

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

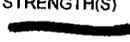
21-778

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-778	
		NAME OF APPLICANT / NDA HOLDER Par Pharmaceutical, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Megestrol Acetate Oral Suspension			
ACTIVE INGREDIENT(S) Megestrol Acetate		STRENGTH(S) _____	
DOSAGE FORM Oral Suspension			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.</p>			
<p>For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.</p>			
<p>FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</p>			
<p>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</p>			
1. GENERAL			
a. United States Patent Number 5,145,684		b. Issue Date of Patent 9/8/1992	c. Expiration Date of Patent 1/25/2011
d. Name of Patent Owner Elan Pharma International Ltd. Shannon, IE		Address (of Patent Owner) Wil House, Shannon Business Park	
		City/State Shannon, County Clare	
		ZIP Code Ireland	FAX Number (if available) +353 61 362 097
		Telephone Number +353 61 362 533	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.	
2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) A method of treating a mammal comprising the step of administering to the mammal an effective amount of the pharmaceutical composition.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
	<input type="checkbox"/> Yes

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)	Date Signed
<i>Michelle Bonomi-Hewala</i>	<i>6/29/04</i>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
Check applicable box and provide information below.	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Par Pharmaceutical, Inc.	
Address One Ram Ridge Road	City/State Spring Valley, New York
ZIP Code 10977	Telephone Number (201) 802-4000
FAX Number (if available) (201) 391-3106	E-Mail Address (if available) mbonomi@parpharm.com
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,592,903		b. Issue Date of Patent 7/15/2003	c. Expiration Date of Patent 9/21/2020
d. Name of Patent Owner Elan Pharma International Ltd. Shannon, IE		Address (of Patent Owner) Wil House, Shannon Business Park	
		City/State Shannon, County Clare	
		ZIP Code Ireland	FAX Number (if available) +353 61 362 097
		Telephone Number +353 61 362 533	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?			
		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) **Date Signed**

Michelle Bonomi-Huwala *6/29/04*

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Par Pharmaceutical, Inc.	
Address One Ram Ridge Road	City/State Spring Valley, New York
ZIP Code 10977	Telephone Number (201) 802-4000
FAX Number (if available) (201) 391-3106	E-Mail Address (if available) mbonomi@parpharm.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

06/08/05

EXCLUSIVITY SUMMARY FOR NDA # 21-778 SUPPL # _____

Trade Name Megace ES Generic Name megestrol acetate oral suspension, 125 mg/mL

Applicant Name Par Pharmaceutical Inc. HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / X / NO / ___ /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b) (2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

This is a bioequivalence study, using Cmax and AUC to determine bioequivalence to the reference listed drug, Megace (megestrol acetate) NDA 20-264. Both the reference drug product and the new product are oral suspensions.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative

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Exclusivity Summary
Page 3

(such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	<u>20-264</u>	<u>Megace (megestrol acetate)</u>
NDA#	_____	_____
NDA#	_____	_____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ / NA / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	_____	_____
NDA#	_____	_____
NDA#	_____	_____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS: NOT APPLICABLE

To qualify for three years of exclusivity, an application or

NDA 21-778

Exclusivity Summary

Page 4

supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /X/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!		
IND # _____	YES /___/	!	NO /___/ Explain: _____
		!	
		!	
Investigation #2	!		
IND # _____	YES /___/	!	NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	

Investigation #2	!	
	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
	!	
_____	!	_____
	!	
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be

considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature: Holly Wieland, RN, MPH Date: _____
Title: Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products, HFD-510

Signature: Mary Parks, MD Date: _____
Title: Deputy Division Director, Division of Metabolic and Endocrine Drug Products, HFD-510

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

/s/

Holly Wieland
6/7/05 01:14:11 PM

Mary Parks
6/8/05 12:52:37 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-778 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: June 29, 2004 Action Date: July 29, 2005 (PDUFD Clock extended 3 months from original PDUFA goal date of April 29, 2005).

HFD 510 Trade and generic names/dosage form: Megace ES (megestrol acetate) Oral Suspension

Applicant: Par Pharmaceutical, Inc. Therapeutic Class: 3030450

Indication(s) previously approved: Treatment of anorexia /cachexia or unexplained significant weight loss in AIDS patients.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of anorexia /cachexia or unexplained significant weight loss in AIDS patients.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

{See appended electronic signature page}

cc: NDA 21-778
HFD-960/ Grace Carmouze
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 12-22-03)

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

/s/

Holly Wieland
5/16/05 10:45:07 AM
with concurrence from R. Perlstein, MD

16.0 DEBARMENT CERTIFICATION

Pursuant to Section 306(k) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. Section 335a(k)], Par Pharmaceutical (PAR) hereby certifies that PAR did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

PAR states further that, during the previous five years, it has not sustained convictions described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992:

To the best of PAR's knowledge, no person affiliated with PAR that was responsible for the development or submission of this application has been convicted of an offense described in, subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Senior Director, Regulatory Affairs R&D

6/29/04

Date

17.0 FIELD COPY CERTIFICATION

As required by 21 CFR Section 314.94(d)(5), the undersigned certifies that the third (field) copy is a true copy of the technical sections of the application and was submitted to Jerome G. Woysner, District Director, Food and Drug Administration, New York District Office, 158-15 Liberty Avenue, Jamaica, New York 11433 in accordance with 21 CFR Section 314.440(a)(4).

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Senior Director, Regulatory Affairs R&D

6/29/04

Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Michelle Bonomi-Huvala	TITLE Senior Director, Regulatory Affairs R&D
FIRM / ORGANIZATION Par Pharmaceutical, One Ram Ridge Road, Spring Valley, New York 10977	
SIGNATURE <i>Michelle Bonomi-Huvala</i>	DATE 6/29/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-1

07-05-05

Division of Metabolic and Endocrine Drug Products, HFD-510

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-778

Name of Drug: Megace ES 125 mg/mL (megestrol acetate) Oral Suspension

Applicant: Par Pharmaceuticals, Inc.

Material Reviewed:

Container Labels

Submission Dates: June 29, 2004, and April 25 and May 26, 2005

Package Insert (PI)

Submission Dates: June 29, 2004, and April 25 and May 26, 2005

Background and Summary

Par Pharmaceuticals, Inc. submitted proposed PI and container labeling for NDA 21-778 on June 29, 2004. At the time of the initial submission, the sponsor did not have a trade name listed for megestrol acetate. Par submitted a proposed trade name on August 27, 2004, which was determined to be unacceptable by DMETS; however, the review division, overrode the DMETS decision and in an internal meeting on February 2, 2005, the proposed trade name, Megace ES, was determined to be acceptable and the sponsor was advised. This decision and other labeling revisions were conveyed by telephone conference to the sponsor on February 2, 2005. The sponsor agreed to make the requested revisions to the labeling. The comments and revisions are documented in a memo to file dated February 14, 2005. On February 24, 2005, the sponsor submitted electronic labeling with the requested revisions.

During the biopharmaceutical review, it was determined that the dosage strength, _____ would not meet bioequivalence approval criteria. In a telephone conference on April 6, 2005, the FDA advised the company to submit an amendment with additional chemistry and biopharmaceutical information, and revised labeling for the new (125mg/mL) strength. The sponsor submitted electronically the requested amendment for chemistry on April 7, 2005, and for labeling on April 12, 2005. FDA determined that the chemistry submission was a major amendment and extended the PDUFA goal date from April 29, 2005, to July 29, 2005.

The sponsor was advised by email dated April 22, 2005, that the PI label submitted on April 12, 2005, did not contain already approved geriatric text. On April 25, 2005, the sponsor submitted corrected labeling for the PI that included the geriatric text.

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Page 2

The proposed draft labeling review for both the PI and the container was done on the April 25, 2005, labeling submission. After receiving comments from reviewers and DDMAC, this Project Manager determined the labeling was acceptable with revisions. Comments were conveyed to the sponsor by telephone conferences on May 5 and 25, 2005, and documented in Memos to File dated May 19, 2005, and June 8, 2005.

A final printed labeling (FPL) review was done comparing the April 25, 2005, submission to the May 26, 2005, submission.

Review

The proposed (PI) labeling submitted on April 25, 2005, was compared to the currently approved labeling for the reference product, Megace, NDA 20-264, submitted for S-011 on October 15, 2003, and approved on January 9, 2004.

