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Division of Dockets Management (HFA-305)  
U.S. Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this Citizen Petition, in quadruplicate, pursuant to 21 U.S.C. § 355(j)(8), 21 C.F.R. Part 320, and 21 C.F.R. § 10.30.

**A. ACTION REQUESTED**

That the Food and Drug Administration ("FDA") require all applicants for approval of generic or follow-on formulations of the reference listed drug MEGACE<sup>®</sup> ES (megestrol acetate oral suspension 625 mg/5 ml) to conduct bioequivalence studies, under both fed and fasted conditions, and to demonstrate bioequivalence to MEGACE<sup>®</sup> ES oral suspension in accordance with FDA's standard bioequivalence criteria (80% – 125% bioequivalence limits, at a 90% confidence interval).

**B. STATEMENT OF GROUNDS**

**1. MEGACE<sup>®</sup> ES**

MEGACE<sup>®</sup> ES (megestrol acetate) is a marketed drug product available in oral suspension dosage form, at a dose of 625 mg/5 mL, and is indicated for the treatment of anorexia, cachexia, and unexplained weight loss in patients with a diagnosis of acquired immune deficiency syndrome ("AIDS"). Par Pharmaceutical, Inc. ("Par") holds the approved New Drug Application ("NDA") for MEGACE<sup>®</sup> ES oral suspension. Par also manufactures and markets this drug product.

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## **2. PHARMACOKINETIC PROPERTIES OF MEGACE® ES**

MEGACE® ES oral suspension is an advanced formulation of the initially-marketed megestrol acetate oral suspension, in that MEGACE® ES is manufactured using a proprietary NanoCrystal® technology developed by Elan Corporation and licensed to Par Pharmaceutical, Inc. MEGACE® ES affords superior rates of absorption (higher Cmax values) while maintaining an equivalent extent of exposure (same AUC) of megestrol acetate compared to initially marketed megestrol acetate oral suspension, despite a lower dose.

Specifically, as set forth in the Pharmacokinetic Properties section of the approved labeling for MEGACE® ES oral suspension (annexed Exhibit A), pharmacokinetic studies of megestrol acetate suspension formulations were conducted in healthy subjects across a range of doses extending from 150 mg to 675 mg. This dose range includes the MEGACE® ES dose of 625 mg. In these studies, plasma concentrations of megestrol acetate were measured in subjects after administration of the drug product with an FDA-defined high fat meal or following an overnight fast and the rate (Cmax) and extent (AUC) of exposure was determined. These data show that the rate and extent of absorption of megestrol acetate increases proportionally with increasing dose when the test product is administered with a meal. However, when the test product is administered after an overnight fast, the rate and somewhat the extent of absorption increase less than proportionally than the dose at test product doses above 450 mg. Moreover, these data demonstrate that, under fed conditions, MEGACE® ES oral suspension (625 mg/5 mL) is bioequivalent to the initially-marketed megestrol acetate oral suspension (800 mg/40 mL; see attached package insert, Exhibit A hereto).

## **3. FOOD EFFECT ON MEGACE® ES ABSORPTION**

To ascertain whether there is a food effect on the rate and extent of absorption (taking MEGACE® ES oral suspension with food vs. taking it without food), Par evaluated the data from the fed and fasted pharmacokinetic studies described above. Note that these data do not include an evaluation of the pharmacokinetic characteristics of MEGACE® ES in the fasted condition, since this treatment was never administered in a pharmacokinetic study. However based upon the linear pharmacokinetic dose proportionality in the fed state and the reasonably predictable nature of the fasted pharmacokinetic characteristics, Par determined that the most suitable means to determine the effect of food on MEGACE® ES with the data available would be to evaluate the effect of food on the pharmacokinetic characteristics from the next lower dose studied and the next higher dose studied. The next lower dose was the 450 mg dose. In this comparison, the Cmax and AUC<sub>0-∞</sub> values were 12.9% and 24.4% higher, respectively, under fed conditions as compared to fasting conditions. Such values were 54.8% (Cmax) and 43.4% (AUC) higher, respectively, under fed conditions as compared to fasting conditions for the next higher dose of 675 mg. These data, summarized in the Pharmacokinetic Properties section of the approved labeling (Exhibit A and reproduced below), demonstrate the benefit of

MEGACE<sup>®</sup> ES over initially marketed megestrol acetate oral suspension (800mg/40ml) when taken with food.

