DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

AUG 27 2014

Mr. Charles J. Raubicheck
Frommer Lawrence & Haug LLP
745 Fifth Avenue
New York, NY 10151

Re: Docket No. FDA-2006-P-0393[1]

Dear Mr. Raubicheck:

This letter responds to your citizen petition, received September 29, 2006 (Petition), and supplement, dated May 22, 2007 (Supplement). You request that the Food and Drug Administration (FDA or the Agency) *require* all applicants for approval of generic or follow-on formulations of the reference listed drug Megace ES (megestrol acetate oral suspension 125 milligrams (mg)/milliliter (mL))[2] to conduct studies assessing bioequivalence to Megace ES, the reference listed drug (RLD),[3] under both fed and fasting conditions and to demonstrate bioequivalence in accordance with FDA's standard bioequivalence criteria (80% - 125% bioequivalence limits, at a 90% confidence interval).[4] FDA has considered the information provided in your Petition and Supplement, as well as other information available to the Agency, and for the reasons set forth below, your Petition is denied. However, the Agency notes that it currently *recommends* that ANDA applicants for generic products referencing Megace ES demonstrate bioequivalence under fed and fasting conditions using standard bioequivalence criteria. To the extent that you request that FDA make these recommendations a requirement, your request is denied.

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[1] This citizen petition was originally assigned docket number 2006P-0398/CP1. The number was changed as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] This response addresses issues related to the approval of Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). We do not understand your Petition to make a request regarding the approval of drugs under other statutory provisions, including new drug applications described in section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)).

[3] An RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3(b)). FDA identifies RLDs in its *Approved Drug Products with Therapeutic Equivalence Evaluations* 34th Edition (2014) (the Orange Book), available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[4] Your May 22, 2007 Supplement requests that FDA require each future applicant for a generic formulation of Megace ES to conduct a separate bioequivalence study under fed conditions (in addition to such a study under fasted conditions), which: (1) measures the effect of food on the rate and extent of absorption of the drug substance from the generic formulation; and (2) demonstrates that the results in both fed and fasted conditions show 'significant' bioavailability of megestrol acetate, consistent with the findings demonstrated with Megace ES. FDA considers that document a Supplement to the original CP, which provides what you believe to be additional information that FDA should consider in responding to the original CP.

I. BACKGROUND

A. Megace ES

Megestrol acetate, 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate, is a synthetic derivative of the naturally occurring steroid hormone progesterone. Megestrol acetate oral tablets (20 mg and 40 mg), marketed under the name Megace, were the subject of new drug application (NDA) 16-979 held by Bristol Myers Squibb and approved by FDA on August 18, 1971. Megace oral tablets were voluntarily withdrawn from sale, and FDA determined that the withdrawal was not due to safety or effectiveness reasons.[5]

Megestrol acetate oral suspension (40 mg/mL), also marketed under the name Megace, is the subject of NDA 20-264 (also held by Bristol Myers Squibb), which was approved by FDA on September 10, 1993. Megace ES is an oral suspension containing 125 mg of megestrol acetate per mL.[6] Megace ES (NDA 21-778), held by Par Pharmaceutical, Inc., was approved by FDA on July 5, 2005. Megace ES is indicated for the treatment of anorexia, cachexia, or an unexplained and significant weight loss in patients diagnosed with acquired immunodeficiency syndrome (AIDS).

B. Statutory and Regulatory Basis for Approving ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant does not submit clinical studies to demonstrate safety and effectiveness, instead, it relies on FDA's previous finding that the RLD is safe and effective. To rely on this finding, the ANDA must contain (with certain exceptions, not relevant here) information to show that the proposed drug has the same active ingredient(s), indications, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act) and is bioequivalent to the RLD (section 505(j)(2)(A)(iv) and 505(j)(4)(F)of the FD&C Act).

Under the FD&C Act, a generic[7] drug product is bioequivalent to the RLD "if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions" (section 505(j)(8)(B)(i) of the FD&C Act). FDA regulations at 21 CFR 320.1(e) specify that two drug products are bioequivalent if there is an absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at

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[5] *Determination That MEGACE (Megestrol Acetate) Tablets and Nine Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness* (76 FR 11488, March 2, 2011).