The reviewers had additional comments that were relayed to the sponsor and electronic FPL was submitted May 26, 2005. A second review was done to ensure that the requested changes to the April 25, 2005, submission were executed in the May 26, 2005, submission.

Package Insert (PI)

At the top of the PI, the product name has been changed from "Megace® Oral Suspension" to "Megace ES", the generic name and strength has been added underneath the new name, "megestrol acetate 625mg/5mL oral suspension."

The words "Rx only" have been moved from the right side to underneath the generic name and strength.

This is an acceptable editorial revision.

In the **DESCRIPTION** section, the words, "MEGACE® (megestrol acetate) oral suspension" have been changed to "Megace® ES (megestrol acetate) oral suspension." This word change is consistent throughout this labeling submission and will not be noted again. In the third sentence, the following words have been deleted, "17 α (acetyloxy) 6 methylpregna 4, 6 diene," and have been replaced with "17-Hydroxy 6-methylpregna-4, 6-diene-3, 20-dione acetate." The molecular weight has been changed from 384.51 to 384.52. In the following sentence beginning "The empirical formula . . .," the word "empirical" has been changed to "chemical." Under the diagram, the words "megestrol acetate, USP" have been deleted.

This is an acceptable revision according to the Chemistry Reviewer.

The wording in the next paragraph beginning "MEGACE Oral Suspension is supplied. . ." has been changed to say "Megace® ES (megestrol acetate) is a concentrated formula supplied as an

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Page 3

oral suspension containing 125 mg of megestrol acetate per mL.”

In the May 25 PI, the wording in the next paragraph beginning “MEGACE Oral Suspension contains . . .” has been changed to say “Megace® ES (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, hydroxypropyl methylcellulose (hypromellose), natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose”.

These are acceptable editorial revisions according to the Chemistry Reviewer.

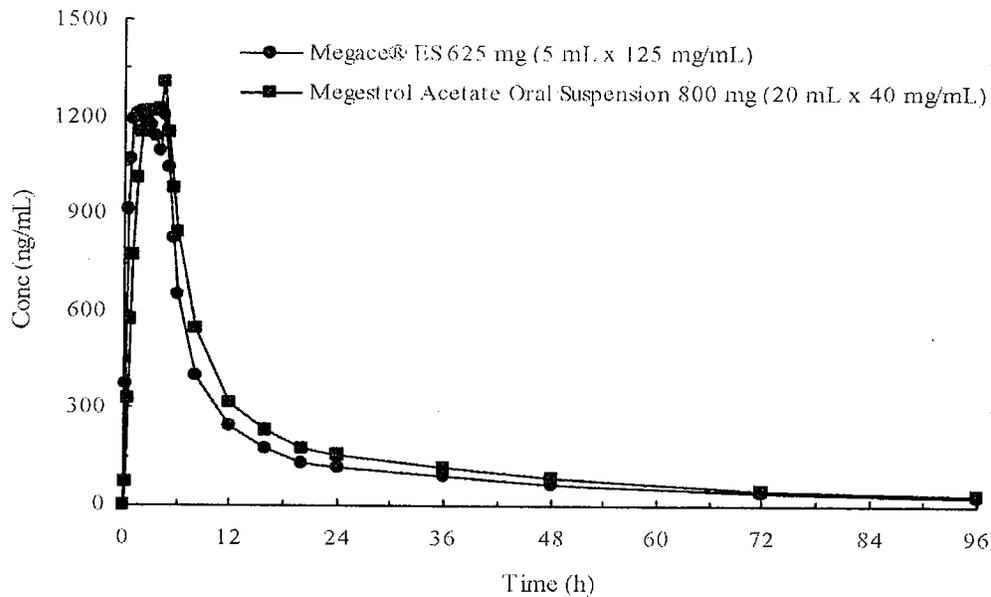
In the **CLINICAL PHARMACOLOGY** section of the referenced product, the first paragraph says “Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.” In Megace ES, this paragraph is moved to become the second paragraph under a new subheading titled “Mechanism of Action.”

The third paragraph in the **CLINICAL PHARMACOLOGY** section beginning, “The major route of drug elimination . . .” has been deleted for Megace ES.

Another subheading has been added to Megace ES titled “Pharmacokinetic Properties” and the following information has been added. “Plasma concentrations of megestrol acetate after administration of 625 mg (125 mg/mL) of Megace® ES (megestrol acetate) oral suspension are equivalent under fed conditions to 800 mg (40 mg/mL) of megestrol acetate oral suspension (see figure below). The following figure, and text, and table have been added.

**Appears This Way
On Original**

Mean plasma concentrations of megestrol acetate after oral administration of 625 mg of Megace® ES (megestrol acetate) oral suspension and 800 mg of megestrol acetate oral suspension to healthy volunteers under fed conditions



In order to characterize the effect of food on the absorption of Megace® ES, pharmacokinetic studies were also conducted under fasting conditions. 625 mg/5 mL was bracketed by 450 mg/5 mL and 675 mg/5 mL to evaluate the effect of food on the Megace® ES formulation. C_{max} and AUC values were 12.9% and 24.4% higher under fed conditions as compared to fasted for 450 mg/5 mL and 54.8% and 43.3% higher for 675 mg/mL, respectively.

Pharmacokinetic Studies Conducted with Megace® 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	
	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed
C_{max} (ng/mL)	412	379	647	588	810	958	955	1079	-	1421	-	1517	1044	1616	187	1364
AUC _{0-∞} (ng·h/mL)	3058	3889	5194	6328	7238	12193	9483	11800	-	14743	-	16082	11879	17029	8942	18625
Tmax (h)	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

*megestrol acetate oral suspension

In the subheading “Metabolism” in the **CLINICAL PHARMACOLOGY** section, the following information has been added. “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.”

In the subheading “Elimination” in the **CLINICAL PHARMACOLOGY** section, the following information has been added. “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%).

In the subheading “Special Populations” in the **CLINICAL PHARMACOLOGY** section, the following information has been added. “The pharmacokinetics of megestrol acetate has not been studied in any special populations.”

These are acceptable revisions according to the Biopharmaceutical Reviewer.

In the **DESCRIPTION OF CLINICAL STUDIES** section, a beginning sentence has been added, “Megestrol acetate oral suspension at a dose of 800 mg/20 mL is equivalent to 625 mg/5 mL of Megace® ES.” This is an acceptable editorial revision.

On page 6, in the **WARNINGS** section, in the last sentence of paragraph 3, the phrase “in conditions of” was changed to “during” in the May 26 PI as requested by the Clinical Reviewer.

In the “Information for Patients” subsection of the **PRECAUTIONS** section, Megace ES contains additional information. The information has been rewritten to include 6 information items for patients as follows:

Patients using Megace® ES (megestrol acetate) should receive the following instructions:

1. This medication is to be used as directed by the physician.

2. _____

3. _____

4. Use contraception while taking this medication if you are a woman capable of becoming pregnant.

5. _____

6.

These were not acceptable revisions according to the Clinical Reviewer. The Clinical Reviewer made the following recommended changes which PAR submitted on May 26, 2005:

The numbered instructions in the "Information for Patient" subsection state the following and the last two sentences of this section have been deleted:

1. This medication is to be used as directed by the physician.
2. Megace® ES (625 mg/5 mL) does not contain the same amount of megestrol acetate as Megace® oral suspension or any of the other megestrol acetate suspensions. Megace® ES contains 625 mg of megestrol acetate per 5 mL, whereas Megace® oral suspension and other megestrol acetate suspensions contain 800 mg per 20 mL.
3. **The prescriber should inform the patient about the product differences to avoid overdosing or underdosing of megestrol acetate. The recommended adult dosage of Megace® ES is one teaspoon (5 mL) once a day. Please see table in DOSAGE and ADMINISTRATION section.**
4. Report any adverse reaction experiences while taking this medication.
5. Use contraception while taking this medication if you are a woman capable of becoming pregnant.
6. Notify your physician if you become pregnant while taking this medication.

There is additional information under the **PRECAUTIONS** section under "Drug Interactions." Two sentences stating, "A pharmacokinetic study demonstrated that co-administration of megestrol acetate and indinavir results in a significant decrease in the pharmacokinetic parameters (~36% for C_{max} and ~28% for AUC) of indinavir. Administration of a higher dose of indinavir should be considered when coadministering with megestrol acetate" have been inserted before the sentence beginning "The effects of zidovudine . . ." In that same sentence, after "effects of" an additional drug, "indinavir", has been listed.

