

NDA 21-208  
HFD-120/Div. File  
HFD-120/R.Katz/T.Laughren/A.Mosholder/P.David  
ADVICE TELECON

181  
6-30-00  
7

APPEARS THIS WAY  
ON ORIGINAL

# Electronic Mail Message

DAVID

**Date:** 6/6/00 10:58:35 AM  
**From:** Jerry Phillips ( PHILLIPSJ )  
**To:** Paul David (DNPDP/ODEI) ( DAVID )  
**Cc:** Peter Honig ( HONIGP )  
**Cc:** Sammie Beam ( BEAMS )  
**Subject:** Remeron Soltab (OPDRA Consult #00-0149)

Paul:

OPDRA has reviewed the proposed modifier "Soltab" for the Orally Disintegrating Tablet of Remeron (Mirtazapine) and has no objections to its use. This "expedited" review is in response to your 5/16/00 consult to OPDRA and you may consider this our official response. If you have further questions, please feel free to call me or Sammie Beam. Thanks!

Jerry Phillips  
Associate Director, OPDRA

*Trademark acceptability  
conveyed to Carol Schickman.  
at origin on 6-8-00  
/S/*

*cc: ADA 21-208  
FD-120 / R. Kitz / T. Kay / Len  
FD-120 / A. Hoshikawa / P. David  
HD-120 / Div. File.*

# Electronic Mail Message

**Date:** 10/12/00 8:35:11 AM  
**From:** Jerry Phillips ( PHILLIPSJ )  
**To:** Paul David (DNPDP/ODEI) ( DAVID )  
**Cc:** Sammie Beam ( BEAMS )  
**Subject:** Remeron SolTab - Final Approval

Paul:

This is in response to your 9/27/00 E-mail requesting a final clearance for the proprietary name Remeron SolTab (Mirtazapine Orally Disintegrating Tablets) for NDA 21-208. OPDRA has no objections to the use of SolTab as the modifier for Remeron to represent this orally disintegrating tablet dosage form. I have reviewed the labeling recently submitted and have a few suggestions:

1. I have some concerns that Remeron and Remeron SolTab will be confused if the labeling is not distinctively different, since they both will have identical strengths (15 mg, 30mg and 45 mg). In this regard the color and format of the labeling between Remeron and Remeron SolTab should be distinctly different. In addition, I would recommend that "SolTab" be more distinct (possibly a different color than Remeron) when presented on the label.

2. The Unit Dose label should be revised to be singular in nature, since each blister contains one tablet. Revise to read:

(mirtazapine) Orally Disintegrating Tablet

If you have further questions, please feel free to call me at 827-3246.  
Thanks.

Jerry Phillips  
Associate Director, OPDRA

**APPEARS THIS WAY  
ON ORIGINAL**

## MEETING MINUTES

Date: May 4, 1999; 9:00 - 9:45 AM  
Location: Conference Room E; WOC2  
Firm: Organon Inc.  
Type: Face-to-Face  
Drug:  
Participants:

### FDA:

Drs. Raman Baweja, Sayed Al-Habet, Robert Seevers, Andrew Mosholder, and Mr. David

### Organon:

Albert Mayo	Executive Director, Regulatory Affairs
Carol Shichman	Assistant Manager, Regulatory Affairs
John Panagides, Ph.D.	Head Clinical Projects
Sees Timmer, Ph.D.	Drug Metabolism and Kinetics
Henk denijs, Ph.D.	Project Leader
Jan Paanakker, Ph.D.	International Project Leader

### PURPOSE

Organon submitted a request in correspondence dated March 12, 1999, for Agency advice regarding their stability proposal and their bioequivalence study needed to support this new formulation. Dr. Robert Seevers provided the sponsor with feedback to their stability questions in a telephone communication dated April 9, 1999. However, the Agency considered that feedback regarding the biopharmaceutics development program would best be conveyed in a face to face meeting.

### DISCUSSION

#### Chemistry, Manufacturing, and Controls

- The Agency cautioned Organon regarding the use of an artificial sweetener in their formulation since the Agency has seen the reaction of such a sweetener with some drug substances to produce impurities. Organon should submit the results of impurity tests in order to demonstrate that they are able to exclude or control impurities with the use of aspartame.
- Since the formulation is a compressed tablet, and not lyophilized, the sponsor will not have difficulty with tablet color or embossing on the drug product.
- The amount of stability data submitted at the time of NDA submission will directly correlate with the expiration of the drug product. Organon may amend their application with additional stability data. However, if this amendment is submitted late in the NDA review cycle, it may impact on the total review time, i.e., an extension of the review cycle.

- The Agency has some concerns about their proposed trade name of \_\_\_\_\_ It was recommended that Organon consider \_\_\_\_\_

**Miscellaneous**

- Although the sponsor has not requested feedback regarding the preclinical studies needed to support this submission, the Agency recommended that the sponsor submit a formal request for determination of the type of studies that would be required.

**Biopharmaceutics**

- Organon has proposed studying healthy males in the crossover bioequivalence study comparing their marketed 30 mg immediate release formulation to the new 30 mg formulation. Since mirtazapine demonstrates linear pharmacokinetics, that a 45 mg dose has been administered, and the \_\_\_\_\_ product formulation strengths, i.e., 15 mg, 30 mg, and 45 mg, are compositionally proportional, the sponsor only needs to demonstrate bioequivalence with the 30 mg dose. Additionally, since the pharmacokinetics of mirtazapine are so different in males compared to females, the sponsor must study both sexes, and the sponsor agreed to do so. If the sponsor is concerned about the difference in kinetics and the eventual results from conducting a single dose bioequivalence study, the sponsor may wish to conduct a multiple dose bioequivalence study in order to decrease variability.
- The sponsor mentioned that they will perform dissolution testing on all 3 \_\_\_\_\_ strengths (N = 12 per strength).
- Organon only intends to study the racemate in their proposed study. This is acceptable to the Agency.

**CONCLUSIONS**

- Organon will consider the Agency's recommendations regarding the bioequivalence study.
- Organon will submit a formal request for our determination of what preclinical studies may be required.
- The Agency and Organon will exchange meeting minutes.

