CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-717/S-009

Name:	Provigil Tablets
Generic Name:	modafinil
Sponsor:	Cephalon, Inc.
Approval Date:	07/29/2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-717/S-009

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter(s)	
Final Printed Labeling	
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-717/S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-717/S-009

Cephalon, Inc.
Attention: Paul Kirsch
Senior Director, Regulatory Affairs
145 Brandywine Parkway
West Chester, PA 19380-4245

Dear Mr. Kirsch:

Please refer to your Supplemental New Drug Application submitted on March 28, 2003, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Provigil® (modafinil) Tablets.

This supplement provides for a new formulation of the drug product, manufacturing changes, and the addition of a new site, [ ] for manufacturing, testing, packaging and labeling of the reformulated drug product.

We acknowledge receipt of your amendments dated June 13, 17 and 18, 2003.

We have completed our review of this supplement and the application is approved.

We also wish to forward the following additional advice for future submissions:

1. Please note that the dissolution test should only use one tablet per vessel rather than two, to allow for the evaluation of the quality of each tablet.

2. In the future, the highest tablet strength, rather than the highest dose, should be used in bioequivalence studies.

If you should have any questions, please call Ms. Anna Marie H. Weikel, Senior Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
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/

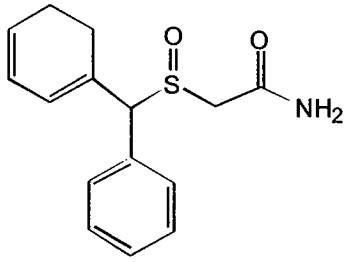
Thomas Laughren
7/29/03 07:54:02 AM
Signed for Russell Katz, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-717/S-009

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-120 DNDP	2. NDA NUMBER 20-717
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Cephalon, Inc. 145 Brandywine Parkway West Chester, PA 19380-4245		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG PROVIGIL®	7. NONPROPRIETARY NAME Modafinil	SCF-009 / 3/31/2003
8. SUPPLEMENT PROVIDES FOR: multiple changes including drug product formulation change, manufacturing process change, a new DP manufacturing site, and corresponding labeling changes.		9. AMENDMENTS DATES Facsimile of 7/10/03 (updated stability data)
10. PHARMACOLOGICAL CATEGORY Narcolepsy	11. HOW DISPENSED Rx √ OTC	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Tablets	14. POTENCY 100 and 200 mg/tablet	
15. CHEMICAL NAME AND STRUCTURE 2-[(Diphenylmethyl)sulfinyl]acetamide 		16. RECORDS AND REPORTS CURRENT YES √ NO ___ REVIEWED YES √ NO ___
17. COMMENTS See review notes.		
18. CONCLUSIONS AND RECOMMENDATIONS APPROVABLE for chemistry provided the sponsor submits the multi-point dissolution data for the reformulated product manufactured at the new site, [ ] (refer to comments in the OCPB review of S-009).		
NAME Chengyi Liang, Ph.D.	SIGNATURE	DATE COMPLETED 7-17-2003

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: C.Y. Liang (HFD-150) Revised by M. Guzewska	CSO: M. Mille, HFD-120	Chemistry Team Leader M. Guzewska (HFD-120)

Redacted 11 page(s)

of trade secret and/or

confidential commercial

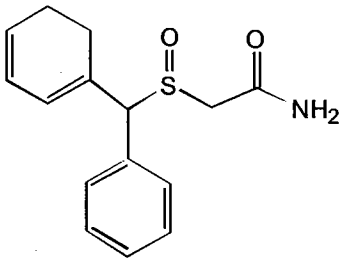
information from

Chemistry Review #1

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

/s/

Maryla Guzewska
7/17/03 01:50:00 PM
CHEMIST

CHEMIST'S REVIEW	1. ORGANIZATION HFD-120 DNDP	2. NDA NUMBER 20-717
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Cephalon, Inc. 145 Brandywine Parkway West Chester, PA 19380-4245		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG PROVIGIL®	7. NONPROPRIETARY NAME Modafinil	SCF-009 | 3/28/2003
8. SUPPLEMENT PROVIDES FOR: multiple changes including drug product formulation change, manufacturing process change, a new DP manufacturing site, and corresponding labeling changes.		9. AMENDMENTS DATES 17-JUL-03
10. PHARMACOLOGICAL CATEGORY Narcolepsy	11. HOW DISPENSED RX √ OTC	12. RELATED IND/NDA/DMF IND 42,873
13. DOSAGE FORM(S) Tablets	14. POTENCY 100 and 200 mg/tablet	
15. CHEMICAL NAME AND STRUCTURE 2-[(Diphenylmethyl)sulfinyl]acetamide 		16. RECORDS AND REPORTS CURRENT YES √ NO ___ REVIEWED YES √ NO ___