These are acceptable revisions according to the Biopharmaceutical Reviewer.

On page 10, in the OVERDOSAGE section, in the second sentence of the first paragraph after the word “diazability”, the comma has been changed to a semi-colon, as requested by the Clinical Reviewer.

In the **DOSAGE AND ADMINISTRATION** section, the company has added the following information and table, “The recommended adult initial dosage of Megace® ES (megestrol acetate) oral suspension is 625 mg/day (5mL/day or one teaspoon daily). **Please refer to the table below for correct dosing and administration.** Shake container well before using.”

PRODUCT DIFFERENCES		
	Megace® ES Oral Suspension	Megace® and other megestrol acetate oral suspensions
mg/mL	125 mg/mL	40 mg/mL
Recommended Daily Dose	625 mg	800 mg
Daily Volume Intake	5 mL (teaspoon) 	20 mL (dosing cup) 
Formulation	Concentrated formula	Regular formula

In the first sentence under the table, still in the **DOSAGE AND ADMINISTRATION** section, after . . . “daily doses of 400 and 800 mg/day . . .” the words “of megestrol acetate oral suspension (800 mg/20 mL equivalent to 625 mg/5 mL of Megace® ES formula)” were added.

These are acceptable revisions according to the Clinical Reviewer.

In the **HOW SUPPLIED** section, the original information for MEGACE® has been replaced with information specific to Megace® ES. The new information states, “Megace® ES (megestrol acetate) oral suspension is a concentrated formula available as a milky white, lemon-lime flavored oral suspension containing 125 mg of megestrol acetate per mL.”

This is an acceptable revision according to the Chemistry Reviewer.

The NDC number has been changed from “NDC 0015 0508 42” to “NDC 49884-949-69”.

The words, “Bottles of 240 mL (8 fl. oz.)” for Megace have been changed to “Bottles of 150 mL (5 fl. oz.) for Megace ES.”

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The manufacturing information has been changed from, "BRISTOL MYERS SQUIBB ONCOLOGY, Bristol Myers Squibb Company, Princeton, NJ 08453 USA" to "PAR PHARMACEUTICAL, INC. Spring Valley, New York 10977 www.MegaceES.com."

The labeling identification number on the new product is "OS949-69-1-01." The date is stated "Revised: 05/05." A final sentence at the bottom of the proposed PI label states, "Megace® is a registered trademark of Bristol Myers Squibb Company licensed to Par Pharmaceutical, Inc."

These are acceptable editorial revisions.

Container Label - Trade Bottle (150mL/30 daily doses bottle)

On the front panel (the first third of the label) of the 150mL/30 daily doses bottle, the NDC number has been changed from "0015 0508 42" for Megace to "49884-949-69" for Megace ES. The words, "Megace® (megestrol acetate) Oral Suspension" have been changed to "MEGACE ES megestrol acetate". The words, "Each mL contains 40mg micronized megestrol acetate in a lemon-lime flavored oral suspension. Alcohol: max. 0.06%v/v" for Megace have been replaced with the phrase "625mg/5mL oral suspension" for Megace ES immediately beneath the proprietary name. Immediately beneath that, the expression "125mg/mL" appears in less prominent type. "Rx only" has been moved to the far left of the front section and a picture of a teaspoon is located on the right. The BMS logo has been deleted from the front panel.

At the top of the middle third of the label, the words, "Each mL contains 125mg megestrol acetate in a milky white, lemon-lime flavored oral suspension. Alcohol: max. 0.06%v/v" appear. "USUAL DOSAGE," followed by "625mg/5mL per day (one teaspoon)," and "See package insert for dosage schedule" is stated in blue letters. The words, "KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN" have been added. Storage information has been added under the words, "Dispense in a tight container." The storage information states, "Store the oral suspension between 15°-25°C (59°-77°F).(See USP)".

On the last panel (the far right 1/3 portion of the panel), the words, "concentrated formula" have been added above the bar code and at the very bottom of the label. The bar code and UPC code have been modified to reflect the new manufacturer and distributor of the proposed product and "www.MegaceES.com Par Pharmaceutical, Inc. Spring Valley, NY 10977" have been added. The words, "Control No" have been added. There is no expiration date given. The Labeling ID number is LA 949-69-1-01 and the revision date is "R05/05" for FPL dated May 26, 2005.

Container Label – Professional Sample (25 mL/5 daily doses bottle)

On the front panel (the first third of the label) of the 25mL/5 daily doses bottle, the NDC number has been changed from "0015 0508 42" for Megace to "49884-949-95" for Megace ES. The words, "Megace® (megestrol acetate) Oral Suspension" have been changed to "MEGACE ES megestrol acetate". The words, "Each mL contains 40mg micronized megestrol acetate in a lemon-lime flavored oral suspension. Alcohol: max. 0.06%v/v" for Megace have been replaced

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Page 9

with the phrase "625mg/5mL oral suspension" for Megace ES immediately beneath the proprietary name. Immediately beneath that, the expression "125mg/mL" appears in less prominent type. "Rx only" has been moved to the far left of the front section and a picture of a teaspoon is located on the right. The BMS logo has been deleted from the front panel.

At the top of the middle third of the label, the words, "Each mL contains 125mg megestrol acetate in a milky white, lemon-lime flavored oral suspension. Alcohol: max. 0.06%v/v" appear. "USUAL DOSAGE," followed by "625mg/5mL per day (one teaspoon)," and "See package insert for dosage schedule" is stated in blue letters. The words, "KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN" have been added. Storage information has been added under the words, "Dispense in a tight container." The storage information states, "Store the oral suspension between 15°-25°C (59°-77°F).(See USP)".

On the last panel (the far right 1/3 portion of the panel), the words, "concentrated formula" have been added above the bar code and at the very bottom of the label. The bar code and UPC code have been modified to reflect the new manufacturer and distributor of the proposed product and "www.MegaceES.com Par Pharmaceutical, Inc. Spring Valley, NY 10977" have been added. The words, "Control No" have been added. The Labeling ID number is LA 949-95-1-01 and the revision date is "R05/05" for FPL dated May 26, 2005.

The labels submitted May 25, 2005, satisfy the requests of the Chemistry Reviewer and DDMAC.

However, DDMAC stated the spoon logo is acceptable on the containers, but would not be acceptable in reminder advertisements. (Refer to 21 CFR 202.1(e)(2)(i) for further information.) This restriction was communicated to the firm by phone on May 25, 2005.

Conclusions

The sponsor made all of the requested changes to the PI labeling in the submission dated May 26, 2005. The approved product identifier number is OS949-69-1-01, revised 05/05.

The sponsor made all of the requested changes to the container labeling in the submission dated May 26, 2005. The approved product identifier number for the professional sample container is LA 949-95-1-01, R05/05. The new UPC/Bar Code is N3 49884-949-95 2. The approved product identifier number for the trade container is LA 949-69-1-01, R 05/05. The new UPC/Bar Code is N3 49884-949-69 3.

This labeling is acceptable for final printed labeling (FPL). This should be communicated to the sponsor in the NDA action letter.

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{See appended electronic signature page}

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Supervisory Comment/Concurrence:

Enid Galliers
Chief, Project Management Staff

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

/s/

Holly Wieland

7/5/05 06:45:07 AM

CSO

with Concurrence: Enid Galliers, CPMS

07-05-05

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 21-778	Efficacy Supplement Type SE-	Supplement Number
Drug: Megace ES (megestrol acetate) Oral Suspension 125 mg/mL		Applicant: Par Pharmaceutical, Inc.
RPM: Holly Wieland	HFD-510	Phone # 301-827-6410
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-264 Megace Oral Suspension 40 mg/mL</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority 5 NA	
❖ User Fee Goal Dates	April 29, 2005, clock extended 3 months to July 29, 2005	
❖ Special programs (indicate all that apply)	<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver • User Fee exception 	<input checked="" type="checkbox"/> Paid UF ID number 4761 (1/2 fee \$287,750) <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) NA <input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) NA	

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)	NA
• OC clearance for approval	NA
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	NA
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>

filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

In a letter dated March 22, 2005, Par Pharmaceutical stated the 45-day period after notification had passed and the patent owner, Bristol Myers Squibb, had not sued Par.