Minutes Preparer:

Paul A. David, R.Ph.  
Project Manager, DNDP

Chair Concurrence:

(or designated signatory)

**DRUG:** \_\_\_\_\_ (mirtazapine) Orally Disintegrating 15 mg, 30 mg, and 45 mg Tablets

**SPONSOR:** Organon, Inc.

**INDICATION:** Depression

**DATE/TIME:** February 14, 2000; 10:00 AM

**LOCATION:** Conference Room E; WOC2

**ATTENDEES:** HFD-120: Dr. Russell Katz, Dr. Tom Laughren, Dr. Andrew Mosholder, Dr. Glenna Fitzgerald, Dr. Linda Fossom, and Mr. Paul David  
HFD-860: Dr. Ray Baweja, Dr. Hong Zhao

### CHEMISTRY AND MANUFACTURING

The application is fileable. The completion date for chemistry is June 2000.

### BIOPHARMACEUTICS

The sponsor has provided one bioequivalence study between the 30 mg marketed immediate release tablet and the 30 mg orally disintegrating tablet. They have requested a bio waiver for the higher (45 mg) and lower (15 mg) tablet strengths. The application is fileable. The completion date, along with supervisory sign-off, will be May 2000.

### PHARMACOLOGY

The sponsor has submitted a 2 week gastrointestinal study in dogs to support this new formulation. The application is fileable.

### CLINICAL

There are no clinical studies except for the 1 bioequivalence study and there were no adverse events noted in that study. The application is fileable.

### ADMINISTRATIVE

- The primary UF goal date is 10-3-00, and the secondary UF goal date is 12-3-00.
- The pivotal bioequivalence study, conducted in Europe, will be consulted out to the Division of Scientific Investigations.
- The Division still has concerns about the sponsor's proposed tradename of \_\_\_\_\_  
The Agency will inform the sponsor that they should consider an alternative tradename.

Minutes Preparer: \_\_\_\_\_

*PS*  
Paul A. David, R.Ph.  
Project Manager, DNDP

Chair Concurrence: \_\_\_\_\_

*PS*  
(or designated signatory)

cc:

NDA:ORIG 21-208

NDA:DIV FILE

HFD-120/RKatz/TLaughren/AMosholder

HFD-120/GFitzgerald/LFossom

HFD-120/RSeevers/

HFD-120/PDavid

HFD-860/RBaweja/HZhao

DOC# \_\_\_\_\_ .DA21-208\2-14-00 FILE-RTF MEETING MINUTES.DOC

MEETING MINUTES

**APPEARS THIS WAY  
ON ORIGINAL**

FOOD AND DRUG ADMINISTRATION  
Division of Neuropharmacological Drug Products  
HFD-120, Room 4030  
1451 Rockville Pike  
Rockville, MD 20852

DATE: October 10, 2000



TO:

Name: Carol Shichman, Regulatory Affairs

Fax No: 973-325-4769

Phone No: 973-325-4655

Location: Organon

FROM:

Name: Paul David, Regulatory Project Manager

Fax No: (301) 594-2858

Phone No: (301) 594-2850

Location: FDA, Division of Neuropharmacological Drug Products

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Total Pages (including cover page) = 21

Comments:

Carol,

In order to expedite the final action for this application, the Division is attempting to seek labeling agreement at the Team Leader level. Attached, to this fax, is the Agency's proposed labeling for Remeron SolTab. Please note that it also includes a Phase 4 commitment to conduct a clinical pharmacology study to determine if there is a dose-related lengthening of the QT interval associated with mirtazapine. Additionally, our OCPB team is requesting that Organon adopt the following dissolution method and specification for all strengths of the Remeron SolTab (mirtazapine) Orally Disintegrating 15 mg, 30 mg, and 45 mg Tablets:

Apparatus: USP Apparatus 2 (Paddle) at 50 rpm

Medium: 900 mL 0.1 N HCl at 37°C±0.5°C

Specification: \_\_\_\_\_ in 15 minutes

If you have any questions regarding this fax, please do not hesitate to contact me directly.  
Paul

NDA 21-208  
HFD-120/Div. File  
HFD-120/R.Katz/T.Laughren/A.Mosholder  
HFD-120/P.David

**APPEARS THIS WAY  
ON ORIGINAL**

**Number of Pages**  
**Redacted** 20

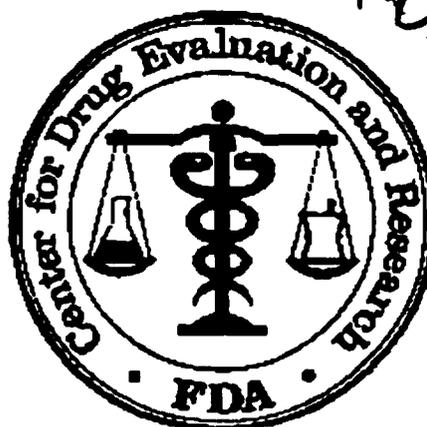


Draft Labeling  
(not releasable)

FOOD AND DRUG ADMINISTRATION  
Division of Neuropharmacological Drug Products  
HFD-120, Room 4030  
1451 Rockville Pike  
Rockville, MD 20852

DATE: April 25, 2000

P. David



TO:		FROM:	
Name:	<b>Carol Schickman, Regulatory Affairs</b>	Name:	<b>Paul David, Regulatory Project Manager</b>
Fax No:	973-325-4769	Fax No:	(301) 594-2858
Phone No:	973-325-4655	Phone No:	(301) 594-2850
Location:	Organon	Location:	FDA, Division of Neuropharmacological Drug Products

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Comments:

Carol,

OCPB has requested the following information during the course of their review of the mirtazapine orally disintegrating application, NDA, 21-208. Please provide a formal response to the NDA as well as a desk copy to me.

Thanks,  
Paul

1. On Page 0226 of Vol. 1.11, it states that the analysis of Org 3770 in human plasma has been validated and described elsewhere (SDGRR3147). Please inform the Agency where this report (SDGRR3147) may be located.
2. Pooled data for both males and females should be provided for the test and reference tablets including mean concentration-time curves and the following parameters:  $AUC_{0-24}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$  and elimination half-life, presented as arithmetic mean, standard deviations and coefficient of variation. For  $AUC_{0-24}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ , geometric mean, ratio of means and 90% confidence intervals should also be provided.

