.9964		
Intra-run Precision for QC Samples (%CV)	3.11 - 10.62		
Intra-run Accuracy for QC Samples (%)	93.72 - 114.72		
Inter-run Precision for Standards (%CV)	1.94 - 4.36		
Inter-run Accuracy for Standards (%)	98.21 - 102.68		
Inter-run Precision for QC Samples (%CV)	3.20 - 6.19		
Inter-run Accuracy for QC Samples(%)	96.90 - 104.84		
Selectivity	no interference		
Stability (%) of Plasma Samples (ng/mL) a) 25 hours at room temperature b) 4 Freeze-Thaw Cycles d) 140 days at <-20°C	5.91 104.2 99.8 95.4	148 101.2 100.2 94.6	
Percent Recovery (%) of Plasma Samples and Internal standard (ng/mL),	5.91 95.8	148 94.2	Intn. Std (40) 94.4

During-Study Validation:
Data presented below in Table 2 are from 23 standard curves, each with duplicates of the 3 levels of QC samples.

Table 2: During-Study Validation	
Sensitivity/LLOQ (ng/mL)	2.01
Quality Control Conc.(ng/mL)	6.02, 70.3, 151
Linear Range (ng/mL)	2.01 - 201
Correlation Coefficient	≥0.9989
Precision (%CV) for Standards	0.56 - 5.36
Precision (%CV) for QC Samples	2.33 - 3.95
Accuracy (%Actual) for standards	97.51 - 101
Accuracy (%Actual) for QC Samples	101.05 0 102.2

Comment on the Analytical Method:
The analytical method and validation data are acceptable.

Results:

Drop-out:
Of the 38 subjects enrolled in the study, 36 completed the study. Subjects #19 (sequence AB) & #21 (sequence BA) withdrew from the study prior to period 2 for personal reasons.

Protocol Deviation:
Approximately one small drop of the 2 mL dose for subject #7, period 1 (treatment B), was left in the cap of the syringe which was used to administer the study drug. Subjects #26 and #29 (both of sequence AB) did not return for the 36-hour blood draw during period 2.

Adverse Event:
A total of 30 events were reported, 15 during each treatment. Eight (8) events occurred during treatment B and 1 during treatment A were judged to be possibly related to the study drug. These complaints that were related to study drugs included nausea, drowsiness, fatigue, headache, cough, abdominal cramps and loose stool. No clinically significant laboratory abnormalities were observed at the end of the study except for subjects #21 and #36 who each had 5.5 mmole/L of urine glucose. This was judged unlikely related to study drug.

Plasma Concentration:
Samples from 36 subjects were assayed for megestrol acetate. Among the 1437 plasma samples analyzed, 20 were repeated due to anomalous values (per firm's SOP).

In addition to the 2 missing samples due to protocol deviation, 9 more samples were reported as "no reportable value (NRV)". Among these 9 samples, 4 actually had assayed values in the raw data section but were reported as NRV in the final report and data diskette. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.

The mean plasma concentrations of megestrol acetate at each sampling time point after both treatments are presented in Figure 1. The same data and the mean pharmacokinetic parameters are presented below in Tables 3-4.