Par Pharmaceutical's original Paragraph 4 Certification named the strength. On June 17, 2005, Par stated that the Paragraph 4 certification is still accurate and applicable for the 125 mg/mL strength.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary 	Exclusivity summary June 8, 2005; there is no unexpired exclusivity for this product.
<ul style="list-style-type: none"> Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Filing meeting 09/10/04; Amended 06/23/05 and 06/30/05.
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	PDUFA Clock extended on 04/07/05; new PDUFA goal date 07/29/05
<ul style="list-style-type: none"> Status of advertising (approvals only) 	() Materials requested in AP letter (X) NA () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes (X) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	NA
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	May 26, 2005
<ul style="list-style-type: none"> Original applicant-proposed labeling 	June 29, 2004
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	RPM Labeling Review 06/30/05 DMETS Review February 1, 2005 DDMAC Review May 23, 2005
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	NA
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	NA
<ul style="list-style-type: none"> Applicant proposed 	May 26, 2005
<ul style="list-style-type: none"> Reviews 	RPM Labeling Review 06/30/05
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	NA
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate meeting date) 	Pre-IND 08/28/02

<ul style="list-style-type: none"> • Pre-NDA meeting (indicate meeting date) 	Pre-NDA 04/28/04
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (indicate date; approvals only) 	NA
<ul style="list-style-type: none"> • Other 	Included
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> • Date of Meeting 	NA
<ul style="list-style-type: none"> • 48-hour alert 	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	NA
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	May 13, 2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NA
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	May 16, 2005
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (indicate date for each review)	NA
❖ Biopharmaceutical review(s) (indicate date for each review)	August 26, 2004, April 5 and 12, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> • Clinical studies 	NA
<ul style="list-style-type: none"> • Bioequivalence studies 	March 29, 2005
CMC Information	
❖ CMC review(s) (indicate date for each review)	April 5, May 17, 2005
❖ Environmental Assessment	
<ul style="list-style-type: none"> • Categorical Exclusion (indicate review date) 	April 5, 2005
<ul style="list-style-type: none"> • Review & FONSI (indicate date of review) 	April 5, 2005
<ul style="list-style-type: none"> • Review & Environmental Impact Statement (indicate date of each review) 	NA
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: March 22, 2005 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not Required
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	August 17, 2004; March 15, 2005
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data) **NO**
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA) **YES**
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.) **NO**
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11). **NO**

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

/s/

Holly Wieland
7/5/05 10:33:20 AM

**NDA REGULATORY FILING REVIEW
SECOND ADDENDUM
(See filing reviews dated 09/10/04 and 06/23/05)
(Including Memo of Filing Meeting)**

NOTE: Changes made to the original document will be made in **BOLD ITALICS**.
NDA # 21-778

Trade Name: **Megace ES**
Generic Name: Megestrol Acetate Oral Suspension (megestrol acetate)
Strengths: **125 mg/mL**
Applicant: PAR Pharmaceutical, Inc.

Date of Application: June 29, 2004
Date of Receipt: June 29, 2004
Date clock started after UN: N/A
Date of Filing Meeting: August 17, 2004
Filing Date: August 28, 2004
Action Goal Date (optional): March 29, 2005 User Fee Goal Date: **July 29, 2005**

Indication(s) requested: Treatment of anorexia, cachexia or an unexplained significant weight loss in AIDS patients

Type of Original NDA: (b)(1) _____ (b)(2) X
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*
- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

____ NDA is a (b)(1) application OR ____ NDA is a (b)(2) application

Therapeutic Classification: S X P _____
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: X YES NO

User Fee Status: Paid June 23, 2004 UFID# 4761 Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES X NO

If yes, explain:

There is no UNEXPIRED exclusivity for this product (NDA 20-264).

- Does another drug have orphan drug exclusivity for the same indication? YES X NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? X NA YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES X NO
 If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? X YES NO
- Does the submission contain an accurate comprehensive index? X YES NO
- Was form 356h included with an authorized signature? X YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? X YES NO

If no, explain:

Submission is acceptable for filing but additional information is needed. Chemistry, BioPharm, and Pharm/Tox all have requests for information that is detailed in the 74 day letter dated August 28, 2004.

- If an electronic NDA, does it follow the Guidance? N/A X YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Table of Contents (Index)

Item 6, Study # 109307 "Pharmacokinetics of Megestrol Acetate Following Oral Administration of Megestrol Acetate Suspension Formulations (10mg/kg) to Fed or Fasted Beagle Dogs"

Item 8, "Navigation for Item 8 Clinical Study Reports"

Labeling

Case Report Tabulations (CRTs)

Case Report Forms (CRFs)

- If in Common Technical Document format, does it follow the guidance? N/A YES X NO
- Is it an electronic CTD? N/A YES X NO

If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? X YES NO
 Patent #1: 5,145,684 drug product and method of use
 Patent #2: 6,592,903 drug product only
- Exclusivity requested? YES, 3 years X NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
It was not requested in the original NDA, but in an amendment dated April 28, 2005.
- Correctly worded Debarment Certification included with authorized signature? X YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."
- Financial Disclosure forms included with authorized signature? X YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
 Form 3454 submitted, reported nothing to disclose.
- Field Copy Certification (that it is a true copy of the CMC technical section)? X YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? X YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. X YES NO
- List referenced IND numbers: IND 65,178
- List referenced NDA numbers: NDA 20-264
- Pre IND Meeting? Date August 28, 2002 NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting? Date April 28, 2004 NO
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? X NA YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? X YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? X N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? X N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? X N/A YES NO
- Has DOTCDP been notified of the OTC switch application? X N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? X N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? X YES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? X YES NO
 EER submitted on August 19, 2004
- If a parenteral product, consulted to Microbiology Team (HFD-805)? X N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 17, 2004

BACKGROUND:

This is a new formulation and a new strength of an existing approved product, NDA 20-264 Megace® Oral Suspension, 40 mg/mL (approved September 10, 1993). The new formulation proposes to use nano-crystal dispersion, [REDACTED] for the treatment of anorexia, cachexia, or an unexplained significant weight loss in AIDS patients.

ATTENDEES:

Robert Perlstein, MD, Medical Officer
Hae Young Ahn, PhD, OCPB Team Leader
Xiao-Xiong Wei, PhD, Biopharmaceutical Reviewer
Steve Moore, PhD, Chemistry Team Leader
John Hill, PhD, Chemistry Reviewer
Jeri El Hage, PhD, Pharmacology/Toxicology Team Leader
Hee Rhee, PhD, Pharmacology/Toxicology Reviewer
Kati Johnson, CPMS
Holly Wieland, RPM

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Robert Perlstein, MD
Pharmacology:	Hee Rhee, PhD
Chemistry:	John Hill, PhD
Environmental Assessment (if needed):	Not needed
Biopharmaceutical:	Xiao-Xiong Wei, PhD
DSI:	C.T. Viswanathan, PhD
Regulatory Project Management Supervisor	Kati Johnson, CPMS
Regulatory Project Management	Holly Wieland, RPM
ODS/DMETS	To Be Determined

Per reviewers, are all parts in English or English translation?
If no, explain:

X YES NO

CLINICAL FILE X REFUSE TO FILE _____

- Clinical site inspection needed: X YES NO
- Advisory Committee Meeting needed? YES, date if known _____ X NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
X N/A YES NO

CLINICAL MICROBIOLOGY X NA FILE _____ REFUSE TO FILE _____

STATISTICS X NA FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE X REFUSE TO FILE _____

- Biopharm. inspection needed: X YES NO

PHARMACOLOGY NA _____ FILE X REFUSE TO FILE _____

- GLP inspection needed: YES X NO

CHEMISTRY FILE X REFUSE TO FILE _____

- Establishment(s) ready for inspection? X YES NO
- Microbiology X NA YES NO

ELECTRONIC SUBMISSION:

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 Item 8, "Navigation for Item 8 Clinical Study Reports"
 Labeling
 Case Report Tabulations (CRTs)
 Case Report Forms (CRFs)

REGULATORY CONCLUSIONS/DEFICIENCIES:

- _____ The application is unsuitable for filing. Explain why:
- X _____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- _____ No filing issues have been identified.
- _____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

NOTE: A 74 day letter was issued September 7, 2004. No filing issues were identified.

Holly Wieland

Regulatory Project Manager,
DMEDP, HFD-510

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
NO
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
YES
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
NO
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).
NO

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? X YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

NDA 20-264 Megace (megestrol acetate) Oral Suspension 40mg/mL

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent to the product proposed in the 505(b)(2) application that is already approved? YES X NO

The strengths are different.