Pharmacokinetic Studies Conducted with MEGACE <sup>®</sup> ES																
Amount Dosed	150 mg		250 mg		375 mg		450 mg		575 mg		625 mg		675 mg		800 mg	
Dose	5 mL		5 mL		5 mL		5 mL		5 mL		5 mL		5 mL		20 mL	
State	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed
C <sub>max</sub> (ng/mL)	412	379	647	588	810	958	955	1079	-	1421	-	1517	1044	1616	187	1364
AUC <sub>i</sub> (ng*hr/mL)	3058	3889	5194	6328	7238	12193	9483	11800	-	14743	-	16082	11879	17029	8942	18625
T <sub>max</sub> (hr)	1.74	3.80	1.58	3.38	1.56	3.42	1.74	3.16	-	3.75	-	2.52	1.96	2.76	5.89	3.85

The above data show a food effect at doses bracketing the marketed dose (625 mg/mL) of MEGACE<sup>®</sup> ES oral suspension. Recently, Par submitted to FDA the report of a food effect study of MEGACE<sup>®</sup> ES oral suspension at the marketed 625 mg/mL dose. C<sub>max</sub> and AUC<sub>0-∞</sub> values were greater under fed conditions as compared to fasted conditions. These data demonstrate that MEGACE<sup>®</sup> ES can be taken without regard to consumption of meals.

#### 4. **ABSORPTION OF MEGACE<sup>®</sup> ES VS. ABSORPTION OF INITIAL PRODUCT, UNDER FASTED CONDITIONS**

It is important to note that while the above comparative studies show a food effect on the rate and extent of absorption of megestrol acetate from MEGACE<sup>®</sup> ES oral suspension, additional comparative data show that the absorption of megestrol acetate produced by MEGACE<sup>®</sup> ES, under fasted conditions, is much greater than the absorption of initially-marketed megestrol acetate oral suspension under fasted conditions. (See Exhibit B) MEGACE<sup>®</sup> ES oral suspension had C<sub>max</sub> and AUC<sub>0-∞</sub> values (> 500% and 35% higher, respectively) than initially-marketed megestrol acetate oral suspension. Indeed, megestrol acetate from initially-marketed megestrol acetate oral suspension is very poorly absorbed under fasted conditions. This finding demonstrates that, in a fasting state, a patient will still absorb a substantial amount of the active drug substance from MEGACE<sup>®</sup> ES oral suspension.

#### 5. **CLINICAL SIGNIFICANCE**

The above pharmacokinetic data, showing substantially greater absorption of megestrol acetate from MEGACE<sup>®</sup> ES oral suspension under fasted conditions as compared to initially-marketed megestrol acetate oral suspension under the same conditions, is particularly important for this drug. Patients with anorexia or cachexia with AIDS experiencing concomitant weight loss typically have difficulty gaining weight because of appetite suppression and reluctance to consume food. In these situations, such patients are essentially in a chronic fasted state.

The beneficial effects of MEGACE® ES have been demonstrated in a pilot study in 63 patients with HIV-associated unintended weight loss. In this study, megestrol acetate NanoCrystal® dispersion oral suspension manufactured by Par (similar to MEGACE® ES, but at a lower dose of 575 mg) once-daily administration for 12 weeks was associated with improvements in weight gain over the initially marketed megestrol acetate oral suspension. The mean weight change over 12 weeks of therapy was 5.4 kg (55.6 kg to 61 kg, 10% of baseline body weight) and 3.5 kg (54.4 kg to 57.9 kg, 6% of baseline body weight) for MEGACE® ES and initially marketed megestrol acetate oral suspension, respectively. Differences from baseline, in the mean changes in weight, were observed as early as Day 3 ( $p=0.024$ , Wilcoxon Rank Sum) favoring MEGACE® ES and statistical differences were generally present at weekly intervals thereafter. No increase in body weight occurred until the second week for initially marketed megestrol acetate oral suspension. In addition, there were differences in effects on caloric intake, lean body mass, and other measures of body composition favoring MEGACE® ES. Thus, the altered pharmacokinetic characteristics of the MEGACE® ES formulation appear to translate into differences in measured clinical outcomes (e.g., weight change, intake, body composition, etc.).<sup>1</sup>

## 6. GENERIC FORMULATIONS: BIOEQUIVALENCE STUDIES

Given the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, it is possible that, at some point, there will be one or more applicants seeking FDA premarket approval of generic formulations of MEGACE® ES oral suspension via an Abbreviated New Drug Application ("ANDA"). To obtain such approval, an ANDA applicant must show that its generic formulation is bioequivalent to MEGACE® ES oral suspension (no significant difference in rate and extent of absorption). 21 U.S.C. § 355(j)(8)(B), 21 C.F.R. §§ 320.1(e), 320.23. Such a showing must be made *in vivo*, when the dosage form of a particular drug product is intended to deliver the active moiety to the bloodstream for systemic absorption to the human body. 21 C.F.R. § 320.24(b). This is the case for MEGACE® ES oral suspension, and for generic formulations thereof.