[6] Megace ES labeling dated 5/2013.

[7] The term *generic* is used in this petition response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[8]

Section 314.94(a)(7) (21 CFR 314.94(a)(7)) of FDA's regulations sets forth the bioequivalence requirements for an ANDA. Procedures for determining bioequivalence are set forth in FDA's regulations in 21 CFR part 320. The regulations discuss the various methods of establishing bioequivalence in general descending order of accuracy, sensitivity, and reproducibility.[9] These methods include in vivo tests, pharmacokinetic and pharmacodynamic studies, comparative clinical trials, and in vitro studies ensuring human bioavailability.[10] Significantly, FDA has flexibility in defining the appropriate bioequivalence method needed for approval of an ANDA. The regulations at section 320.24(b)(6) specify that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."[11] The courts have expressly upheld FDA's regulatory implementation of the FD&C Act's bioequivalence requirements (e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397- 401 (3rd Cir. 1995) (statute does not limit FDA's discretion in determining what tests or studies will provide it with appropriate information from which to determine bioequivalence); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (the factual determination of how bioequivalence is determined properly rests within FDA discretion).

FDA's standard recommendation for bioequivalence testing of orally administered and systemically absorbed drug products is a single-dose, two-way crossover study.[12] Single-dose studies generally are more sensitive than multiple-dose studies in assessing release of the drug substance from the drug product into the systemic circulation, which makes it easier to detect differences in formulations.[13] FDA recommends administration of single doses of the test and reference drug products to subjects representative of the general population with measurement of the plasma concentrations of the test and reference drugs over time.[14] As a general matter, FDA

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[8] See also 21 CFR 320.23(b).

[9] 21 CFR 320.24.

[10] Id.

[11] 21 CFR 320.24(b)(6).

[12] See FDA guidance for industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (March 2003, Rev 1) (March 2003 BA and BE Guidance) at 6-11; see also FDA draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) at 3 (ANDA BE Draft Guidance). The ANDA BE Draft Guidance recommends that for most dosage forms that release a drug intended to be systemically available, the applicants perform a two-period, two-sequence, two-treatment, single dose, crossover study using healthy subjects. Id. at 3. In this draft guidance, FDA continues to recommend single-dose pharmacokinetic studies for immediate and modified release drug products to demonstrate bioequivalence because these studies are generally more sensitive than steady-state studies in assessing differences in the release of the drug substance from the drug product into the systemic circulation. Id. at 3 and 5. The ANDA BE Draft Guidance, when finalized, will represent FDA's current thinking on this topic. It is intended to revise and replace parts of two FDA guidances for industry — the March 2003 BA and BE Guidance and FDA guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies* (December 2002) (2002 Food-Effect Guidance), cited at page 1. All cited guidance documents are available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[13] See March 2003 BA and BE Guidance at 6 and 8; ANDA BE Draft Guidance at 5.

[14] March 2003 BA and BE Guidance at 7-8; ANDA BE Draft Guidance at 3-5.

recommends that bioequivalence for a suspension be established in the same manner as for immediate-release solid oral dosage forms.[15]

FDA recommends that bioequivalence evaluations assess systemic exposure measures that reflect comparable rates and extents of absorption.[16] Exposure measures are generally defined relative to early, peak, and total portions of the plasma, serum, or blood-concentration-time profile.[17] Product quality parameters for bioequivalence frequently rely on pharmacokinetic measures of AUC and C_{max} that are reflective of systemic exposure.[18] To evaluate the rate and extent of test drug absorption, the measured plasma concentrations for each subject should be plotted graphically against time of measurement. The graph depicts the plasma sampling time on the horizontal (x) axis and corresponding plasma drug concentration on the vertical (y) axis. The relevant pharmacokinetic parameters calculated from these data include the area under the plasma concentration curve versus time (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). This parameter represents the extent of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant pharmacokinetic parameter is the maximum or peak drug concentration (C_{max}), which is used to reflect the rate of absorption.[19]