FIGURE 1: MEAN PLASMA CONCENTRATIONS OF MEGESTROL ACETATE AFTER 2 X 40 MG/ML ORAL SUSPENSION OF MEGESTROL ACETATE

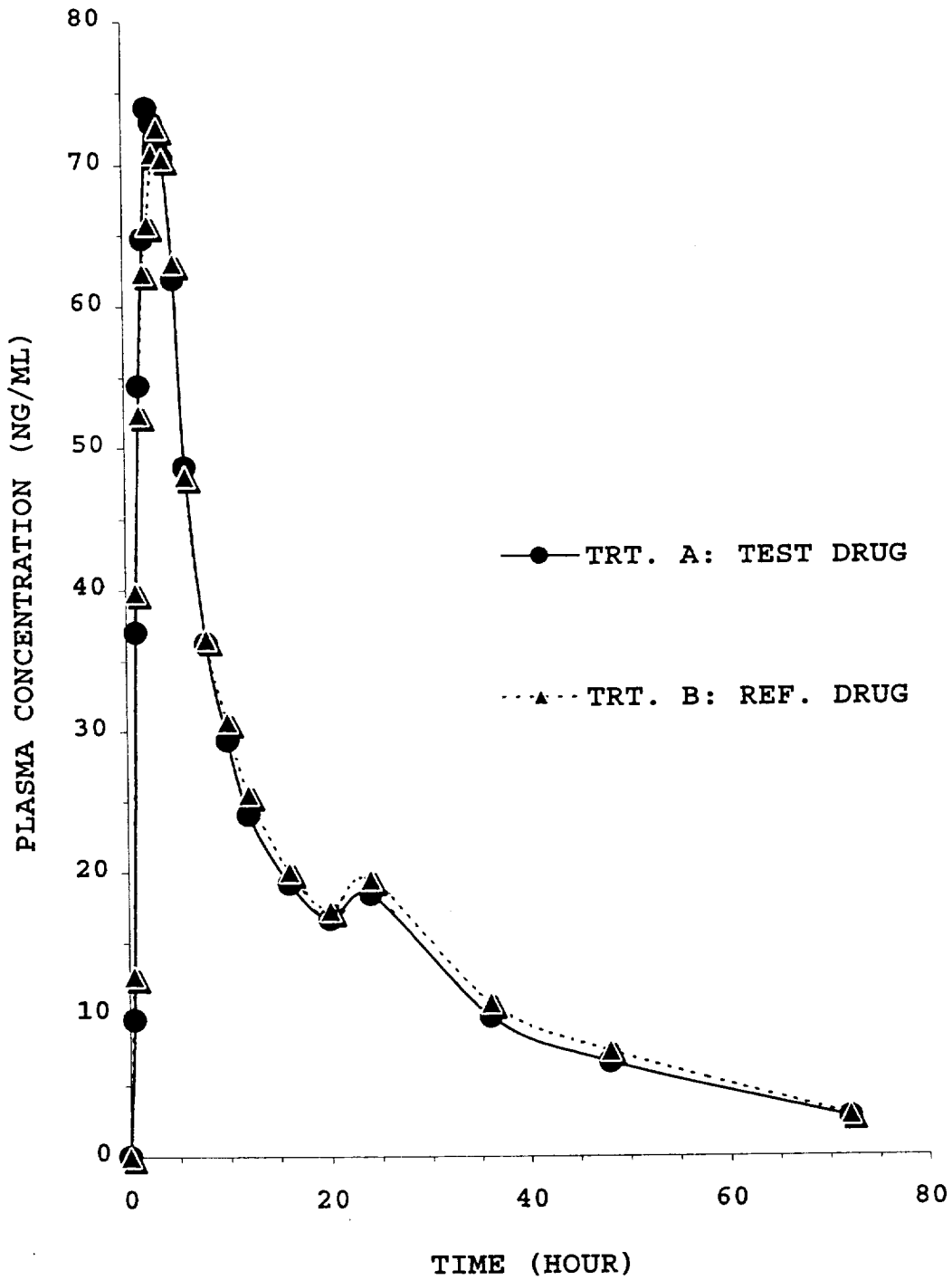


TABLE 3: MEAN PLASMA COMCENTRATIONS (NG/ML) OF MEGESTROL ACETATE AFTER 2 X 40 MG/ML ORAL SUSPENSION (n=36)

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	9.59	11.95	12.65	10.04	0.76
1	37.02	30.42	39.82	22.66	0.93
1.5	54.39	35.19	52.37	28.52	1.04
2	64.75	35.96	62.35	32.28	1.04
2.5	73.94	35.76	65.75	31.31	1.12
3	72.93	32.12	70.80	29.04	1.03
3.5	71.20	28.27	72.57	32.20	0.98
4	70.50	28.88	70.44	31.04	1.00
5	61.92	29.60	63.05	26.27	0.98
6	48.64	21.58	48.03	18.16	1.01
8	36.24	13.66	36.55	12.55	0.99
10	29.36	10.28	30.67	12.96	0.96
12	24.06	6.94	25.50	9.51	0.94
16	19.18	5.99	20.04	6.73	0.96
20	16.67	5.35	17.28	6.64	0.96
24	18.42	7.05	19.48	8.66	0.95
36	9.81	4.06	10.76	4.61	0.91
48	6.60	2.83	7.37	3.98	0.90
72	2.66	1.98	2.84	1.97	0.93

TABLE 4: MEAN PHARMACOKINETIC PARAMETERS AFTER 2 X 40 MG/ML ORAL SUSPENSION OF MEGESTROL ACETATE

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER					
AUCI (NG*HR/ML)	1257.18	383.33	1278.24	362.11	0.98
AUCT (NG*HR/ML)	1111.05	323.57	1175.06	341.79	0.95
CMAX (NG/ML)	88.77	35.35	84.74	35.34	1.05
KE	0.04	0.01	0.04	0.01	0.99
LAUCI	7.09120	0.31	7.11301	0.29	0.98a
LAUCT	6.97110	0.30	7.02692	0.30	0.95a
LCMAX	4.41183	0.39	4.35991	0.41	1.05a
THALF (HR)	20.18	7.10	18.79	4.09	1.07
TMAX (HR)	3.06	1.25	3.13	1.16	0.98

a = RATIO OF GEOMETRIC MEANS

Mean Ratio of Test to Reference Products:

Variable	N	Mean	Std Dev	Minimum	Maximum
AUCT	36	0.97	0.22	0.54	1.61
AUCI	36	1.02	0.30	0.55	1.99
CMAX	36	1.14	0.47	0.50	2.47
TMAX	36	1.08	0.58	0.30	3.33
KE	36	1.00	0.28	0.32	2.00
THALF	36	1.10	0.44	0.50	3.14

Mean Ratio of AUCT/AUCI:
0.90 (0.38-0.97) for treatment A and 0.92 (0.82-0.96) for treatment B. During treatment A, all subjects' ratios were >0.8 except those of subjects #10 and #11, which were 0.38 and 0.77, respectively.

Statistical Analysis:
ANOVA was conducted by the firm on the log-transformed data. No significant sequence or treatment effect was detected for any pivotal parameters. Results in Table 5 conducted by the reviewer are identical to those submitted by the firm.

TABLE 5: LS MEANS AND 90% CONFIDENCE INTERVALS

	TEST LSM	REF. LSM	TEST/REF.	90% CONF. INT.
PARAMETER				
AUCI (NG*HR/ML)	1257.18	1278.24	0.98	90.44 - 106.26
AUCT (NG*HR/ML)	1111.05	1175.06	0.95	87.96 - 101.15
CMAX (NG/ML)	88.77	84.74	1.05	93.52 - 115.99
LAUCI	1201.35a	1227.84a	0.98b	91.06 - 105.13
LAUCT	1065.39a	1126.56a	0.95b	88.94 - 100.56
LCMAX	82.42a	78.25a	1.05b	94.50 - 117.38

a = Geometric LS Mean, b = Ratio of Geometric LS Means,

Comments on Results of Bioequivalence Study:

1. The potency of the reference drug used in this fasting *in vivo* bioequivalence study was not provided.

2. Four (4) plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-

A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.

3. The computation of pharmacokinetic parameters and the confidence intervals conducted by the firm has been confirmed by the reviewer using data supplied by the firm in its data diskette.

4. At present there are no generic product of megestrol acetate oral suspension 40 mg/mL available in the market. However, four ANDAs for generic megestrol acetate tablets, 20 mg and/or 40 mg, have been approved by the Agency based on acceptable single-dose, two-way crossover, fasting studies where the plasma sample collection time were up to 72-96 hours after dosing. None of these generic firms had conducted food effect study on megestrol acetate tablets.