NDA 20-264 Megace (megestrol acetate) Oral Suspension 40 mg/mL

NDA 21-778 MEGACE® ES (megestrol acetate) NCD Oral Suspension 125 mg/mL

(*Pharmaceutical equivalents* are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent cited as the listed drug? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? X YES NO
NDA 20-264 Megace (megestrol acetate) Oral Suspension

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times

and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NDA 20-264 Megace (megestrol acetate) Oral Suspension

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application proposes two possible changes, a possible change in strength and a possible change in formulation. The proposed new strength is 125mg/mL, w/5mL/dose, an increase from the RLD strength of 40mg/mL, w/20mL/dose. The proposed new formulation is an oral suspension using nanocrystal dispersion technology (NCD).

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES X NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES X NO
10. Are there certifications for each of the patents listed for the listed drug(s)? X YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent #5,338,732

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

_____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

X YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

X YES NO

“There is no unexpired exclusivity for the listed drug. The only exclusivity that was granted was Orphan Drug exclusivity which expired on September 10, 2000.” per email dated August 26, 2004, from M. Bonomi, PAR pharmaceutical, Inc.
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A X YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?

X N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

Firm requested exclusivity ten months after submission of the NDA.

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

X YES NO

Data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new. This is a new formulation, dose, and strength. The applicant claims that a new comparative bioavailability study meets this requirement.

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES X NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # 65178

NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES

NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

X YES

NO

Notified on August 17, 2004

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/s/

Holly Wieland
6/30/05 03:01:10 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

06/29/05

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-778

Par Pharmaceutical Inc.
Attention: Michelle Bonomi-Huvala
Senior Director, Regulatory Affairs Research & Development
300 Tice Boulevard
Woodcliff Lake, New Jersey 07677

Dear Ms. Bonomi-Huvala:

Please refer to your submission dated April 26, 2005, requesting a waiver for pediatric studies for Megace ES (megestrol acetate) Oral Suspension.

We have reviewed the submission and agree that a waiver is justified for Megace ES (megestrol acetate) Oral Suspension for treatment of anorexia, cachexia or an unexplained significant weight loss in AIDS patients for the entire pediatric population because of safety concerns that prolonged exposure to Megace ES could result in suppression of growth, Cushingoid phenomena, and inhibition of the hypothalamic-pituitary-adrenal axis.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have questions, contact Holly Wieland, Regulatory Project Manager, at (301) 827-6410.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
6/29/05 08:49:11 AM
Signing for Dr. Orloff

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2005

TO: Division of Metabolic and Endocrine Drug Products, HFD-510

THROUGH : David G. Orloff, M.D., Division Director

FROM: Robert Perlstein, M.D., Medical Officer

SUBJECT: **Financial Disclosure and Pediatric Waiver**
NDA 21-778 Megace ES (megestrol acetate) Oral Suspension
125mg/mL

Financial disclosure information is acceptable. Sponsor signed FDA Form 3454 and attached the names of all Clinical Investigators.

Pediatric studies are "fully waived" because of safety concerns. Prolonged exposure to Megace ES could result in suppression of growth, as well as inhibition of the hypothalamic-pituitary-adrenal axis/secondary adrenal atrophy and Cushingoid phenomena.

Robert Perlstein, M.D.
Medical Officer
DMEDP/HFD-510

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/s/

Holly Wieland
6/16/05 10:36:31 AM
CSO
signing for Dr. Robert Perlstein, Medical Officer, DMEDP, HFD-510

Holly Wieland
6/16/05 10:40:03 AM
CSO

MEMORANDUM OF TELECON

DATE: May 25, 2005

APPLICATION NUMBER: NDA 21-778

BETWEEN:

Name: Michele Bonomi
Phone: 845-639-5120
Representing: PAR Pharmaceuticals, Inc.

AND

Name: Holly Wieland, RPM
FDA/CDER/Division of Metabolic and Endocrine Drug Products,
HFD-510

SUBJECT: Labeling Revisions

A teleconference call was held on May 25, 2005, to discuss proposed labeling revisions requested by FDA reviewers, including the Clinical Reviewer, the Chemistry Reviewer, and the Biopharmaceutical Reviewer. The report from the DDMAC consult was also discussed.

The labeling revisions requested by the **Clinical Reviewer** were in the package insert "Information for Patient" section, and two minor editorial changes in the package insert. The Information for Patients section is numbered one through six and should state:

- 1) This medication is to be used as directed by the physician.
- 2) Megace® ES (625 mg/5 mL) does not contain the same amount of megestrol acetate as Megace® oral suspension or any of the other megestrol acetate suspensions. Megace® ES contains 625 mg of megestrol acetate per 5 mL, whereas Megace® oral suspension and other megestrol acetate suspensions contain 800 mg per 20 mL.
- 3) **The prescriber should inform the patient about the product differences to avoid overdosing or underdosing of megestrol acetate. The recommended adult dosage of Megace® ES is one teaspoon (5 mL) once a day. Please see table in DOSAGE and ADMINISTRATION section.**
- 4) Report any adverse reaction experiences while taking this medication.
- 5) Use contraception while taking this medication if you are a woman capable of becoming pregnant.
- 6) Notify your physician if you become pregnant while taking this medication.

NDA 21-778

Page 2

The editorial revisions requested by the **Clinical Reviewer** are as follows:

- On page 6, in the WARNINGS section, in the last sentence of paragraph 3, change “in conditions of” to “during”.
- On page 10, in the OVERDOSAGE section, in the second sentence of the first paragraph after the word “diazability”, change the comma to a semi-colon.

The labeling revisions requested by the **Chemistry Reviewer** were for both containers, the professional sample bottle and the patient prescription bottle.

- Delete the number of doses per bottle. **List total contents only.**
- Place parenthesis around the unit dose (125mg/mL) and move it to underneath the 625 mg/5mL oral suspension.
- Move the spoon down so it does not appear to be underlining any text.

The **Biopharmaceutical Reviewer** did not recommend any revisions.

The **DDMAC consult** requested the revisions listed.

- Decrease the font size of the modifier to be consistent with the name, i.e., “Megace” and “ES” should be the same font size.
- The “spoon” logo is acceptable on the containers, but would not be acceptable in reminder advertisements. (Refer to 21 CFR 202.1(e)(2)(i) for further information.)
- Delete the daily dose when describing total content of the bottles. The numeric equivalent “150 mL/30 daily doses or 25 mL/5 daily doses” may be confusing because that is the recommended initial dosage for adults; however, the clinician may alter the dose, increasing or decreasing it.

All of the labeling revisions were conveyed to the sponsor and the sponsor agreed to make the requested changes.

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

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/s/

Holly Wieland
6/8/05 09:26:25 AM
CSO

**05-MAY-2005 Telecon with PAR : CMC Information Request in Support of
NDA 21-778**

A short telephone conference was held with PAR on 05-MAY-2005 from 10:30 a.m. to 11:00 a.m. to convey three CMC information requests (IR) and comments from the medical officer's (MO) labeling review.

The CMC IR comments were:

1. Please update lot release data and stability data to reflect the new dissolution test if data are available.
2. Please verify that correct values have been reported for particle size in the stability data section (volume 5, pp 30-125).
3. Please update the methods validation package to include the new dissolution method.

Labeling comments were conveyed as per MO review. The sponsor agreed to make requested changes in the Patient Information section, and two minor editorial changes, one in the WARNINGS section, and one in the OVERDOSAGE section. The sponsor was advised not to send in revised labeling until other reviewers have completed their reviews and their comments have been conveyed to the sponsor.

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/s/

Holly Wieland
5/19/05 01:54:41 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

04/15/05

NDA 21-778

PAR Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
Senior Director, Regulatory Affairs R&D
One Ram Ridge Road
Spring Valley, NY 10977

Dear Ms. Bonomi-Huvala:

Please refer to your June 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Megesterol Acetate Oral Suspension,

On April 7, 2005, we received your April 7, 2005, major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 29, 2005.