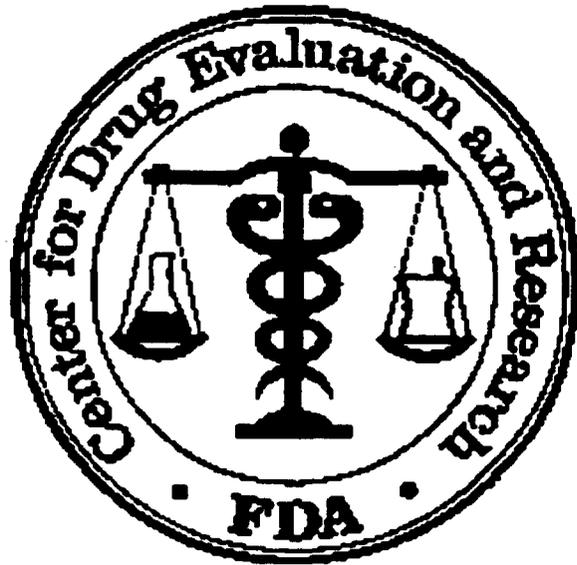
NDA 21-208  
HFD-120/Div. File  
HFD-120/R.Katz/T.Laughren/A.Mosholder  
HFD-120/P.David  
HFD-860/R.Baweja/H.Zhao  
INFORMATION REQUEST

151 4-25-00

APPEARS THIS WAY  
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION  
DIVISION OF NEUROPHARMACOLOGICAL  
DRUG PRODUCTS  
DOCUMENT CONTROL ROOM, HFD-120  
5600 FISHERS LANE  
ROCKVILLE, MARYLAND 20857

DATE February 28, 2000



TO:

FROM:

Name Carol Schichman, Regulatory Affairs

Name Paul David, R.Ph.

Fax No. (973) 325-4769

Fax No. (301) 594-2859

Phone No. (973) 325-4655

Phone No. (301) 594-5530

Location Organon, Inc.

Location FDA:CDER:ODE1:HFD-120

Total Pages: 1

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**Comments:**

Carol,

I am faxing you the requests generated from our Office of Clinical Pharmacology and Biopharmaceutics regarding the \_\_\_\_\_ application, NDA 21-208. Below are the requests:

- 1) Please provide representative chromatograms of mirtazapine plasma concentration determinations in the bioequivalence study.
- 2) Please provide a description of the dissolution method used to generate the dissolution data.

Additionally, when Organon is ready to respond to the above requests, please provide me with a desk copy of the submission.

Thanks,  
Paul

cc:

NDA 21-208

HFD-120/Div. File

HFD-120/AMosholder/TLaughren/RKatz

HFD-120/PDavid

HFD-860/RBaweja/HZhao

DOC # *1* /2-28-00 FAX OCPB REQUESTS.DOC

MEMO TO THE FILE

*1* *IS* *Sent 2-28-00*

APPEARS THIS WAY  
ON ORIGINAL



Telefax Transmittal  
Cover Sheet

Organon Inc.

**Organon Inc.  
Regulatory Affairs Department**

375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052  
Telefax No.: (973) 325-4769

DATE: June 21, 1999 TOTAL PAGES SENT: 4  
TO: R. Seevers, PhD, Chemistry Team Leader FAX: 301-594-2859  
FROM: C. Shichman FAX: 973-325-4769  
SUBJECT: NDA 20-415 -  Tablets  
cc Embossment Codes  
P. David, CSO

Dear Dr. Seevers:

Enclosed per our conversation of a short time ago are drawings of embossments for the 15, 30 and 45mg  Tablets. Our question is whether this embossment will be acceptable. I look forward to hearing the comments, and appreciate your comments. Please call me at 973-325-4655 if you have any questions.

Sincerely,



Carol B. Shichman  
Assistant Manager, Regulatory Affairs

If transmittal is not good or if you do not receive all pages, please call Ann DePasquale at (973) 325-4831 as soon as possible. Thank you.

**Number of Pages**  
**Redacted** 3



Draft Labeling  
(not releasable)



Food and Drug Administration  
Rockville MD 20857

JUN 14 1999

Organon Inc.  
Attention: Albert P. Mayo  
Director, Regulatory Affairs  
375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052

Dear Mr. Mayo:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Remeron (mirtazapine) tablets.

We additionally refer to the meeting between representatives of your firm and FDA on May 4, 1999. The purpose of the meeting was to discuss the bioequivalence requirements of a new formulation of mirtazapine.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

RS 6/7/99

Russell Katz, M.D.  
Acting Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*3 pages*



If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

*RS*

8/16/00

Robert Seevers

Chemistry Team Leader

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

cc:

Archival NDA 21-208

HFD-120/Div. Files

HFD-120/P.David

HFD-120/S. McLamore

HFD-120/R. SeEVERS

HFD-810/DNDC Division Director

DISTRICT OFFICE

Drafted by: SDM/August 15, 2000

Initialed by:

final:

filename: 21-208 I

INFORMATION REQUEST (IR)

APPEARS THIS WAY  
ON ORIGINAL



OCT - 6 1999

NDA 20-415

Organon Inc.  
Attention: Albert P. Mayo  
Director, Regulatory Affairs  
375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052

DAVID

Dear Mr. Mayo:

Please refer to your New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron (mirtazapine) tablets.

Reference is also made to an Agency letter dated June 26, 1998, requesting that you propose language into the PRECAUTIONS section of labeling providing for a description of two torsades de pointes cases found in the Agency's spontaneous postmarketing reports database.

We acknowledge receipt of your submission dated September 25, 1998, responding to our June 26, 1998 letter, and declining to make any labeling changes based upon your review of the data.

In that submission, you argued that the arrhythmia in the 70 year old female might be due to concomitant medications rather than Remeron. We concede that it is impossible to make a causal attribution to a single medication in such a case. Another interpretation, however, would be that an interaction between Remeron and a second medication provoked the arrhythmia. With respect to the 48 year old female who required defibrillation, you argued that this patient's polymorphic ventricular arrhythmia was not classic torsades de pointes; we do not regard this as reassuring, however. With respect to your clinical trial data analysis in that submission, we concede that a dose dependent QT prolongation was not observed; however, the fact that most of the clinical trials with Remeron involved flexible dosing limits the interpretation of dose-response.