***IN Vitro* Dissolution Test:**

Following dissolution data were submitted by the firm:

Table 6 - In Vitro Dissolution Testing

Drug (Generic Name): Megestrol Acetate
Dosage Form: Oral Suspension
Dose Strength: 40 mg/mL
ANDA No.: 75-671
Firm: Par Pharmaceutical, Inc.
Submission Date: 7/14/99

Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 75 No. Units Tested: 12
Medium: 1% sodium lauryl sulfate in water Volume: 900 mL
Tolerance:
Reference Drug: Megace Oral Suspension (Bristol-Myers Squibb)
Assay Methodology:

Results of In Vitro Dissolution Testing:

Sampling Times (minute)	Test Product Lot #22618 Strength (mg/mL): 40			Reference Product Lot #MDN51 Strength (mg/mL): 40		
	Mean %	Range	%CV	Mean %	Range	%CV
5	96.7		5.0	91.5		1.9
10	96.3		5.3	93.3		2.6
20	96.9		5.0	95.6		3.0
30	98.0		5.2	95.5		3.0

Comment on Dissolution Data:

-Not Releasable through FOI-

Megestrol acetate oral suspension is not a USP product. The approval of Megace® 40 mg/mL oral suspension through NDA #20264 on 9/10/93 for Bristol Myers Squibb was based on a interim dissolution method shown below:

Medium: 0.5% sodium lauryl sulfate; 900 mL
Apparatus: USP 23 apparatus 2 (paddle), 25 rpm
Tolerance: in 30 minutes

Overall Comments:

1. The potency of the reference drug used in the fasting *in vivo* bioequivalence study was not provided.

2. Four (4) plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.

3. The dissolution method conducted by the firm is different than that conducted by the innovator firm, Bristol Myers Squibb.

4. Since at present there are no generic product of megestrol acetate oral suspension 40 mg/mL available in the market, a request to inspect both clinical and analytical sites for the *in vivo* bioequivalence study was made on 8/19/99.

Deficiencies:

1. The firm should provide the potency of the reference drug used in the fasting *in vivo* bioequivalence study.

2. The firm should explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.

3. The dissolution method conducted by the firm is unacceptable. The following dissolution method is recommended:

   Medium: 0.5% sodium lauryl sulfate; 900 mL
   Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Recommendation:

1. The bioequivalence study conducted by Par Pharmaceutical Inc. on its megestrol acetate 40 mg/mL oral suspension, batch #22618, comparing it to Megace[R] 40 mg/mL oral suspension, lot #MDN51, manufactured by Bristol Myers Squibb, has been found to be incomplete due to deficiencies #1-2.

2. The dissolution testing conducted by Par Pharmaceutical Inc. on its megestrol acetate 40 mg/mL oral suspension, batch #22618, comparing it to Megace[R] 40 mg/mL oral suspension, lot #MDN51, has been found unacceptable. The following dissolution method is recommended:

   Medium: 0.5% sodium lauryl sulfate; 900 mL
   Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Lin-Whei Chuang 9/20/99

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG 9/20/99

Concur Date: 9/21/99
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-671 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Megestrol Acetate Oral Suspension 40 mg/mL

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

1. Please provide the potency of the reference drug used in the fasting *in vivo* bioequivalence study.

2. Please explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.

3. Please conduct the dissolution method according to the method shown below and submit the dissolution data to the Agency for review.

   Medium: 0.5% sodium lauryl sulfate; 900 mL
   Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Sincerely yours,

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

OCT -5 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-671 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Megestrol Acetate Oral Suspension 40 mg/mL

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

1. Please provide the potency of the reference drug used in the fasting *in vivo* bioequivalence study.

2. Please explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.

3. Please conduct the dissolution method according to the method shown below and submit the dissolution data to the Agency for review.

   Medium: 0.5% sodium lauryl sulfate; 900 mL
   Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Sincerely yours,

Dale P. Conner

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-671 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Megestrol Acetate Oral Suspension 40 mg/mL

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water, at 37° C using USP Apparatus 2 at 25 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

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

Sincerely yours,

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

Megestrol Acetate
40 mg/mL Oral Suspension
ANDA 75-671
Reviewer: Lin-Whei Chuang
V:\FIRMSNZ\PAR\LTRS&REV\75671AM.N99

Par Pharmaceutical Inc.
Spring Valley, NY
Submission Date:
November 3, 1999

Review of an Amendment to a Bioequivalence Study and Dissolution Data

Background:

Results of an *in vivo* bioequivalence study and dissolution data submitted on 7/14/99 and 8/10/99 were found to be incomplete due to the following deficiencies:

1. *The firm should provide the potency of the reference drug used in the fasting in vivo bioequivalence study.*

2. *The firm should explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.*

3. *The dissolution method conducted by the firm is unacceptable. The following dissolution method is recommended:*

   Medium: 0.5% sodium lauryl sulfate; 900 mL
   Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Firm's Response:

1. *The firm should provide the potency of the reference drug used in the fasting in vivo bioequivalence study.*

   Response: The potency of the reference drug used in the fasting *in vivo* bioequivalence study was reported by the firm as 99.9%.

2. *The firm should explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-72, 15-B-1-24, 15-B-1-48, and 32-A-1-48.*

Response: The actual sampling time of these 4 plasma samples were deviated from the scheduled sampling time by an inconclusive amount of time and therefore were not reportable.

3. *The dissolution method conducted by the firm is unacceptable. The following dissolution method is recommended:*

Medium: 0.5% sodium lauryl sulfate; 900 mL
Apparatus: USP 23 apparatus 2 (paddle), 25 rpm

Response: *In vitro* dissolution tests were conducted by the firm according to Agency's recommendation. The dissolution method and results are presented in Table 1.