If you have any questions, call Holly Wieland, Regulatory Project Manager, at 301-827-6410.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
4/15/05 10:58:56 AM

MEMORANDUM OF T-CON MEETING MINUTES

MEETING DATE: April 6, 2005
TIME: 11:00a.m.-12:30p.m.
LOCATION: Dr. David Orloff's office
APPLICATION: NDA 21-778
DRUG NAME: Megace ES
TYPE OF MEETING: Internal meeting followed by Telephone Conference

MEETING CHAIR: David Orloff, MD

MEETING RECORDER: Holly Wieland, Regulatory Project Manager

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolic and Endocrine Drug Products, HFD-510
David Orloff, MD, Division Director
Robert Perlstein, MD, Clinical Reviewer
Kati Johnson, Chief, Project Management Staff
Hae Young Ahn, PhD, Biopharmaceutical Review Team Leader
Jim Wei, PhD, Biopharmaceutical Reviewer
John Hill, PhD, Chemistry Reviewer
Holly Wieland, RN, MPH, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Par Pharmaceuticals, Inc.

Michelle Bonomi-Huvala, Senior Director, Regulatory Affairs
Robert Femia, PhD, Executive Vice President, Scientific Affairs
Shankar Hariharan, PhD, Chief Scientific Officer
Janis Picurro, Director, Regulatory Affairs
Lynn Kramer, MD, Senior Vice President, Clinical Development and Medical Affairs
John MacPhee, Senior Vice President, Brand Sales & Marketing

BACKGROUND:

In a PIND (65,178) meeting dated August 28, 2002, Par Pharmaceutical notified FDA of their intent to develop a NanoCrystal formulation of Megestrol acetate oral suspension. The firm advised FDA that comparative pK studies were the only efficacy studies planned for a 505 (b)(2) NDA.

In a letter dated June 13, 2003, the firm requested, but was denied a meeting with FDA. The firm's questions were answered in writing in a letter dated September 10, 2003. In that September 10, 2003, letter, the firm was advised by FDA that they could use the unadjusted Cmax of the recommended dosage of Megace® (800mg) under fed conditions as the reference standard to determine/calculate the bioequivalent (BE) NanoCrystal-based dosage to be developed. The firm was not required to match AUC because they stated that they could not meet that parameter. They also provided an article claiming that efficacy was correlated with Cmax.

In their NDA, submitted June 29, 2004, the firm submitted BE data for 3 dosage strengths, 115 mg/mL, 125 mg/mL, and 135 mg/mL. After reviewing the data, the biopharmaceutical reviewer noted that while the dosage strength 115 mg/mL met Cmax BE criteria, the other two strengths met **both** the Cmax and AUC criteria for bioequivalence. The chemistry review, dated April 5, 2005, recommended approval of the product. A telephone conference was initiated to discuss the product that could be approved. The goal date for this application is April 29, 2005.

DISCUSSION POINTS:

1. Dr. Orloff explained to the firm that the FDA agreed to work with the firm, based on the firm's contention that it was not possible to establish BE according to regulatory standards, using Cmax and AUC parameters. However, the firm has demonstrated that there is a dose of Megace ES that is bioequivalent to the approved Megace based on both parameters.
2. The submitted article does not exclude using AUC as an important parameter, but recognizes that AUC is more highly variable, and perhaps harder to capture. In addition, the study may have not been sufficiently powered to show any correlation between AUC and efficacy.
3. The conclusion reached by the article cited by the firm to justify using Cmax alone for establishing BE is no longer valid because the firm showed it was possible to meet both Cmax and AUC with either 125 mg/mL or 135 mg/mL strengths.

DECISIONS (AGREEMENTS) REACHED:

1. The firm will send in a chemistry data package in support of the 125 mg/mL strength product. This will include six months of room temperature stability data, an executed batch record, and a detailed description of the differences in the manufacturing process of the 125 mg/mL products.
2. The firm will send in revised labeling for the 125 mg/mL strength. This will be submitted after the chemistry amendment.
3. Based on the content of the amendments, the FDA will make a determination whether or not the review clock will be extended three months as allowed under the Food and Drug Administration Modernization Act.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

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/s/

Holly Wieland
4/15/05 12:57:35 PM

02/14/05
NDA 21-778

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 2, 2005

TO: Division of Metabolic and Endocrine Drug Products, HFD-510

THROUGH : Robert Perlstein, MD
Jim Wei, PhD
Kati Johnson, CPMS

FROM: Holly Wieland, RPM

SUBJECT: **Internal Meeting: Trade Name Discussion**
IND 21-778, Megace ES (megestrol acetate) oral suspension

An internal meeting was held today to discuss the issues concerning the proposed trade name for megestrol acetate (NDA 21-778) and to make a final recommendation to the company. The decision was made to accept the proposed trade name, "Megace ES".

Megace (NDA 20-264) and "Megace ES" (NDA 21-778) are **not** precisely bioequivalent by the legal definition of bioequivalence. However, they are very comparable because the two required parameters of legal bioequivalence, AUC and Cmax, were very close. The Cmax passed the 90% confidence interval for bioequivalence and the AUC was only slightly off from the 80-125% criteria. In a previous discussion with the sponsor, FDA agreed to use Cmax as the main criteria to judge comparability since Cmax has been shown to be related to clinical efficacy for megestrol acetate.

Therefore, having determined by clinical judgment that these two products are "essentially" bioequivalent, and in that this comparability will be the basis for approval, the Division agrees with the sponsor that "Megace" is an acceptable "root" for the new product's trade name.

The sponsor originally submitted names for review, "Megace ES", [redacted]. The proposed names were sent for DMETS review and were found to be unacceptable. The DMETS review team concluded that using the suffix, "ES", was "promotional and misleading", stating that "most products that employ this modifier provide an extra strength dose of the same active ingredient".

In the discussion section of its consultation, the DMETS review team referred to the example of Extra Strength Tylenol. A single tablet or capsule of Extra Strength Tylenol provides a bigger dose (more mg) of acetaminophen than Tylenol. With the "Megace ES formulation", the

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/s/

Holly Wieland

2/14/05 08:30:54 AM

CSO

Signed by Holly Wieland, RPM with concurrence from Robert
Perlstein, MD



DEPARTMENT OF HEALTH & HUMAN SERVICES

01-07-05
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-778

INFORMATION REQUEST LETTER

Par Pharmaceutical, Inc
Attention: Michelle Bonomi-Huvala
Senior Director, Regulatory Affairs R&D
300 Tice Boulevard
Woodcliff Lake, NJ 07677

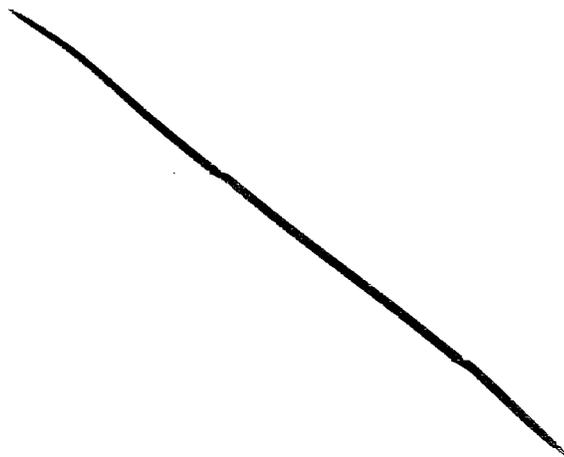
Dear Dr. Bonomi-Huvala:

Please refer to your June 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Megace ES (megestrol acetate) oral suspension ~~_____~~ ~~_____~~

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product:

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.



If you have any questions, call Holly Wieland, Regulatory Project Manager, at 301-827-6410.

Sincerely,

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, for the
Division of Metabolic and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Stephen Moore
1/7/05 03:20:09 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
KLN Rm. 6-34**

FROM: Holly Wieland, RPM
DMEDP, HFD-510
CDER
301-827-6410

DATE 11/01/2004	IND NO.	NDA NO. NDA 21-778	TYPE OF DOCUMENT Trade Name Consult Request	DATE OF DOCUMENT 08/27/04
--------------------	---------	-----------------------	--	------------------------------

NAME OF DRUG Megace ES Oral Suspension (megestrol acetate oral suspension)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE 01/07/2005
---	------------------------------------	-----------------------------	---------------------------------------

NAME OF FIRM: Par Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

The company sent a list of names in order of preference: MEGACE® ES, . This is a 505 (b)(2) application using other NDAs as reference products (NDAs 16-979 and 20-264 Megace oral suspension, sponsor BMS). The sponsor advised that the brand names provided cleared the trade mark search conducted. The company also licensed the trade mark MEGACE®, U.S. Registration No. 834996 from licensor's Mead Johnson and Company and Bristol-Meyers Squibb Company for use in connection with the sale of this product. The sponsor advised ES = extra strength.