Accordingly, we are requesting that you make the following labeling revisions:

**Under PRECAUTIONS, Use in Patients with Concomitant Illness**

The following sentence should be deleted:

\_\_\_\_\_

**Under PRECAUTIONS, Drug Interactions**

Add the following sentence after the first paragraph:

**Under ADVESE REACTIONS, ECG Changes**

The following paragraph should be deleted:

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~  
~~T \_\_\_\_\_~~  
~~J \_\_\_\_\_~~  
~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~

These changes, as outlined above, should be submitted as final printed labeling exactly as specified in this letter in the form of a "SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED" as described under 21 CFR 314.70(c). Please incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit twenty copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

This supplement should be submitted within 2 months from the date of this letter.

In addition, in view of the limited data currently available on mirtazapine's effects on EKG parameters, particularly the lack of dose response data, we are requesting that you conduct a clinical pharmacology study to determine if there is a dose-related lengthening of the QT interval associated with mirtazapine. Alternatively, if EKG data are being collected in your ongoing fixed dose depression study 003-042, this trial may provide some useful information. We would be happy to provide further advice on this at your request.

If you have any questions, contact Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

RS

Russell Katz, M.D.  
Acting Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

cc:

Archival NDA 20-415

HFD-120/Div. Files

HFD-120/RKatz/TLaughren/AMosholder

HFD-120/PDavid

HFD-430/KBennett

HFD-110/Kin Maung U

rd:09/22/99pd

rev:09/23/99am;tl

rev:09/30/99am

ft:10/04/99pd

filename: REMERON\NDA\TORSADES SUPPLEMENT REQUEST LETTER.DOC

*10-5-99*

*10/4/99*

*10-7-99*

SUPPLEMENT REQUEST (SR)

APPEARS THIS WAY  
ON ORIGINAL



NDA 21-208

JAN - 6 2000

Organon Inc.  
Attention: Albert P. Mayo  
Director, Regulatory Affairs  
375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052

DAVID

Dear Mr. Mayo:

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: \_\_\_\_\_

Review Priority Classification: Standard (S)

Date of Application: December 30, 1999

Date of Receipt: December 30, 1999

Our Reference Number: NDA 21-208

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 30, 2000 and the secondary user fee goal date will be December 30, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

**U.S. Postal Service:**  
Center for Drug Evaluation and Research  
Division of Neuropharmacological  
Drug Products, HFD-120  
Attention: Division Document Room, HFD-120  
5600 Fishers Lane  
Rockville, Maryland 20857

**Courier/Overnight Mail:**  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological  
Drug Products, HFD-120  
Attention: Document Room HFD-120  
1451 Rockville Pike  
Rockville, Maryland 20852

If you have any questions, please contact Mr. Paul David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

*JS* 1/6/00

John S. Purvis  
Chief, Project Management Staff  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

NDA :ORIG 21-208

NDA:DIV FILE

HFD-120/RKatz/TLaughren/AMosholder

HFD-120/GFitzgerald

HFD-120/RSeevers/PDavid

HFD-860/VJTammara/RBaweja

DISTRICT OFFICE

Doc #REMERON\NDA 21-208\ORIGINAL NDA ACKNOWLEDGMENT LETTER.DOC  
ACKNOWLEDGMENT (AC)

**APPEARS THIS WAY  
ON ORIGINAL**

DAVID

JUN 13 2000

NDA 21-208

**DISCIPLINE REVIEW LETTER**

Organon, Inc.  
Attention: Carol B. Shichman  
Assistant Manager, Regulatory Affairs  
375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052

Dear Ms. Shichman:

Please refer to your December 30, 1999 new drug application for Remeron (mirtazapine) 15, 30 and 45 mg orally disintegrating tablet.

We also refer to your submissions dated February 17, 2000.

Our reviews of the chemistry sections of your submissions are complete, and we have identified the following deficiencies:

1. On pages 43, 45 and 47 of volume 1.4 you indicate that you use natural and artificial orange flavor as a one of your inactive ingredients. It is not clear which artificial orange flavor you are using in the composition of the drug product. Please clarify and indicate the identity, source, incoming quality control, DMF ref./LOA.
2. Several places in the manufacturing process section you use the term "or equivalent" to describe the equipment to be used. Please be advised that the approval of your application is based on the information that is specified in this application. Please provide a commitment that states that changes made to the application after approval will be submitted per the requirements in the regulations.
3. In your application on page 311 of volume 1.4 you explain that the ingredients are transferred to a "suitable blender". Please be advised that the approval of your application is based on the information provided in this application. Accordingly, the information provided should be as specific as possible. Please provide specific information pertaining to the type of blender that you intend to use.



In the certificates of analysis for the 15, 30 and 45 dosage forms you list the following:

Please clarify.

13. In volume 1.7 on pages 88, 95 and 101 batches 990027, 990028 and 990029 were identified as full-scale production batches. On page 157 of volume 1.7 you indicate that these batches will be used in the stability protocol. Please provide certificates of analysis for each of these batches as indicated in 21 CFR 314.50(d)(1)(ii)(b).
14. You indicate on page 98 of volume 1.7 in the table pertaining to the package insert that the requirements for the dimension, fold and stock are "meets specification" however it is not clear what these specifications are. Please clarify.
15. You indicate on page 99 of volume 1.7 in the table pertaining to the folding cartons that the requirements for the bar code, style, dimension and stock/board are "meets specification" however it is not clear what these specifications are. Please clarify.
16. \_\_\_\_\_ ) is deficient for section 124, \_\_\_\_\_  
\_\_\_\_\_ The DMF Holder is being notified of this by separate letter which includes a list of the deficiencies
17. In table 6 on page 163 of volume 1.7 you include the specification tests and methods however you do not include the proposed specifications. Please confirm that these specifications are identical to the end of shelf life specification for the drug product.
18. Please provide method validation for the chemical test for the drug product (mirtazapine content by \_\_\_\_\_
19. The proposed cartons and blister backing for the drug product has \_\_\_\_\_  
\_\_\_\_\_ ; listed as the name of the drug product. As you were advised on November 3, 1999, this name is not an approved or accepted name. Please commit to submitting revised container closure information when a new name is agreed upon.
20. With respect to the levels of phenylalanine specified on the proposed carton, please provide the calculations to support these levels.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