FDA generally considers generic and RLD products bioequivalent when the calculated 90% confidence interval for the log transformed ratio of geometric means for AUC and C_{max} values between the products falls entirely within an 80% to 125% acceptance interval (0.8-1.25).[20] The use of an 80% to 125% acceptance interval to compare two products with the same active ingredient, dosage form, route of administration, and strength is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific study and analysis of the variability of product characteristics within and between batches, as well as biological variability in patients.[21] FDA therefore has generally concluded that the variability in pharmacokinetic values allowed under this acceptance interval will not adversely affect clinical outcomes because this variability is within the range of differences that can arise because of other product-specific and biological factors.[22]

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[15] March 2003 BA and BE Guidance at 12; ANDA BE Draft Guidance at 10. The ANDA BE Draft Guidance (at 10) also recommends that applicants seeking additional information on bioequivalence study design consult the FDA website to see if a product-specific guidance is available (see discussion I.D.).

[16] March 2003 BA and BE Guidance at 8; ANDA BE Draft Guidance at 2-3.

[17] March 2003 BA and BE Guidance at 8-9; ANDA BE Draft Guidance at 3, 6 and 13.

[18] See, e.g., March 2003 BA and BE Guidance at 6; ANDA BE Draft Guidance at 3, 6 and 13.

[19] March 2003 BA and BE Guidance at 8-9; ANDA BE Draft Guidance, Attachment: General Design and Data Handling of Bioequivalence Studies with Pharmacokinetics Endpoints, pp. 17-19.

[20] *See* FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence* (January 2001) at 2 (2001 BE Statistical Approaches Guidance).

[21] Generally, 2001 BE Statistical Approaches Guidance; Orange Book at viii- ix.

[22] See, e.g., FDA's May 8, 2014 Citizen Petition Response to Sigmapharm Laboratories, LLC, Docket No. FDA-2013-P-1623, at 4, available at http://www.regulations.gov, citing Dighe, S.V., and Adams, W.P., "Bioequivalence: A United States Regulatory Perspective" in *Pharmaceutical Bioequivalence* (Welling, P.G. et al., eds.), pp. 347-380 (1991).

C. FDA Guidance on Food-Effect and Fed Studies

Recognizing the potential effects of food on the bioavailability and bioequivalence of a drug product, FDA developed its 2002 Food-Effect Guidance to provide industry with information on (1) how food-effects on oral dosage forms impact the bioavailability and bioequivalence requirements in the regulations (2) when food-effect bioavailability and fed bioequivalence studies should be conducted, and (3) how the studies should be designed and the resulting data analyzed.[23]

Fed bioequivalence studies are conducted for ANDAs to demonstrate the bioequivalence of the test product to the reference listed drug under fed conditions because food can change the bioavailability of a drug and influence bioequivalence between test and reference drug products.[24] The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the gastrointestinal tract that affect drug product transit time, luminal dissolution, drug permeability, and systemic availability.[25] The food effect is usually greatest when the drug product is administered immediately following a high-fat, high-calorie meal.[26]

Accordingly, FDA generally recommends that ANDA applicants conduct a bioequivalence study under fed conditions, in addition to fasting conditions, for orally administered drug products.[27] However, FDA has recognized that this general recommendation may, in certain circumstances, not be appropriate. FDA's 2002 Food-Effect Guidance describes three circumstances in which FDA does not recommend that sponsors conduct bioequivalence studies under both fed and fasting conditions: (1) when both the test product and the RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability; (2) when the DOSAGE AND ADMINISTRATION section of the RLD labeling states that the product should be taken only on an empty stomach; or (3) when the RLD labeling does not make any statements about the effect of food on absorption or administration.[28] In FDA's 2013 ANDA BE Draft Guidance, FDA recommends that when a fasting in vivo bioequivalence study is recommended for an orally administered, immediate release product, FDA also recommends that ANDA applicants conduct a fed study, except when the *dosage and administration* section of the RLD labeling states that the product should be taken only on an empty stomach.[29] When finalized, this ANDA BE Draft Guidance is intended to replace parts of the 2002 Food-Effect Guidance.[30]

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[23] Generally, 2002 Food-Effect Guidance.

[24] 2002 Food-Effect Guidance at 2-3; March 2003 BA and BE Guidance at 17; ANDA BE Draft Guidance 2013 at 6.

[25] 2002 Food-Effect Guidance at 2-3.

[26] Id.

