DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-264/S-009

Bristol Myers Squibb Co.
Attention: Steven Knapp
Executive Director of Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Knapp:

Please refer to your supplemental new drug application dated April 6, 2000, received April 10, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Megace (megestrol acetate) Oral Suspension.

We acknowledge receipt of your submissions dated December 13, 2000.

This "Changes Being Effected" supplemental new drug application provides for the following revisions to the package insert:

1. Deletion of the black boxed warning contraindicating Megace Oral Solution use in pregnancy.
2. Revision of the CONTRAINDICATIONS section to delete the statement, "As a diagnostic test for pregnancy."
3. Revision of the third paragraph of the WARNINGS section with regard to glucocorticoid activity.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling submitted April 6, 2000, with the third paragraph of the WARNINGS section revised as follows:

> The glucocorticoid activity of MEGACE Oral Suspension has not been fully evaluated. Clinical cases of new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and overt Cushing's syndrome have been reported in association with the chronic use of MEGACE. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic MEGACE therapy in the stressed and non-stressed state. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic MEGACE therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic MEGACE-therapy who

presents with symptoms and/or signs suggestive of hypoadrenalism (e.g., hypotension, nausea, vomiting, dizziness, or weakness) in either the stressed or non-stressed state. Laboratory evaluation for adrenal insufficiency and consideration of replacement or stress doses of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic MEGACE therapy, consideration should be given to the use of empiric therapy with stress doses of a rapidly acting glucocorticoid in conditions of stress or serious intercurrent illness. (e.g., surgery, infection).

These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-264/S-009." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

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

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

/s/

David Orloff

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