 6/13/08

Robert H. Seevers, Ph.D.  
Chemistry Team Leader, Psychiatric Drugs for the  
Division of Neuropharmacological Drug Products,  
(HFD-120)  
DNDC I, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

cc:

Archival NDA 21-208

HFD-120/Div. Files

HFD-120/P.David

HFD-120/R.Seever

HFD-120/S.McLamore

HFD-810/DNDC Division Director, J.Simmons

Drafted by: SDM/June 8, 2000

Initialed by:

final: SDM

filename: 21208 IN

DISCIPLINE REVIEW LETTER (DR)

**APPEARS THIS WAY  
ON ORIGINAL**

**Organon Inc.**  
**Regulatory Affairs Department**

375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052  
Telefax No.: (973) 325-4769

Date: October 30, 2000 No. of Pages: 2  
To: Mr. Paul David, CSO FAX: 301-594-2859  
From: Carol Shichman, Organon, Inc. FAX: 973-325-4769  
Subject: NDA 21-208 – Remeron® SolTab™ (mirtazapine) Orally  
Disintegrating Tablets

---

Dear Mr. David:

This is to notify the Agency that Organon Inc hereby withdraws the following establishment from the pending application for NDA 21-208:

Establishment # 2211109  
Organon Inc Sub Akzona Inc  
375 Mt Pleasant Avenue  
West Orange, NJ 07052

This establishment was a possible second site for quality control testing and release for Remeron® SolTab™ (mirtazapine) Orally Disintegrating Tablets. As stated in NDA 21-208, (see attached page from Volume 1.5 of NDA 21-208) full quality control and release testing will be carried out at:

CIMA LABS INC  
10000 Valley View Road  
Eden Prairie, Minnesota 55344.

Please call me at 973-325-4655 if you have further questions.

Sincerely,



Carol B. Shichman  
Assistant Manager, Regulatory Affairs

CONFIDENTIAL

21 CFR 314.50 (d) (1)

Subsection (ii): Drug Product

---

2.6 Specifications/Analytical Procedure

Test and Release Facility

The intermediate product, coated mirtazapine, will be quality control tested and released by \_\_\_\_\_

The following tests will be performed:

- Appearance (Visual)
- Identification, Mirtazapine (TLC and \_\_\_\_\_)
- Assay
- Impurities (Individual, Others, Total)
- Dissolution (0.1 N HCl)
- Water Content \_\_\_\_\_
- Sieve Analysis
- Residual Solvents

\_\_\_\_\_ 15 mg, 30 mg and 45 mg, will be quality control tested and released by \_\_\_\_\_

The following tests will be performed:

- Appearance (Visual Inspection)
- Identification, Mirtazapine (HPLC) (TLC)\*
- Moisture
- Disintegration
- Dissolution (0.1 N HCl)
- Weight Variation/Uniformity of Mass\*
- Average Tablet Weight\*
- Mirtazapine Content by HPLC
- Content Uniformity (UV)
- Related Substances (HPLC)
  - Individual, Single Others, Total
- Total Aerobic Count
- Fungi
- E. coli*

\*Test performed at time of release only. Not performed for stability purposes.

\_\_\_\_\_ may also be quality control tested and released by Organon Inc., 375 Mount Pleasant Avenue, West Orange, New Jersey 07052.

**Organon Inc.  
Regulatory Affairs Department**

375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052  
Telefax No.: (973) 325-4769

Date: October 27, 2000 No. of Pages: 3  
To: Mr. Paul David, CSO FAX: 301-594-2859  
From: Carol Shichman, Organon, Inc. FAX: 973-325-4769  
Subject: NDA 21-208 – Remeron® SolTab™ (mirtazapine) Orally  
Disintegrating Tablets

---

Dear Mr. David:

Attached please find the CMC information requested October 26, 2000.  
Please call me at 973-325-4655 if you have any questions.

Sincerely,

*Carol B Shichman*

Carol B. Shichman  
Assistant Manager, Regulatory Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

**Number of Pages  
Redacted** 2



Confidential,  
Commercial Information

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-208

SPONSOR: ORGANON

DRUG: MIRTAZAPINE (REMERON)

MATERIAL SUBMITTED: ORIGINAL NEW DRUG APPLICATION FOR ORALLY DISINTEGRATING TABLETS

DATE SUBMITTED: 12/30/99

DATE RECEIVED: 1/3/00

USER FEE DUE DATE: 10/30/00

This NDA provides for an orally disintegrating dosage form of mirtazapine. The proposed strengths are identical to the marketed tablets, namely 15 mg, 30 mg, and 45 mg.

This submission includes the requisite chemistry, manufacturing and controls information, a report of a 14 day gastrointestinal toxicity study with this dosage form in dogs, and a report of a clinical bioequivalence study.

Bioequivalence Study: Study 22527 was a single dose, two way open label crossover trial comparing 30 mg marketed tablets to 30 mg orally disintegrating tablets. Forty healthy adult volunteers participated in the trial. The two single doses were separated by a 2 week washout period. The orally disintegrating tablet was administered with nothing to drink, while the marketed tablet was administered with 200 cc of water.

The pharmacokinetic data showed the two formulations to be bioequivalent on Cmax and AUC. No gender differences were noted although women tend to show a longer half life than men for mirtazapine (see Remeron labeling under Clinical Pharmacology).

Adverse events included somnolence (in every subject) and orthostatic hypotension. No subjects discontinued for adverse events or had a serious adverse event. ECGs were obtained at baseline and 96 hours after the second dose; the mean heart rate increased by 6 bpm and the mean QTc interval increased by 10 msec, although these findings are difficult to interpret without a control group. Overall there were no unusual safety findings in this study.

Trade Name: With respect to the proposed trade name, Jerry Phillips, Associate Director of OPDRA, has indicated in an email dated 6/6/00 that the modifier "Soltab" is acceptable to OPDRA. The sponsor's original proposal of \_\_\_\_\_ was not considered acceptable.