In an *in vivo* bioequivalence trial, the concentration of the active moiety in whole blood, plasma, or serum must be measured as a function of time. *Id.* Such an experiment is usually a crossover study measuring whole blood, plasma or serum concentrations of the active moiety of the test drug product (generic formulation) against the reference drug product (already approved innovative formulation) in the same subjects. See FDA's *Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* ("General Bioequivalence Guidance"), March 2003, at 7.

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<sup>1</sup> Cilla DD Jr, Gutierrez JL, Femia RA, et al. A pilot study comparing megestrol acetate concentrated suspension (MA-CS) with megestrol acetate oral suspension (MA-OS) on weight gain in patients with HIV-associated unintended weight loss (UWL). Poster presented at: Annual meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy; December 17, 2005; Washington, DC. Abstract LB-15 (see Exhibit B).

In a single-dose fed bioequivalence study, peak active drug substance concentration ( $C_{max}$ ) and area under the blood/plasma/serum–time curve from time zero to time infinity ( $AUC_{0-\infty}$ ), as well as AUC from time zero to time  $t$  ( $AUC_{0-t}$ ), are required to achieve bioequivalence standards. General Bioequivalence Guidance, at 9.

A generic formulation is deemed to be bioequivalent to a reference listed drug when the ratio of geometric means of  $C_{max}$  and  $AUC_{0-\infty}$  values for the generic formulation are within the range of 80% to 125%, at a 90% confidence interval, of such values for the reference drug product. FDA's *Guidance for Industry, Statistical Approaches to Establishing Bioequivalence*, January 2001, at 2. These are the standard FDA criteria for establishing bioequivalence.

#### **7. FED/FASTED BIOEQUIVALENCE STUDIES**

FDA requires that bioequivalence of a generic formulation to a reference listed drug be demonstrated under both fed and fasted conditions. FDA's *Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies* ("Food Effect Guidance"), December 2002, at 2. This requirement is intended to demonstrate that the administration of a test formulation when taken with food is the same as that of the reference formulation when taken with food. The requirement is fulfilled by conducting a randomized, balanced, single-dose, two-treatment (test fed vs. reference fed), two period, two-sequence crossover study and analyzing  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  to determine whether the 90% CI of the ln-transformed ratio (test/reference) lies within the bounds of 80% to 125%.

When a food effect is shown, it must be so stated in the labeling for the drug product. Food Effect Guidance, at 7.

#### **8. FDA SHOULD REQUIRE GENERIC FORMULATIONS OF MEGACE® ES TO CONDUCT SUCCESSFUL BIOEQUIVALENCE STUDIES, UNDER BOTH FED AND FASTED CONDITIONS**

Under the regulatory criteria set forth above, it is quite clear that generic formulations of MEGACE® ES oral suspension have to be tested for bioequivalence under both fed and fasted conditions. Bioequivalence must be demonstrated in both fed and fasted states by meeting FDA's standard bioequivalence criteria (80%–125% limits, at a 90% confidence interval). The agency must mandate that generic applicants satisfy this standard.

#### **9. GENERIC FORMULATIONS DO NOT QUALIFY FOR ANY BIOEQUIVALENCE EXCEPTION**

An exception to the fed-fasted bioequivalence standard is provided in one of three instances: (1) both test and reference drug products are rapidly dissolving, have similar dissolution profiles, and contain a highly soluble and highly permeable active moiety; (2) when

the approved labeling states that the drug should be taken only on an empty stomach; or (3) when the labeling of the reference drug product does not make any statement about the effect of food on absorption or administration. General Bioequivalence Guidance, at 3-4.

Generic formulations of MEGACE<sup>®</sup> ES oral suspension will not qualify for a bioequivalence exception, because they fail to satisfy any of these conditions. Megestrol acetate oral suspension has low solubility. The approved labeling for MEGACE<sup>®</sup> ES does not state that the drug should be taken on an empty stomach, and such labeling does make the statement that there is a food effect associated with administration of the drug.

C. **CONCLUSION**

For the foregoing reasons, this Citizen Petition should be granted in full.

D. **ENVIRONMENTAL IMPACT**

Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

E. **ECONOMIC IMPACT**

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of this Petition.

F. **CERTIFICATION**

The undersigned certifies that, to their best knowledge and belief, this Citizen Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to the Petition.

Dated: September 28, 2006

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: \_\_\_\_\_



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Enclosures

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