PDUFA DATE:04/29/2005
 ATTACHMENTS: Draft Package Insert , Container Label. There is no carton label.
 CC: Wieland, Holly; Galliers, Enid; Johnson, Kati
 Archival IND 65,178
 Archival NDA 19-979 and NDA 20-264
 DMEDP, HFD-510/Division File
 -510/RPM Holly Wieland
 HFD-510/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY <input checked="" type="checkbox"/> MAIL (Interdepartmental) <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Holly Wieland

11/5/04 11:30:34 AM

Chemistry Issues:

- 1) Provide a summary narrative discussion of the drug product manufacturing process development.
- 2) Provide a summary narrative discussion of the pharmaceutical formulation development of the drug product.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Holly Wieland, Regulatory Project Manager, at (301) 827-6410.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

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/s/

Holly Wieland
9/7/04 12:37:59 PM
Holly Wieland signing for Kati Johnson



DEPARTMENT OF HEALTH & HUMAN SERVICES

ack letter
07/15/04

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-778

Par Pharmaceutical Inc.
Attention: Michelle Bonomi-Huvala
Senior Director, Regulatory Affairs Research & Development
300 Tice Boulevard
Woodcliff Lake, New Jersey 07677

Dear Ms. Bonomi-Huvala:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Megestrol Acetate Oral Suspension _____
Review Priority Classification:	Standard
Date of Application:	June 29, 2004
Date of Receipt:	June 29, 2004
Our Reference Number:	NDA 21-778

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 28, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 29, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 21-778

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Diseases, HFD-510
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301)827-6410.

Sincerely,

{See appended electronic signature page}

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

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/s/

Holly Wieland

7/15/04 04:43:40 PM

NDA 21-778

TIMING
P/T review
8/17/04

NDA Filing Meeting Checklist

HRhee

NDA #: 21-788

DRUG: Megestrol Acetate

Sponsor: Par Pharmaceuticals, Inc.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		No pharmacology/toxicology data, using Megace as referred product, were provided.
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? (Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA - e.g., safety pharm, genotox, reprotox, chronic tox, carcinogenicity)		X	Have electronic files of the carcinogenicity studies been submitted for statistical review? No carci data. The sponsor will submit 3-month toxicology study as requested. Division agreed to accept study during the review cycle.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?		X	3-Month toxicology study to be submitted.
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?		X	<p>The sponsor depended heavy on other NDAs (#16-979 and 20-264) for Megestrol acetate oral suspension. In this application they proposed to use Nanocrystal dispersion.</p> <p>3-Month rat toxicology study should bridge the nanocrystal formulation to existing toxicology data for approved NDAs.</p>
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m ² or comparative serum/plasma AUC levels?	X		Sponsor using labeling from approved products as is required for 505(b)(2) applications.

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

 Reviewing Pharmacologist

 Supervisory Pharmacologist

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/s/

Herman Rhee
8/17/04 01:36:40 PM
PHARMACOLOGIST

Jeri El Hage
8/17/04 02:02:39 PM
PHARMACOLOGIST

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

Completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS
Par Pharmaceutical
One Ram Ridge Road
Spring Valley, New York 10977

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-778

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
 YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(201) 802-4128

3. PRODUCT NAME
Megestrol Acetate Oral Suspension

6. USER FEE I.D. NUMBER
4761

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Michelle Bonomi-Huvala

TITLE

Michelle Bonomi-Huvala
Senior Director, Regulatory Affairs R&D

DATE

6/18/2004

amt pd: \$286,750
date pd: June 23, 2004

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 21-778 SUPP TYPE & # Ø Division 510 UFID # 4761

Applicant Name: Par Pharmaceutical Inc Drug Name: Megestrol

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

- 1. Was a Cover Sheet submitted?
 Yes No
- 2. Firm in Arrears?
 Yes No
- 3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees"
<http://www.fda.gov/cder/guidance>
 Yes No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)

NDA #/Doc Type	Div.	Fee? (Y/N)
<u>NDA 21-778</u>	<u>510</u>	<u>Y</u>

- 5. Type 6?
 Yes No
Type 6 to which other application?
NDA # _____ Supp Type & # _____
- 6. Clinical Data Required for Approval? (Check one)
 Yes*
 Yes, by reference to another application
NDA # _____ Supp Type & # _____
 No

* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

- 7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)"
<http://www.fda.gov/cder/guidance>
 Yes No To be determined
- 8. Subpart H (Accelerated Approval/Restricted Distribution)?
 Yes No To be determined
- 9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)
List of exclusions:
2 - No fee - administrative split
4 - No fee - 505b2
7 - Supplement fee - administrative split
9 - No fee Subpart H supplement- confirmatory study
11 - No fee Orphan Exception
13 - No fee State/Federal exemption from fees
- 10. Waiver Granted?
 Yes (letter enclosed) No
Select Waiver Type below: Letter Date: _____
 Small Business Barrier-to-Innovation
 Public Health Other (explain)
- 11. If required, was the appropriate fee paid?
 Yes No
- 12. Application Review Priority
 Priority Standard To be determined
- 13. Fast Track/Rolling Review Presubmission?
 Yes No

Comments
HRWila 07/09/04
PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

CC: original archival file Processor Name & Date QC Name & Date
HFD-007

5/24/04

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 28, 2004
TIME: 3:00 p.m. - 4:00 p.m.
LOCATION: Parklawn Conference Room 13B39 (Teleconference)
APPLICATION: IND 65,178
DRUG NAME: Megestrol Acetate Oral Suspension. ~~_____~~
TYPE OF MEETING: PreNDA Meeting
MEETING CHAIR: David G. Orloff, M.D.
MEETING RECORDER: Monika Johnson, Pharm.D.

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolic and Endocrine Drug Products, HFD-510
David G. Orloff, MD/Director
Monika Johnson, PharmD/Regulatory Project Manager

Division of New Drug Chemistry II, HFD-820
William Adams, PhD/Chemistry Reviewer
Blair Fraiser, PhD/Deputy Director

Division of Biopharmaceutic Evaluations II
Xiaoxiong (Jim) Wei, MD, PhD/Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Par Pharmaceuticals, Inc.
Robert Femia, PhD/Executive VP, Science & Regulatory Affairs
N. Ragunathan, PhD/Senior Director, Analytical R&D
Michelle Bonomi-Huvala/Senior Director, Regulatory Affairs R&D
Janis A. Picurro/Director Regulatory Affairs, R&D

BACKGROUND:

A request for a pre-NDA meeting was submitted on March 31, 2004, and received on April 1, 2004, to discuss plans for submitting a 505(b)(2) application and provide background information. A revised listing of questions was submitted on April 7, 2004, and received on April 8, 2004.

DISCUSSION POINTS:

Following introductions, the Agency began to respond to the Sponsor's questions of April 7, 2004.

- I. The studies conducted by Par in support of our 505(b)(2) for megestrol acetate are conducted in healthy normals. It is not the intention of these studies to assess efficacy or safety of the product in the target population. We plan to present the safety information obtained from the bioavailability studies by summarizing the safety data for the individual studies with a non-integrated safety summary without biostatistics. SAS datasets for the bioavailability studies will be made available to the Agency. **Is this acceptable to the Agency?**

FDA comment: Yes, however, when the final formulations for the commercial product are available, you may need to conduct a bioequivalence bridging study.

- II. Will summaries of recent clinical literature on megestrol acetate be required (past three years)?

FDA comment: No.

- III. Par intends to file a paper 505(b)(2) application for megestrol acetate. However, to reduce paper volume, we would like to provide the following items electronically: all clinical study reports, all reference published literature, CRF tabulations, and all CRFs for deaths and discontinuations (if applicable). **Is this acceptable to the Agency?**

- a) If acceptable, please clarify if this information should be provided in electronic NDA format; or, can it be indexed to match the sections?
b) Please confirm if electronic submission of the label is required (as per new guidance).

FDA comment: Yes, please provide the information in electronic NDA format according to the industry guidance document for providing regulatory submission in electronic format. Please submit proposed labeling electronically, (word format would be most beneficial) in accordance with the industry guidance document for electronic format-content of labeling.

- IV. At the time of submission Par will provide six _____ accelerated and _____ months long-term primary stability data in the NDA for the _____ strength stability batches. Par also intends to provide _____ accelerated and _____ months long-term stability data on the selected NDA strength _____ 125 mg/mL _____ strength).