Proposed labeling: This was submitted 2/17/00. It includes descriptions of the new dosage form (under Description and How Supplied), and a statement that Remeron conventional tablets and orally disintegrating tablets have been shown to be bioequivalent

(  
(under Clinical Pharmacology). There is also a paragraph under Dosage and Administration describing how the tablets are to be taken (i.e., without water).

I have one proposed addition to the Overdosage section, as follows: "Because of the rapid disintegration of Remeron Soltab tablets, pill fragments may not appear in gastric contents obtained with lavage."

I also recommend that we take this opportunity to add to the Remeron labeling the statement we requested regarding QT prolongation, which the sponsor has previously refused to implement. Please refer to my clinical review of the sponsor's 11/16/99 submission.

Appearance of the tablets and container labeling: I had an opportunity to examine samples of the tablets and the container labeling with the Chemistry review team. Previously, the Remeron container labels had caused confusion and probably some prescription errors because the number of tablets can be the same as one dosage strength (30). Organon revised the container labeling to make the distinction more obvious. This does not appear to be a problem with this drug product. My one comment here is that the tablets bear only the designation "TZ1," "TZ2," or "TZ4." Ideally, the mg strength would also appear on the tablets, to further reduce the possibility of mixup.

Conclusions and recommendations: (1) I propose adding the above statement to the Overdosage section of labeling. (2) I propose adding the previously requested labeling statements about QT prolongation. (3) If possible, the tablets should be marked with their mg strength. (4) The NDA is approvable from a clinical standpoint.

151  
8/21/00  
Andrew Mosholder, M.D.  
Medical Officer, HFD-120

NDA 21-208  
Div file  
HFD-120 Laughren, David, Mosholder

10-22-00  
I agree that this NDA is  
approvable. See memo to file  
for detailed comment.

151  
7/2, ADA

# Electronic Mail Message

**Date:** 10/17/00 3:42:12 PM  
**From:** Raman Baweja ( BAWEJA )  
**To:** Thomas Laughren ( LAUGHREN )  
**To:** Paul David (DNPDP/ODEI) ( DAVID )  
**Cc:** Mehul Mehta ( MEHTA )  
**Cc:** Hong Zhao ( ZHAOH )  
**Cc:** Raman Baweja ( baweja )  
**Subject:** NDA 21,208, Remeron Orally Disintegrating Tablet

OCPB's review of this NDA indicated that the orally disintegrating tablet can be approved based on the successful outcome of a BE study and dissolution testing (OCPB review dated September 18, 2000). A memo from DSI to the clinical division mentioned that the results of the BE study should not be used due to the failure of the sponsor to retain study drug samples. OCPB would like to mention that because of the successful outcome of the BE study and dissolution testing, it would have no reason to suggest any repeat or further testing from units of these lots. Therefore, the issue of not retaining samples is moot.

Hong Zhao and Ray Baweja

APPEARS THIS WAY  
ON ORIGINAL

ANNOTATED TO SHOW THE CORRECTIONS. APPROVAL IS RECOMMENDED AT THE DISTRICT  
LEVEL FOR THIS PRODUCT.

OC RECOMMENDATION 10-AUG-2000

**ACCEPTABLE** DAMBROGIOJ  
DISTRICT RECOMMENDATION

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: 020415

Responsibilities: \_\_\_\_\_

Profile: CSN OAI Status: NONE

Estab. Comment: \_\_\_\_\_ (on 01-FEB-  
2000 by S. MCLAMORE (HFD-810) 301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-JAN-2000				ROCCAL
SUBMITTED TO DO	02-FEB-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	07-FEB-2000			<b>ACCEPTABLE</b> BASED ON FILE REVIEW	EGASM
BASED ON EI OF 10/1/98					
OC RECOMMENDATION	08-FEB-2000			<b>ACCEPTABLE</b> DISTRICT RECOMMENDATION	EGASM

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: 020415

Responsibilities: \_\_\_\_\_

Profile: CSN OAI Status: NONE

Estab. Comment: \_\_\_\_\_ (on 01-FEB-  
2000 by S. MCLAMORE (HFD-810) 301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-FEB-2000				MCLAMORES
SUBMITTED TO DO	02-FEB-2000	10D			DAMBROGIOJ
ASSIGNED INSPECTION	07-FEB-2000	GMP			EGASM
INSPECTION SCHEDULED	16-AUG-2000		19-OCT-2000		IRIVERA
INSPECTION PERFORMED	23-OCT-2000		17-OCT-2000		IRIVERA
DO RECOMMENDATION	27-OCT-2000			<b>ACCEPTABLE</b> INSPECTION	EGASM
INSPECTION WAS NAI, NOT VAI					
OC RECOMMENDATION	27-OCT-2000			<b>ACCEPTABLE</b> DISTRICT RECOMMENDATION	EGASM

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA:

Responsibilities: \_\_\_\_\_

Profile: CRU OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Estab. Comment: \_\_\_\_\_  
\_\_\_\_\_

(on 14-APR-2000 by S. MCLAMORE (HFD-810)

301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-APR-2000				MCLAMORES
SUBMITTED TO DO	18-APR-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	08-MAY-2000	PS			LJARRELL
INSPECTION SCHEDULED	17-JUL-2000		29-JUN-2000		LJARRELL
INSPECTION PERFORMED	17-JUL-2000		29-JUN-2000		LJARRELL

IN THE FUTURE.

DO RECOMMENDATION 01-AUG-2000 ACCEPTABLE LJARRELL  
ADEQUATE FIRM RESPONSE

FIRM RESPONDED ON JULY 14, 2000, TO THE FDA-483. RESPONSE ACCEPTABLE BASED  
ON THE FIRM'S ACTIVITIES.