Table 1: In Vitro Dissolution Tests Conducted by Par Pharmaceutical Inc.

Drug (Generic Name): Megestrol Acetate
Dosage Form: Oral Suspension
Dose Strength: 40 mg/mL
ANDA No.: 75-671
Firm: Par Pharmaceutical, Inc.
Submission Date: 11/3/99

Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 25 No. Units Tested: 12
Medium: 0.5% sodium lauryl sulfate in water Volume: 900 mL
Tolerance: NLT in 20 minutes
Reference Drug: Megace Oral Suspension (Bristol-Myers Squibb)
Assay Methodology:

Results of In Vitro Dissolution Testing:

Sampling Times (minute)	**Test Product** Lot #22618 Strength (mg/mL): 40			**Reference Product** Lot #MDN51 Strength (mg/mL): 40		
	Mean %	Range	%CV	Mean %	Range	%CV
5	77.5		10.3	43.3		16.0
10	86.6		6.7	50.5		3.3
15	89.7		4.7	52.6		3.2
30	92.8		2.1	55.8		2.8
60	94.7		3.0	56.6		3.8

Reviewer's Comments:

1. The firm's responses to all 3 deficiencies are acceptable.

2. -- **NOT FOR RELEASE THROUGH FOI** -

   Presented in Table 2 are the dissolution data conducted by the innovator firm, Bristol-Myers Squibb, on two lots of its Megace tablets. The amount dissolved at various time points (75-94%) are much higher than those conducted and submitted by the firm as shown in Table 1 (29.2-59.6%) on the same product with the same dissolution method.

Table 2: In Vitro Dissolution Tests Conducted by Bristol-Myers Squibb

Drug (Generic Name): Megestrol Acetate
Dosage Form: Oral Suspension
Dose Strength: 40 mg/mL
NDA No.: 20-264 & 20-296
Firm: Par Pharmaceutical, Inc.
Submission Date: 4/1/92 & 8/13/92

Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 25 No. Units Tested: 6
Medium: 0.5% sodium lauryl sulfate in water Volume: 900 mL

Results of In Vitro Dissolution Testing:

Sampling Times (minute)	**Reference Product Lot #E89G309** Strength (mg/mL): 40		**Reference Product Lot #E90K567** Strength (mg/mL): 40	
	Mean %	%CV	Mean %	%CV
5	75	1	77	1
15	88	1	90	1
30	92	0.4	91	1
60	94	0.4	92	0.4

Recommendation:

1. The bioequivalence study conducted by Par Pharmaceutical Inc. on its megestrol acetate 40 mg/mL oral suspension, batch #22618, comparing it to Megace^{R} 40 mg/mL oral suspension, lot #MDN51, manufactured by Bristol Myers Squibb, has been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Par Pharmaceutical Inc. on its megestrol acetate 40 mg/mL oral suspension, batch #22618,

comparing it to Megace^{R} 40 mg/mL oral suspension, lot #MDN51, has been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of 0.5% sodium lauryl sulfate in water at 37° C using USP 23 apparatus 2 (paddle) at 25 rpm. The test products should meet the following specifications:

Not less than ... of the labeled amount of megestrol acetate in the dosage form is dissolved in 20 minutes.

Lin-Whei Chuang 11/17/99

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG 11/29/99

Concur Date: 12/2/99
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-671 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Megestrol Acetate Oral Suspension 40 mg/mL

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water, at 37° C using USP Apparatus 2 at 25 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

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

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-671

ADMINISTRATIVE DOCUMENTS

FINAL APPROVAL

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-671

FIRM: Par Pharmaceuticals
One Ram Ridge Road
Spring Valley, NY 10977

DOSAGE FORM: Suspension

STRENGTH: 40 mg/mL

DRUG: Megestrol Acetate Oral Suspension

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all facilities listed in section # 33 of this ANDA (CR # 2) is acceptable as of 4-26-00.

BIO STUDY:
Bio status: Acceptable.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV: Acceptable per FDA Northeast District.

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

LABELING:
Acceptable for approval per T. Watkins's review completed on 2-16-00.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio/stability batch is lot # 22618 and its size is
(Equivalent to 200 liters):

Source of NDS:
: Adequate per review completed on 12-20-99 and remains adequate per review completed on 2-20-01.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Stability batch is lot # 22618 and its size is

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

Intended production batch size [illegible].

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

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

ANDA Number: 75-671 Date of Submission: July 14, 1999
Applicant's Name: Par Pharmaceuticals, Inc.
Established Name: Megestrol Acetate Oral Suspension, 40 mg/mL

Labeling Deficiencies:

1. CONTAINER (240 mL)

   Satisfactory in draft.

2. CARTON (1 x 240 mL)

   Satisfactory in draft.

3. INSERT

   a. TITLE

      We encourage the inclusion of "Rx only" in this section.

   b. DESCRIPTION

      i. Revise the molecular weight to read "384.52" rather than "384.51".

   c. PRECAUTIONS

      i. Drug Interactions - Revise the first sentence of this subsection to read as follows:

         ...parameters of zidovudine or rifabutin to...

   d. ADVERSE EVENTS

      i. Table - Revise "23" to read "2" in the second numerical column under Trial 1.

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with, 12 copies of final printed carton and insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-671

CORRESPONDENCE

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

Copy 1 (Archival)
Copy 2 (Review)

NAI
19-JUL-2001
NEW CORRESP
NC

July 17, 2001

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 18 2001
OGD

PATENT AMENDMENT

RE: ANDA 75-671
MEGESTROL ACETATE ORAL SUSPENSION 40 MG/ML

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated July 14, 1999 and all subsequent amendments relative to Megestrol Acetate Oral Suspension 40 mg/mL. Reference is also made to the Agency's tentative approval letter dated October 23, 2000 and Par's Minor Amendment of May 4, 2001 to reactivate the application prior to approval.