[27] 2002 Food-Effect Guidance at 3-4; ANDA BE Draft Guidance 2013 at 6.

[28] 2002 Food-Effect Guidance at 3-4.

[29] For orally administered, immediate release products labeled to be taken only with food, fasting and fed studies are recommended, except when serious adverse events are anticipated with fasting administration. For all orally administered, modified-release drug products, we also recommend that applicants conduct a fed bioequivalence study in addition to a fasting bioequivalence study. Id. at 8 and 11.

[30] ANDA BE Draft Guidance at 1.

D. FDA Draft Guidance on Bioequivalence for Megestrol Acetate (125 mg/mL)

In general, FDA has developed a process for making available to the public its guidance on how to design bioequivalence studies for specific drug products to support ANDAs.[31] FDA published a draft product-specific bioequivalence guidance in February 2010 recommending that bioequivalence to oral suspensions of 125 mg/mL megestrol acetate be assessed by conducting a single-dose (125 mg), two-way crossover in vivo study in healthy male subjects under fasting conditions, and conducting a single-dose (125 mg), two-way crossover in vivo study in healthy male subjects under fed conditions.[32] The draft guidance recommends that bioequivalence be established using a 90% confidence interval.[33] In vitro dissolution testing is also recommended to be conducted on 12 dosage units of all strengths of the test and reference products.[34] Like other FDA bioequivalence guidance documents the megestrol acetate (125 mg/mL) draft guidance is nonbinding,[35] and regulated parties "can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations."[36]

II. DISCUSSION

A. Assessment of Bioequivalence to Megace ES Under Both Fed and Fasting Conditions

In your Petition, you request that the Agency require any ANDA for megestrol acetate oral suspension (125 mg/mL) to contain studies assessing bioequivalence to Megace ES, the RLD, under both fed and fasting conditions.

As described above, FDA's March 2003 BA and BE Guidance and 2002 Food-Effect Guidance generally recommend that both single-dose fed and fasted studies be performed to evaluate bioequivalence. The Agency recognizes that circumstances exist in which these general recommendations are not appropriate.[37] However, none of these circumstances are present in this case. First, Megace ES does not contain a "drug substance with high solubility." FDA has

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[31] FDA guidance for industry *Bioequivalence Recommendations for Specific Products* June 2010 (*Product Specific BE Guidance* 2010). The *Product Specific BE Guidance* 2010 states that the Agency intends to develop bioequivalence recommendations based on its understanding of the characteristics of the listed drug, information derived from published literature, Agency research and consultations within different offices in CDER as needed based on the novelty or complexity of the BE considerations. Id. at 2. Separately, FDA recommends that applicants seeking additional information on bioequivalence study designs for a specific product consult the Agency website to determine whether a product-specific guidance has been developed for a proposed product. ANDA BE Draft Guidance at 10.

[32] FDA draft guidance on Megestrol Acetate (125 mg/mL) (February 2010), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm199663.pdf.

[33] Id.

[34] Id.

[35] See 21 CFR 10.115(d) ("Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or the FDA.").

[36] FDA draft guidance on Megestrol Acetate (125 mg/mL).

[37] See section I.C. and footnotes 28-30 of this petition response.

stated that a drug substance is "considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5."[38] The Megace ES labeling indicates that the recommended therapeutic dosage of Megace ES is 625 mg, and the DESCRIPTION section of the labeling states that the solubility of megestrol acetate at 37°C in water is 2 micrograms (mcg) per mL.[39] A 625-mg dose of megestrol acetate would therefore be soluble in 312,500 mL of water, which is well above the 250 mL or less limit necessary for classification as a highly soluble drug substance. FDA therefore does not consider Megace ES to contain a drug substance with high solubility. Second, the DOSAGE AND ADMINISTRATION section of the Megace ES labeling does not state that the product should be taken only on an empty stomach. Third, the label specifically makes statements about the effect of food on absorption or administration. For instance, it states that when Megace ES was administered following a high-fat meal, the Cmax and AUC were 48 percent and 36 percent greater, respectively, than when Megace ES was administered under fasting conditions.[40] Thus, consistent with the general recommendations contained in FDA's March 2003 BA and BE Guidance and the 2002 Food-Effects Guidance, the Agency recommends that ANDA applicants referencing Megace ES conduct studies under both fasted and fed conditions to establish bioequivalence.[41]