OC RECOMMENDATION 01-AUG-2000 ACCEPTABLE DAMBROGIOJ  
BASED ON PROFILE

Establishment: \_\_\_\_\_  
\_\_\_\_\_

DMF No:

AADA:

Responsibilities: \_\_\_\_\_

Profile: CTL

OAI Status: NONE

Estab. Comment: \_\_\_\_\_  
\_\_\_\_\_

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-AUG-2000				MCLAMORES
OC RECOMMENDATION	16-AUG-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 0211109

ORGANON INC SUB AKZONA INC  
375 MT PLEASANT AVE  
WEST ORANGE, NJ 07052

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTL

OAI Status: OAI ALERT

Estab. Comment: QUALITY CONTROL TESTING AND RELEASE (on 01-FEB-2000 by S. MCLAMORE  
(HFD-810) 301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-FEB-2000				MCLAMORES
OC RECOMMENDATION	01-FEB-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
OC RECOMMENDATION	27-OCT-2000			WITHHOLD WARNING LETTER ISSUED	FERGUSONS

*My Inspection letter issued 9-19-00 significant gaps*

ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment: 529406

ORGANON INC SUB AKZONA INC  
6350 HEDGEWOOD DR  
ALLENTOWN, PA 18103

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE

Estab. Comment: SECONDARY PACKAGING (CARTONS) (on 01-FEB-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-FEB-2000				MCLAMORES
OC RECOMMENDATION	01-FEB-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 610342

ORGANON NV  
5340-BH  
OSS, , NL

DMF No:

AADA: 020415

Responsibilities: DRUG SUBSTANCE OTHER TESTER

DRUG SUBSTANCE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: DRUG SUBSTANCE MANUFACTURE AND QUALITY CONTROL TESTING (on 01-FEB-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-FEB-2000				MCLAMORES
SUBMITTED TO DO	02-FEB-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	07-FEB-2000	GMP			EGASM
OC RECOMMENDATION	25-JUL-2000			ACCEPTABLE BASED ON PROFILE	EGASM

APPEARS THIS WAY  
ON ORIGINAL

Office of Compliance  
Division of Manufacturing & Product Quality  
Investigations & Compliance Evaluation Branch, HFD-324  
7520 Standish Place, Room 266  
Metro Park North I  
Rockville, MD 20855  
Phone #301/827-0062/0063 Fax #301/827-0145

NOTE: NEW FAX & PHONE  
NUMBERS

FROM: S. Bergman

DATE: 10/30/00

NO OF PAGES: 11

TO: Paul David

FAX: \_\_\_\_\_

SUBJECT: Argunon 21-208 W/L

COMMENTS: Per your request

IF YOU HAVE ANY PROBLEMS WITH THIS FAX PLEASE CONTACT  
THE ABOVE PHONE NUMBER(S). THANK YOU.

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telephone and return it to us at the above address by mail.

## Memorandum

Date . OCT 27 2000

From CSO, Investigations and Preapproval Compliance Branch (HFD-324)

Subject Recommendation to Withhold Approval  
Multiple NDAs - see list

To John Simmons, Supervisory Chemist (HFD-810)  
Steve Koepke, Supervisory Chemist (HFD-820)  
OPS, ONDC

Firm: Organon, Inc.  
West Orange, New Jersey  
CFN: 2211109

The Division of Manufacturing and Product Quality (DMPQ) has completed its review of the New Jersey District's warning letter dated September 19, 2000. The warning letter noted numerous significant CGMP deficiencies for both sterile and non-sterile products. Approval of these applications should be withheld until the deficiencies have been corrected by the subject firm.

HFD-324 ran an Establishment Specific Report from EES and found seven applications with a pending status. A copy of the report along with the warning letter is attached for your information.

If you have any questions, please contact the undersigned at 301-827-0062.

ISI  
/ Shimette Ferguson U

Attachments

Note: Pending NDAs

\_\_\_\_\_

\_\_\_\_\_

Cc:  
HFD-324 R/F  
HFD-324 (SFerguson)  
HFR-CE300  
Concur:PAIcock:sdf:

PA  
10/27/07

**APPEARS THIS WAY  
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Telephone (973) 526-6010

Food and Drug Administration  
Waterview Corporate Center  
10 Waterview Blvd., 3rd Floor  
Parasippany, NJ 07054

September 19, 2000

WARNING LETTER

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Hans Vemer, President  
Organon, Inc.  
375 Mt. Pleasant Avenue  
West Orange, New Jersey 07052

FILE NO.: 00-NWJ-64

Dear Mr. Vemer:

The U.S. Food and Drug Administration, New Jersey District, conducted an inspection of your manufacturing facility located at 375 Mt. Pleasant Avenue, West Orange, NJ, between July 17 and August 23, 2000. The inspection revealed significant deviations from Current Good Manufacturing Practice regulations (Title 21 Code of Federal Regulations (CFR), Parts 210 & 211) for both sterile and non-sterile products. These deviations cause articles of drugs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). A discussion of the significant deviations follows:

Sterile products are not manufactured in an environment that adequately controls microbiological contamination. This lack of control is due to poor personnel practices, failure to follow procedures, and lack of adequate supervision. For example:

- 1) Filling pumps and stoppering equipment were not sterilized prior to filling. Failure to run the autoclave cycle was not noticed until 4 hours into the filling operation resulting in the rejection of the lot.
- 2) Non-sterile materials were taken into sterile manufacturing room #373 during a validation study.
- 3) Personnel conducting a validation study in room #373 were not trained in proper gowning techniques and were not monitored by QC Microbiology personnel.
- 4) Operators failed to sanitize sterile manufacturing room #373 prior to filling. Environmental monitoring conducted at the time resulted in high counts for mold on a door panel and an operator's glove. The lot was released.
- 5) Following the normal 3X sanitization of the sterile manufacturing area and equipment after a shutdown, 14 sites were found to have high microbial counts. An additional 3X sanitization was required to reduce the counts, resulting in a

September 19, 2000

— Page Two —

lack of assurance that the cleaning procedures are adequate or that the procedures are being followed appropriately.

- 6) Personnel responsible for conducting environmental monitoring of sterile manufacturing areas and personnel failed to label \_\_\_\_\_ during media fill #MD0999383, resulting in the same sampling plate being used to monitor two individuals.
- 7) Manufacturing personnel were operating without supervision and conducted an unauthorized spray cleaning of the \_\_\_\_\_ lyophilizer while \_\_\_\_\_ was being filled and partially stoppered for loading into the \_\_\_\_\_ lyophilizer. The lyophilizers are in the same sterile processing room.
- 8) Personnel were routinely cited as the source of the microbiological growth when high counts were observed during routine environmental monitoring and during media fills. Personnel are not routinely recertified or retrained in gowning procedures, nor is there a system to track which personnel have participated in media fills to assure that all sterile manufacturing personnel participate on a regular basis. In one instance, an individual had not been recertified in five years. Poor practices included passing non-sterilized equipment through the airlocks into the sterile core, an individual failing to notify anyone of his participation in a media fill resulting in no monitoring by QC Microbiology personnel, high counts during personnel monitoring were not followed by retraining and recertification of the operators.