In our Minor Amendment of May 4, 2001 we submitted stability data to 18 months for Batch #22618/Control #017061 conducted at 25°C/60% RH for samples stored in the inverted orientation.

Final printed labeling was submitted on February 11, 2000 and appropriate updated chemistry, manufacturing and controls information were submitted on February 11, 2000 and September 13, 2000 respectively.

Because Bristol-Myers Squibb Company initiated a patent infringement suit against Par in the United States District Court for the Southern District of New York involving a challenge to the '732 patent we also submitted a copy of an order and judgement to address the status of the '732 patent.

On February 9, 2001, the United States District Court for the Southern District of New York issued the final judgment dismissing Bristol's patent infringement claims, ruling that Par does not infringe the Orange Book patent. Bristol appealed that order to the United States Court of Appeals for the Federal Circuit. The Federal Circuit granted Par's request to expedite the appeal, and briefing was complete on May 11, 2001and Oral Arguments were scheduled for July 12, 2001. All documentation pertaining to this process was provided in our May 4, 2001 amendment.

At this time we are submitting a PATENT AMENDMENT as the United States Court of Appeals for the Federal Circuit issued a final appellate ruling on July 16, 2001. (Refer to Attachment I). This court affirmed the judgement that was appealed by Bristol. None of the relief sought in the appeal was granted.

Based on the above, we respectfully request approval of ANDA 75-671 for Megestrol Acetate Oral Suspension, 40 mg/mL. The Agency was and is assured there is no new information that would affect whether final approval should be granted. Introduction or delivery into interstate commerce of the drug product will not occur before the effective final approval date of the application.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

encl./

Desk Copy
Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

N/AM

Copy 1 (Archival)
Copy 2 (Review)
Copy 3 (Field)*

ORIG AMENDMENT

May 4, 2001

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

MINOR AMENDMENT

RE: ANDA 75-671
MEGESTROL ACETATE ORAL SUSPENSION 40 MG/ML

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated July 14, 1999 and all subsequent amendments relative to Megestrol Acetate Oral Suspension 40 mg/mL. Reference is also made to the Agency's tentative approval letter dated October 23, 2000, pertaining thereto. A photostatic copy of the Agency's correspondence is enclosed for reference as Attachment I.

In accordance with the above, we submit this minor amendment to reactivate the application prior to final approval. Please be advised that there are no changes in the conditions under which the product was tentatively approved.

We submit updated stability data to 18 months for Batch #22618/Control #017061 conducted at 25°C/60% RH for samples stored in the inverted orientation. The updated stability data are provided in Attachment II. Stability data to 24 months is not provided as results for preservative effectiveness would not be available until May 18, 2001. The test requires 40 to 60 days to complete from the date the sample is received.

Final printed labeling was submitted on February 11, 2000 and appropriate updated chemistry, manufacturing and controls information were submitted on February 11, 2000 and September 13, 2000 respectively.

Because Bristol-Myers Squibb Company initiated a patent infringement suit against Par in the United States District Court for the Southern District of New York involving a challenge to the '732 patent we also submit a copy of an order and judgement to address the status of the '732 patent.

On February 9, 2001, the United States District Court for the Southern District of New York issued the final judgment dismissing Bristol's patent infringement claims, ruling that Par does not infringe the Orange Book patent. Bristol has appealed that order to the United States Court of Appeals for the Federal Circuit. See Attachment III and IV.

Par expects resolution of the appeal very shortly. While Par cannot predict when the court will ultimately rule, Par fully expects a decision at any time between mid-May and the end of July 2001. The Federal Circuit granted Par's request to expedite the appeal, and briefing will be complete on May 11, 2001. See attachment V. Oral argument is scheduled for July, 2001. Par, however, has requested that the Federal Circuit summarily affirm the district court without oral argument.

Therefore, a final appellate ruling that Par does not infringe is possible any time after the final brief is filed on May 11, 2001.

The Agency is assured there is no new information that would affect whether final approval should be granted.

Introduction or delivery into interstate commerce of the drug product will not occur before the effective final approval date of the application.

Par Pharmaceutical, Inc. certifies that a field copy of this minor amendment has been provided to the FDA New York District Office.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

encl./

* Jerome G. Woyshner
Acting Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 · Telex 131336 · Telecopier (914) 425-7922

Kenneth I. Sawyer
President and CEO

Archival Copy

Request approval upon DC decision. Will not occur pre-3/20/01 decision
11/9/00

November 1, 2000

NEW CORRESP
NC

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

NEW GENERAL CORRESPONDENCE
Request for Effective Approval of ANDA on Date of District Court Patent Decision

Re: ANDA 75-671 – Megestrol Acetate Oral Suspension – 40 mg/ml

Dear Sir/Madam:

Par Pharmaceutical, Inc. ("Par"), applicant for the above-referenced ANDA, after consultation with its counsel, Hyman, Phelps & McNamara, P.C., hereby requests the Food and Drug Administration ("FDA") to make the tentative approval of the above ANDA finally effective on the date of the district court's decision in the action entitled Bristol-Myers Squibb v. Par Pharmaceutical, Inc. (S.D.N.Y. Civ. Action No. 99 CIV. 10822) ("BMS v. Par") that patent number 53383732 ("the '732 patent") is invalid or will not be infringed by Par's megestrol acetate oral suspension drug product ("megestrol suspension"). Par also requests that FDA advise Par within 30 days that the agency will do so. The basis for this request is explained below.

Par received tentative approval for the above ANDA on October 23, 2000. Par's ANDA contains a paragraph IV certification to the '732 patent. Par has been sued by Bristol-Myers Squibb ("BMS") for patent infringement. Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(5)(B)(iii), approval of Par's ANDA is to be made effective on the earlier of February 26, 2002, i.e., 30 months from Bristol's receipt of Par's notification, or "the date of the court decision" that the '732 patent "is invalid or not infringed."