FDA comment: This is acceptable. However.

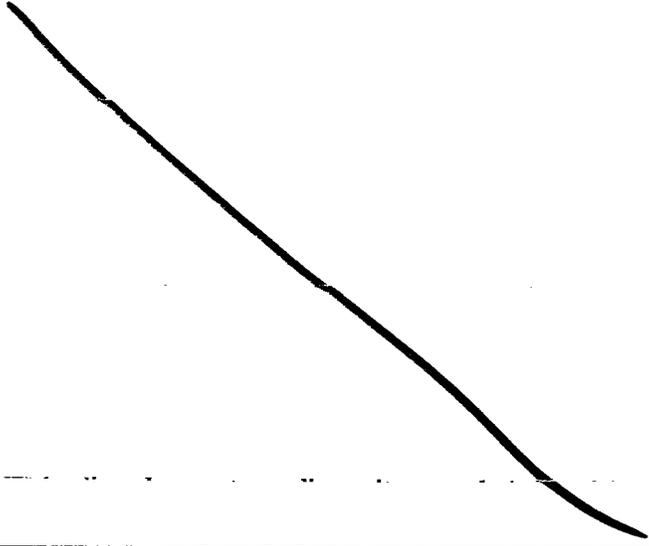
During the first _____ months of the NDA review period, _____ primary stability data will be submitted for batches of the selected NDA strength.

FDA comments: This is acceptable.

Please note that Par's intention to use the _____ stability data as supportive of the strength ultimately chosen was discussed in our October 31, 2003 correspondence to Valerie Jimenez.

FDA comment: This is acceptable.

Par is confirming that this submission strategy is acceptable and offers the following justification:



FDA comment: In regard to the megestrol acetate nanoparticles, please provide information in the NDA submission on the particle size distribution for the drug substance released from the drug product into the gastrointestinal tract.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

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/s/

Monika Johnson
5/24/04 02:43:43 PM

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Name	Title / Affiliation
Michelle Bonomi-Huvala	Senior Director, Regulatory Affairs Par Pharmaceutical, Inc.
Paul V. Campanelli	Vice President, Business Development Par Pharmaceutical, Inc.
Robert Femia, Ph.D.	Executive Vice President, Scientific and Regulatory Par Pharmaceutical, Inc.
Geoff Ripps	Vice President, Marketing, Brand Products Par Pharmaceutical, Inc.

BACKGROUND:

Megestrol Acetate is currently approved as a suspension (40 mg/mL), under the brand name of MEGACE as well as generic formulations, for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

Par Pharmaceutical, Inc. (Par) requested a pre-IND meeting to discuss their plans to develop a novel oral suspension formulation of megestrol acetate, [REDACTED]. Par plans to seek approval of the [REDACTED] formulation of megestrol acetate oral suspension [REDACTED] via a 505(b)(2) application, based on comparative pharmacokinetic data to the approved product. According to the firm, the delivery system increases the bioavailability of the megestrol, thus allowing for a lower dose.

The meeting was requested on May 31, 2002, and contained the background package for the meeting.

MEETING OBJECTIVES:

To reach agreement on the requirements for submission of an IND and ultimately approval of a 505(b)(2) NDA application for the treatment of anorexia, cachexia or an unexplained significant weight loss in AIDS patients.

AGENDA:

The firm's **bolded** questions are followed by the Agency's response and any subsequent discussion.

1. Are the release tests proposed for the new formulation adequate?

For a Phase 1 study, a brief description of the proposed limits and test methods are acceptable. Usually, established specifications need not be submitted at the initial stage. The firm was asked to provide an impurity profile, particle size distribution and polymorph information, and information on how the drug substance is affected by the proposed process. It was noted that the proposed process was used in the preparation of a drug product that has already been approved.

2. A complete battery of nonclinical studies has already been conducted for the innovator product and no novel excipients are introduced in the new drug product. Therefore, Par does not intend to conduct any additional studies. Is this acceptable?

The firm was informed that genotoxicity testing was never conducted using the innovator product. Since the firm has stated their intent to seek approval for use in the AIDS population, and if cancer or AIDS patients are used in the bioequivalence studies, additional preclinical testing is not required. However, should the firm plan, in the future, to broaden the population beyond cancer or AIDS patients, then additional studies will be required.

3. The comparative pharmacokinetic studies are the only studies planned. Are there any other Biopharmaceutics requirements? Are there any recommendations with respect to study design?

The firm stated their intent to conduct 2 pharmacokinetic (pK) studies; one in the fasted state and one in the fed state. Since the half-life of megestrol is long (mean=24 hours) and variable, the firm was encouraged to collect samples for 72 hours to fully characterize the pK profile. Due to the high inter-subject variability, it was suggested that the firm conduct a "pilot" pK study in a few patients to attempt to quantify this variability such that an appropriate pivotal pK study may be conducted. The firm confirmed that information on metabolites will also be collected in this study.

Since AIDS patients generally use more than one drug for relief of symptomatic conditions, the firm was encouraged to consider conducting appropriate drug interactions studies pertinent to the population.

Since the standard treatment for AIDS patients involves protease inhibitors, a drug-drug interaction study with this class of compounds will be required for approval. Megestrol is a 3A4 inhibitor, and information on whether it acts as an inhibitor, substrate, or both, in the face of a potent protease inhibitor, would be essential. The firm agreed to conduct such a study.

4. **Will Par's plan to submit an IND and an NDA under section 505(b)(2) of the FD&C Act for the [REDACTED] formulation for the currently approved indication supported solely by pharmacokinetic data satisfy NDA approval requirements?**

The Agency said that is appeared to be a reasonable approach.

5. **Par is also considering studying megestrol acetate as a treatment for weight loss in other patient populations. One population that has been proposed by experts in the field is geriatric patients with malnutrition (body mass index <25). Would a single trial suffice to expand the indication as follows: the treatment of anorexia, cachexia or an unexplained significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS) or elderly patients who are chronically malnourished? Par would like to discuss inclusion and exclusion criteria and suitable end points.**

Improvements in body weight and body composition, while important secondary endpoints, are not sufficient to obtain an indication for anorexia, cachexia or an unexplained significant weight loss in the geriatric population. The primary endpoint must be some validated measure of functional performance where the clinically important difference has been established. If the firm is wedded to expanding the use of megestrol to the elderly, then they were encouraged consider using the Seeman composite score (continuous), Guralnick composite score (categorical/quartiles) or some derivation of these scores as the primary endpoint.

6. **As described herein, Par has already met with the Division of Oncology Drug Products to discuss requirements for an indication that includes advanced oncology patients. If multiple patient populations are studied, would it be possible to study them all under a single IND submitted to the Division of Metabolic and Endocrine Drug Products, with external consultation as appropriate?**

A separate IND would be required for submission to each review division. However, the firm may reference any information previously submitted to the Agency, to avoid submission of duplicate information.

The firm then notified the Agency of their intent to conduct both the pK study (to establish the equivalent dose to the innovator product) and the pivotal bioequivalence study in Canada. The firm was strongly encouraged to request a meeting, at least 12 months prior to the planned NDA submission, to discuss the chemistry, manufacturing, and controls section of the application.

P-IND 65,178
Page 5

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

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/s/

Julie Rhee
9/27/02 08:00:19 AM
Signed for Kati Johnson

09/27/02

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 28, 2002
TIME: 12 noon – 1:00 pm
LOCATION: Parklawn Conference Center, Chesapeake Room
APPLICATION: PIND 65,178, Megestrol Acetate Oral Solution
TYPE OF MEETING: Pre-IND
MEETING CHAIR: David Orloff, MD
Division of Metabolic & Endocrine Drug Products (DMEDP)
MEETING RECORDER: Kati Johnson

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
David Orloff, MD	Director	DMEDP, HFD-510
Robert Perlstein, MD	Medical Officer	DMEDP, HFD-510
Jeri El-Hage, PhD	Team Leader, Pharmacology	DMEDP, HFD-510
Jim Wei, PhD	Biopharmaceutics Reviewer	Office of Pharmaceutical Sciences, HFD-870
Mike Adams	Chemistry Reviewer	Division of New Drug Chemistry HFD-820
Don Hare	Project Manager	Office of Generic Drugs, HFD-600
Kati Johnson	Supervisory Project Manager	DMEDP, HFD-510