The environmental integrity of the sterile manufacturing area and sterility test suite is questionable because:

- 1) \_\_\_\_\_, subplot A-1, exhibited growth during sterility testing. The organism, identified as Bacillus circulans, was found during environmental monitoring of the sterility test suite. In addition, six other Bacillus species and Staphylococcus epidermidis were found during environmental monitoring of the sterile manufacturing area on the date of manufacture of the \_\_\_\_\_ batch. A passing retest was used to invalidate the failing test and also to release the batch.
- 2) Environmental monitoring of sterile processing room #373 during filling of \_\_\_\_\_, produced two high counts for mold growth (door panel and operator's gloves). The room exhibited growth of the same mold species on subsequent days during filling of \_\_\_\_\_ and \_\_\_\_\_. The investigation found that a housing covering the door switch panel was missing screws, missing caulk, contained moisture, and appeared to be discolored.

The ability of both sterile products and non-sterile (oral) products to meet all specifications throughout the labeled expiry period has not been demonstrated. For example:

September 19, 2000

-- Page Three --

- 1) \_\_\_\_\_ tablets are labeled with an expiry period of 24 months and the assay specification for Ergotamine tartrate is \_\_\_\_\_. At 18 months, two lots were at the minimum of 90% and two additional lots were at 92% and 93%. No investigation was conducted. At the 24-month time period, the assay results inexplicably rose by 7-8% without explanation or investigation.
- 2) \_\_\_\_\_ stability lots were reconstituted and assayed. The specification for reconstituted product is \_\_\_\_\_. At the initial and 6-month time points, two lots produced low results of 94% and 93% respectively, however the expiration period is 24 months. The test method for the reconstituted assay has not been validated, yet it is being used for stability testing.
- 3) Three additional lots of \_\_\_\_\_ failed the pH specification at the 18-month time point; the expiry period is 24 months. The specification is \_\_\_\_\_, yet all three lots had results of 4.3. No investigation was conducted even though pH is a finished product specification.

The Quality Control (QC) Unit has failed to carry out investigations and perform QC functions to assure that products are manufactured in a state of control and meet all finished product specifications. For example:

- 1) Black spots were found during compression of \_\_\_\_\_ Tablets Validation lot \_\_\_\_\_. A single drum of tablets was visually examined. The Quality Unit released the lot, and did not conduct an investigation into the source or identity of the black spots. The black spots were not mentioned in the validation report.
- 2) \_\_\_\_\_ was manufactured and placed on accelerated stability to qualify a new supplier of caffeine. At the 3-month accelerated time point, the tablets failed the appearance specification because they had a brownish appearance. The Quality Unit did not evaluate the lot for an increase in impurities, and the new caffeine supplier was approved.
- 3) \_\_\_\_\_ was manufactured to qualify a new supplier of caffeine. Although the lot failed several in-process tests, including caffeine assay and disintegration, manufacturing continued and final release testing was conducted. In spite of these failures, QC personnel approved a Certificate of Analysis stating "Released for Use" for lot #100542. The lot was still in quarantine at the start of the inspection. During the inspection, a final decision to destroy the lot was made, however, the new caffeine supplier was approved.
- 4) \_\_\_\_\_ failed the appearance specification for color. Quality Control personnel do not use a color standard for comparison, nor did they perform an investigation into the failure and rejection of Batch #199490.
- 5) The Quality Unit routinely fails to review and approve documents that are integral to the evaluation of the manufacturing processes and equipment performance. Items such as Validation Reports, Qualification Reports, Media Fill records, and Product Variance Reports were not reviewed and approved for periods ranging

September 19, 2000

-- Page Four --

from 4 months to 24 months, and some reports had not been reviewed and approved as of the close of the inspection.

- 6) Quality Control analysts and supervisors failed to initiate an investigation when \_\_\_\_\_ lot #499490B, exhibited an out-of-specification result for Unknown Impurities upon initial release testing in August 1999. Although a July 2000 retrospective investigation, conducted during the inspection, determined that the result was erroneously reported, the lot was released for use by the QC Unit at the time of the initial release testing.

Equipment is not maintained in a manner sufficient to assure that products can be manufactured according to the validated processes. For instance:

- 1) On numerous occasions, the \_\_\_\_\_ Oven could not maintain the specified drying temperature. The problem of temperature drops occurred during the drying of at least \_\_\_\_\_  
No maintenance work was conducted on the oven.
- 2) Shelf temperatures and vacuum levels could not be maintained by the lyophilizers during the processing of at least eight batches of \_\_\_\_\_  
\_\_\_\_\_ These equipment problems caused delays during lyophilization and also caused lyophilization steps to be repeated. As a result, the validated lyophilization process was not followed.

The above list of violations is not considered to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure that all requirements of the Federal Food, Drug and Cosmetic Act and all applicable federal regulations are met. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deficiencies. Failure to correct the deviations may result in regulatory action without further notice. This includes seizure and/or injunction.

Please notify this office within 15 working days of receipt of this letter regarding the specific steps you have taken to correct the noted violations. This should also include an explanation of each step taken to prevent the recurrence of similar violations. If the corrective actions cannot be completed within 15 working days, state the reason for the delay and the time needed to complete the corrections.

We have received your correspondence dated September 7, 2000, written in response to the FDA-483 issued to your firm on August 23, 2000. We are in the process of reviewing it.

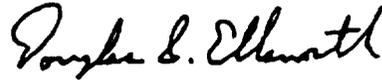
Organon, Inc.  
Warning Letter

September 19, 2000

-- Page Five --

Please submit any additional response to: U.S. Food and Drug Administration, 10  
Waterview Boulevard, 3<sup>rd</sup> Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Feve,  
Compliance Officer.

Sincerely,



Douglas I. Ellsworth  
District Director  
New Jersey District

cc: Michael G. Ferrante  
Director, Quality Assurance

**APPEARS THIS WAY  
ON ORIGINAL**