Par has filed a motion for summary judgment of non-infringement in BMS v. Par. Par believes there is a substantial likelihood that the motion will be granted, and that it will be granted well before February 26, 2002. If the motion is denied, Par believes it will prevail after trial, and that judgment after trial will be granted well before February 26, 2002.

The district court in Mylan Pharm., Inc. v. Shalala, 81 F. Supp. 2d 30 (D.D.C. 2000), held that the "court decision" referred to in 21 U.S.C. § 355(j)(5)(B)(iii)(I) includes the decision of a district court. The Mylan court issued a declaratory judgment that FDA's interpretation of the term "court" in the implementing regulation at 21 C.F.R. § 314.107(e) (the "court that enters final judgment from which no appeal can be or has been taken") is contrary to the plain meaning of "court decision" in the cited provision of the FDCA, and that the regulation was therefore invalid.

FDA issued a guidance document dated March 30, 2000, stating that FDA would apply the district court's holding to paragraph IV ANDAs submitted after March 30, 2000, but that it would apply the agency's invalidated interpretation to paragraph IV ANDAs submitted prior to March 30, 2000. Par's ANDA for megestrol suspension was submitted prior to March 30, 2000.

On June, 15, 2000, at Par's request, Hyman, Phelps & McNamara submitted comments on the guidance document. A copy is enclosed for your reference. To our knowledge, FDA has not responded to these or any other comments on the guidance document.

On July 13, 2000, FDA repealed its regulation containing the agency's invalidated interpretation of "court decision." The Federal Register notice stated that the action did not affect the policy announced in the guidance document, i.e., that the correct interpretation of "court decision" as stated in the Mylan case will be applied only prospectively, to ANDAs submitted after March 30, 2000.

If FDA refuses to make the approval of Par's ANDA for megestrol suspension effective as of the date of the anticipated district court decision of non-infringement in BMS v. Par, Par believes the agency's action will be unlawful for the following reasons.

FDA lacks statutory authority to apply different interpretations of "court decision" to different categories of ANDAs. The only statutory authority FDA has is the FDCA, as interpreted by the courts. The term "court decision" in the FDCA has one meaning, not two. Having elected not to appeal Mylan, FDA must apply the meaning of "court" decision announced in that case. There is no provision of the FDCA, judicial precedent, or principle of administrative law which authorizes FDA to apply an alternative, invalidated interpretation of "court decision" to paragraph IV ANDAs submitted prior to March 30, 2000.

Even if FDA had the statutory authority to continue to apply the invalidated interpretation of "court decision," the prospective-only approach in the March 30, 2000, guidance document is arbitrary and capricious. FDA based its decision to continue to apply the invalidated "court decision" interpretation on extra-statutory factors. Those included avoiding unspecified ANDA applicants' theoretical detrimental reliance on FDA's invalidated interpretation of "court decision" in unspecified circumstances relating to ANDAs submitted prior to March 30, 2000, and avoiding lawsuits against the agency from persons aggrieved by application of the correct

interpretation of "court decision." Nothing in the FDCA authorizes FDA to take such factors into account in implementing the FDCA.

The March 30, 2000, guidance document is also arbitrary and capricious because it fails to consider important aspects of the issue and alternative approaches. An important aspect overlooked in the guidance document is that, although the purpose of the policy is to protect "first-filers" of paragraph IV ANDAs, not all first-filers wish to be protected. Indeed, it is not the case that there is always a "second-filed" paragraph IV ANDA for the first-filed ANDA applicant to be protected from. One obvious alternative to FDA's across-the-board application of its invalidated "court decision" interpretation would be to permit first-filed paragraph IV ANDA applicants to waive the protection against detrimental reliance the agency is concerned about. But there is no evident consideration of this alternative in the agency's March 30, 2000, guidance document.

In addition, the March 30, 2000, guidance constitutes a rule issued without required procedure. The policy announced in the guidance is clearly a rule. It is, in fact, the identical standard that was in effect until July 13, 2000, as codified (after APA rulemaking) in 21 C.F.R. § 314.107(e), but applicable only to a subset of ANDAs. FDA's continued application of that standard despite rescission of the codified regulation does not change its character as a rule. Rather, it constitutes an illegally issued revised rule providing for the application of the standard only to ANDAs submitted before March 30, 2000. Had FDA followed the required APA notice-and-comment procedure, comments would have brought to the agency's attention the issues summarized in the preceding paragraphs, possibly paving the way for a more reasonable (although still legally unauthorized) approach.

For all of the above reasons, Par requests FDA to advise Par that the agency will apply the correct interpretation of "court decision" to Par's ANDA for megestrol suspension, and make the approval of the ANDA effective as of the date of a district court decision of non-infringement in BMS v. Par. Par needs confirmation that FDA will make Par's ANDA effective in accordance with the statute. Par intends to be in a position to market megestrol suspension immediately upon issuance of the district court's decision. For Par to do so, Par must know now that the tentative ANDA approval will be made finally effective upon entry of the district court's judgment, as provided by 21 U.SC. § 355(j)(5)(B)(iii)(I). Uncertainty about FDA's position has already begun to affect Par's ability to pursue this lawful business opportunity in a timely, economically rational manner.

If you have questions, or believe it would be useful to meet, please contact the undersigned. However, if Par does not receive a response to this letter within 30 days, it will assume that the FDA intends to apply the March 30, 2000, guidance by refusing to make the approval of Par's ANDA effective on the date of the district court's non-infringement decision in BMS v. Par.

Sincerely yours,

Kenneth I. Sawyer
President and CEO
Par Pharmaceutical, Inc.

Attachment
cc: Mr. Gary Buehler
Acting Director Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 286
Rockville, Maryland 20855

ANDA 75-671

OCT 23 2000

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, New York 10977

Dear Madam:

This is in reference to your abbreviated new drug application dated July 14, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Megestrol Acetate Oral Suspension, 40 mg/mL.