In addition, FDA has issued draft product specific guidance that specifically addresses establishing bioequivalence to megestrol acetate oral suspensions.[42] This guidance, when finalized, will represent the Agency's current thinking on the design of bioequivalence studies for megestrol acetate (125 mg/mL) drug products. The draft guidance recommends studies consisting of two-way crossover studies in vivo in healthy male subjects under fasting and fed conditions, in addition to dissolution studies.[43] Accordingly, FDA draft recommendations are that ANDAs for megestrol acetate oral suspension (125 mg/mL) contain studies assessing bioequivalence to Megace ES under both fed and fasting conditions.[44]

B. Demonstrating Bioequivalence to Megace ES in Accordance with FDA's Standard Bioequivalence Criteria

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[38] See guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (August 2000) at 2.

[39] Megace ES labeling (as revised 5/2013) at 8, available on the Internet at http://www.accessdata.fdagov/scripts/cder/drugsatfda/index.cfm.

[40] Megace ES labeling (as revised 5/2013) at 9. In addition, as you observe in your Supplement, at 1, the Megace ES labeling states that Megace ES can be taken without regard to meals.

[41] As described above in section I.C, we also note that the ANDA BE Draft Guidance states that when a fasting in vivo bioequivalence study is recommended for an orally administered, immediate-release product, FDA also recommends that applicants conduct a fed study, except when the *dosage and administration* section of the RLD labeling states that the product should be taken only on an empty stomach. ANDA BE Draft Guidance at 6. The *dosage and administration* section of the Megace ES labeling does not make such a statement and under FDA's ANDA BE Draft Guidance, the Agency would recommend that ANDAs referencing Megace ES contain both fed and fasting studies.

[42] See draft guidance on Megestrol Acetate (125 mg/mL)(February 2010).

[43] Id.

[44] Id.

You further request that FDA require any ANDA applicant for megestrol acetate oral suspension (125 mg/mL) to demonstrate bioequivalence to Megace ES in accordance with FDA's standard bioequivalence criteria.[45] As discussed above, under FDA's standard criteria for assessing bioequivalence, the Agency generally considers a generic product to be bioequivalent to an RLD if the 90% confidence interval for the log transformed ratio of geometric means for the AUC and C_{max} values between the products falls entirely within an 80% to 125% acceptance interval (0.8-1.25).[46] We agree that these criteria for evaluating bioequivalence generally may be used for megestrol acetate oral suspensions (125 mg/mL).

However, we decline at this time to "require" all ANDA applicants for megestrol acetate oral suspension (125 mg/mL) to demonstrate bioequivalence in the manner described in your Petition.[47] As indicated above, FDA recommendations for demonstrating bioequivalence, which are described in guidance documents, are not mandatory. If an ANDA applicant for megestrol acetate oral suspension (125 mg/mL) sought approval using an alternative approach that satisfies the requirements of the applicable statutes and regulations, FDA has the discretion to accept that approach.

III. CONCLUSION

For the reasons discussed above, we deny your Petition to the extent that it requests that FDA require ANDAs referencing Megace ES to demonstrate bioequivalence under both fed and fasted conditions and to demonstrate bioequivalence to the RLD in accordance with the standard bioequivalence criteria (80%-125% bioequivalence limits, at a 90% confidence level). However, consistent with the recommendations of the FDA guidance documents described above, we note that FDA expects any ANDA referencing Megace ES to contain bioequivalence studies under both fed and fasted conditions and, as a general matter, applies the standard bioequivalence criteria (80%-125% acceptance interval, at a 90% confidence interval).

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[45] Petition at 5.

[46] Orange Book, at viii-xi; 2001 BE Statistical Approaches Guidance at 2.

[47] Similarly, to the extent that your Supplement requests that FDA impose requirements that ANDAs referencing Megace ES must contain certain data and information from fed and fasted studies, FDA declines at this time to impose such a blanket requirement but notes that FDA expects any such ANDA to demonstrate bioequivalence under both fed and fasted conditions, consistent with the recommendations of the FDA guidance documents described in this response.