Reference is also made to your amendment dated September 13, 2000.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). It is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application, Megace Oral Suspension of Bristol Myers Squibb, is subject to a period of patent protection which expires on August 16, 2011, (U.S. Patent No. 5,338,732 [the '732 patent]). Your application contains a Paragraph IV Certification to the '732 patent under Section 505(j)(2)(A)(vii) (IV) of the Act. This certification states that your manufacture, use, or sale of this drug product will not infringe upon the '732 patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against Par

Pharmaceutical, Inc. (Par) for infringement of the patent that is the subject of the certification (the '732 patent). You have notified the agency that Par has complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, Bristol Myers Squibb Company initiated a patent infringement suit against Par in the United States District Court for the Southern District of New York involving a challenge to the '732 patent (Bristol-Myers Squibb Company v. Par Pharmaceutical, Inc., Civil Action No. 99 CIV.10822). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of a court decision [505(j)(5)(B)(iii)(I), (II), or (III)], or,

   c. the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60-days (but not more than 90-days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data appropriate. This amendment also serves to reactivate this application within the Office of Generic Drugs and should also be submitted even if none of these changes were made. The amendment should also provide a copy of an order or judgement, settlement agreement between the parties, or a licensing agreement between you and the patent holder, if applicable, or any other relevant information to address the status of the '732 patent. The amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the agency may request at any time prior to the date of final approval that your submit an additional amendment containing the information described above. Failure to submit either or, if requested, both amendments may result in

rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application, as well as the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Furthermore, this drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" list, the "Orange Book", published by the agency.

Prior to submitting the amendment(s), please contact Michelle Dillahunt, Project Manager, (301) 827-5848, for further instructions.

Sincerely yours,

Robert Lumpkin/for 10/23/2000

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

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

√ Copy 1
Copy 2
Copy 3 (Field*)

NDA ORIG AMENDMENT
N/Ac

February 11, 2000

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

MAJOR AMENDMENT

RE: ANDA 75-671
MEGESTROL ACETATE ORAL SUSPENSION 40 MG/ML

Dear Sir/Madam:

Reference is made to our abbreviated new drug application submitted July 14, 1999 as well as additional information submitted August 10, 1999 for Megestrol Acetate Oral Suspension 40 mg/mL. Reference is also made to the Agency's facsimile of January 14, 2000, provided in Attachment I, which outlines the following chemistry, labeling and bioequivalence comments relevant to ANDA 75-671.

CHEMISTRY COMMENTS

Comment 1

a.

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

2/11/00

e.

...conversation with Michele Dillahunt, Project Manager, on January 19, 2000...

...Attachment VI

f.

g.

In addition to responding to the deficiencies presented above, Par Pharmaceutical, Inc., notes and acknowledges the following comments:

1. Labeling deficiencies need to be addressed in our reply.

2. An acceptable compliance evaluation is needed for approval. Par understands that the Agency has requested an evaluation from the Office of Compliance.

3. Additional stability data for the exhibit batch should be submitted, if available. Additional room temperature stability data for Batch #22618/Control #017061, up to and including the 9 month testing interval, is provided in Attachment IX.

4. Our response dated November 3, 1999 regarding bioequivalence issues is pending review. However, according to the bioequivalency comments provided, the Division of Bioequivalence has completed its review and has no further questions at this time.

5. A satisfactory Methods Validation is needed to support the ANDA. Par Pharmaceutical, Inc., understands that the Agency will schedule the validation after the testing issues are resolved.

LABELING COMMENTS

Comment 1

Container (240 mL) satisfactory in draft.

Comment 2

Carton (1 x 240 mL) satisfactory in draft.

Comment 3

Insert

a. TITLE

We encourage the inclusion of "Rx only" in this section.

b. DESCRIPTION

I. Revise the molecular weight to read "384.52" rather than "384.51".

c. PRECAUTIONS

I. Drug Interactions - Revise the first sentence of this subsection to read as follows: ...parameters of zidovudine or rifabutin to...

d. ADVERSE EVENTS

I. Table - Revise "23" to read "2" in the second numerical column under Trial 1.

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Response

Par's insert labeling has been revised in accordance with the Agency's recommendations with the exception of the inclusion of the "Rx only" statement below the title of the insert. Our insert is folded to 1¼ x 1¼. The amount of printed text is limited and the space does not allow for the additional text under the title. Because the "Rx only" statement is not a requirement for package insert labeling, per the Industry Guidance for Implementation of Section 126 of the FDA Modernization Act of 1997, the statement has not been added.

Enclosed, as Attachment X, find 12 final printed copies of our revised insert labeling. To facilitate review,

and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the proposed insert labeling with our July 14, 1999 submission, with all differences annotated and explained, is provided in Attachment XI.

In addition, Par Pharmaceutical, Inc., acknowledges that our container label and carton labeling were found satisfactory in draft. Therefore, we enclose 12 final printed container labels and 12 final printed computer generated cartons, true in size and color (flat sheets), for your review in Attachments XII and XIII respectively.

Par also acknowledges, that prior to approval, it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug. The website will be monitored for any approved changes.

BIOEQUIVALENCY COMMENTS

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water, at 37° C using USP Apparatus 2 at 25 rpm. The test product should meet the following specifications:
>
> Not less than [redacted] the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Response

Par acknowledges that the Division of Bioequivalence has completed its review and has no further questions at this time. The dissolution testing, specified above, has been incorporated into Par's stability and quality control programs. A copy of the Finished Product and Stability Specifications/Procedures for Megestrol Acetate Oral Suspension 40 mg/mL, Document # F/S-907-006, is provided in Attachment V.

Par Pharmaceutical, Inc., certifies that a field copy of this major amendment has been provided to the FDA New York District Office. This concludes our response to the Agency's facsimile of January 14, 2000. Please contact us if additional information is required.

Sincerely.
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

* Brenda Holman, District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
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√ Copy 1
Copy 2

NDA ORIG AMENDMENT
N/AB

November 3, 1999

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

BIOEQUIVALENCE AMENDMENT

RE: ANDA 75-671
MEGESTROL ACETATE ORAL SUSPENSION 40 MG/ML

Dear Sir/Madam:

Reference is made to our abbreviated new drug application submitted July 14, 1999 for Megestrol Acetate Oral Suspension 40 mg/mL. Reference is also made to the Agency's facsimile of October 5, 1999, provided in Attachment I, which outlined the following bioequivalency deficiencies.

Comment 1
Please provide the potency of the reference listed drug used in the fasting in vivo bioequivalence study.

Response
The potency of the reference listed drug used in the fasting in vivo bioequivalence study was provided in Report # M99-024.0, Comparative Study Report on Megace (Megestrol Acetate) Oral Suspension, 40 mg/mL (Bristol-Myers Squibb) and Megestrol Acetate Oral Suspension, 40 mg/mL (Par Pharmaceutical, Inc.), on page 2251 of the original application. Report # M99-024.0 is being resubmitted for your immediate reference in Attachment II. The information requested can be found on page 10 of this bioequivalence amendment.

Comment 2
Please explain why 4 plasma samples reported as "No Reportable Value" actually had assayed values in the raw data section. They were, listed as subject #-treatment-period-sampling hour, 2-A-1-71, 15-B-1-24, 15-B-1-48, and 32-A-1-48.

Response

The four (4) plasma samples are listed in the time deviation table, section 1.8.1, page 00021 (page 158 of the original application) and have NR (No Recorded Time) for sampling time.

As stated in the statistical report, section 1.7.1, page 00018 (page 155 of the original application), for any

sample with no valid time or no concentrations reported, NRV (No Reportable Value) was recorded in the concentration tables for statistical analysis. The samples are set as missing for pharmacokinetic and statistical analysis.

Table C2 in the clinical report, page 00117 (page 254 of the original application), confirms that no sampling times are available for these samples.

Comment 3
Please conduct the dissolution method according to the method shown below and submit the dissolution data to the Agency for review.

Medium:	0.5% sodium lauryl sulfate; 900 mL
Apparatus:	USP 23 apparatus 2 (paddle), 25 rpm

Response
Dissolution testing was conducted according to the method above. The dissolution data is provided in Report # M99-024.1, Comparative Study Report on Megace (Megestrol Acetate) Oral Suspension, 40 mg/mL (Bristol-Myers Squibb) and Megestrol Acetate Oral Suspension, 40 mg/mL (Par Pharmaceutical, Inc.), which can be found in Attachment III.

This concludes our response to the Agency's facsimile received on October 5, 1999. Please contact us if additional information is required.

Sincerely.
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

Enclosures

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

ORIG AMENDMENT

AB

August 10, 1999

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

RE: ANDA 75-671
Megestrol Acetate Oral Suspension 40 mg/mL

Reference is made to our abbreviated new drug application for Megestrol Acetate Oral Suspension 40 mg/mL submitted July 14, 1999. Reference is also made to my telephone conversation today with Paras Patel of the Agency. Mr. Patel requested additional copies of the analytical methods as well as a diskette containing parameter data for the bioequivalence study.

Enclosed, please find three (3) separately bound copies of the analytical methods required to test the bulk active and finished dosage form.

In addition, a diskette containing parameter data for Study Number 98078 conducted by Anapharm is enclosed.

At this time we also wish to provide an updated stability summary report for Batch Number 22618/Control Number 017061 for samples stored at 40°C/75% RH. The stability summary report was updated to provide the results of the Preservative Effectiveness Test conducted at the three month test interval.

Par Pharmaceutical, Inc., certifies that a field copy of the technical section was forwarded to the FDA Brooklyn District Office.

We apologize for any inconvenience incurred.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

cc: Brenda Holman, District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

Par
Pharmaceutical,
Inc.

✓ Copy 1
Copy 2
Copy 3 (field)*

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JUL 14 1999

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Megestrol Acetate Oral Suspension 40 mg/mL

Dear Sir or Madam:

We submit, herewith, in duplicate, an abbreviated new drug application for Megestrol Acetate Oral Suspension 40 mg/mL. The application is submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

The official name of the drug relied upon as the basis upon which this application may be filed is Megestrol Acetate, USP. The proprietary name of said drug is Megace® Oral Suspension. The certification concerning the patent is set forth under SECTION III. The approved insert labeling for the listed drug is enclosed in SECTION V. The third (field) copy certification is provided in SECTION XXI.

A copy of the appropriate pages of the Approved Drug Products with Therapeutic Equivalence Evaluations List is enclosed to show that the proposed drug is the same as the listed drug.

Please find enclosed three (3) separately bound copies of the analytical methods and descriptive information required to test the bulk active and finished dosage form.

A comparative, open-label, randomized, 2-way crossover bioavailability study was conducted of Par Pharmaceutical, Inc. and Bristol-Myers Squibb (Megace®) 40 mg/mL Megestrol Acetate Oral Suspension administered as 2 mL (80 mg) oral suspension in healthy adult males under fasting conditions. The bioavailability study is submitted along with the **in-vitro** dissolution data and financial disclosure statement in SECTION VI.

Please contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs/R&D
Enclosures

CENTER FOR DRUG
REC'D
JUL 15 1999
OGD
EVALUATION AND RESEARCH

* Brenda J. Holman, District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

ANDA 75-671

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

AUG 18 1999

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 also made to the telephone conversation dated August 8, 1999.

NAME OF DRUG: Megestrol Acetate Oral Suspension, 40 mg/mL

DATE OF APPLICATION: July 14, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 15, 1999

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement

from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Harvey Greenberg, Acting Chief, Regulatory Support Branch, at (301)827-5862.

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:

Michelle Dillahunt
Project Manager
(301) 827-5846

Sincerely yours,

for

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

cc:

8/17/99
8/17/99