17. COMMENTS

This is a review #2 of S-009. Dissolution results in multiple media (Case C dissolution) for the DP made in [redacted] were submitted on July 17, 2003, and reviewed by the OCPB reviewer on July 18, 2003. The similarity of the dissolution profiles supports the SUPAC level II equipment change and level III site change for the [redacted] site. The OCPB found the additional data for the [redacted] site acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVAL of S-009 is recommended

NAME	SIGNATURE	DATE COMPLETED
Maryla Guzewska, Ph.D.		7-28-2003

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: M. Guzewska	CSO: M. Mille, HFD-120	Chemistry Team Leader M. Guzewska

Appears This Way
On Original

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

/s/

Maryla Guzewska
7/28/03 10:29:23 AM
CHEMIST

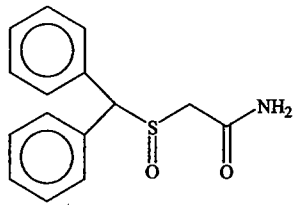
Maryla Guzewska
7/28/03 10:30:18 AM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **20-717**
4. SUPPLEMENT NUMBERS/DATES: **SCF-009(FA)**
   letterdate: 8-JAN-2004
   stampdate: 9-JAN-2004
5. AMMENDMENTS/REPORTS/DATES:
6. RECEIVED BY CHEMIST: 17-MAR-2004

7. APPLICANT NAME AND ADDRESS: Cephalon, Inc.
   145 Brandywine Parkway
   West Chester, PA 19380.

8. NAME OF DRUG: Provigil®
9. NONPROPRIETARY NAME: modafinil
10. CHEMICAL NAME/STRUCTURE: 2-[(diphenylmethyl)sulfinyl]acetamide
    CAS registry # [68693-11-8]



11. DOSAGE FORM(S): Tablets

12. POTENCY: 100, 200 mg
13. PHARMACOLOGICAL CATEGORY: Treatment of narcolepsy and hypersomnia

14. HOW DISPENSED: XXX (RX) ___ (OTC)
15. RECORDS & REPORTS CURRENT: XXX (YES) ___ (NO)
    SPECIAL PRODUCTS ___ (YES) XXX (NO)
16. RELATED IND/NDA/DMF:

17. **SUPPLEMENT PROVIDES FOR:** Final Printed Labeling for the commercial labels for 100-count, 100 mg; 100-count, 200 mg, and the package insert.

18. **COMMENTS**: A reformulation of Provigil drug product was approved in July 2003 (SCF-009). The package insert ingredients list was updated to reflect this. The barcode and NDC numbers in the package insert and on the bottle labels for the two dosage forms were similarly updated.

19. CONCLUSIONS AND RECOMENDATIONS: The final printed labeling is acceptable.

20. REVIEWER NAME SIGNATURE DATE COMPLETED

David J. Claffey, Ph.D. _____ 14-APR-2004

cc: Orig. NDA 20-717
HFD-120/DivFile
HFD-120/MMille
HFD-120/DClaffey
INT: MG

filename: N 20-717(SCF-009-FA) Provigil modafinil.doc

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review #3

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

/s/

David Claffey
4/15/04 02:59:43 PM
CHEMIST

Maryla Guzewska
4/15/04 03:02:37 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-717/S-009

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-717 (SCF-009)
Brand Name:	Provigil
Generic Name:	Modafinil
Type of Dosage Form:	Oral Tablets
Strengths:	100 mg, 200 mg
Indications:	Narcolepsy
Type of Submission:	CMC Supplement
Sponsor:	Cephalon Inc.
Submission Dates:	March 28, 2003 June 13, 2003
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This NDA review evaluates *in vivo* and *in vitro* data regarding PROVIGIL tablets (100 mg and 200 mg). The Sponsor has submitted data to support a SUPAC level III formulation change at [ ] will not continue to manufacture the drug product. Therefore, the Sponsor has submitted documentation to link the [ ] site and the [ ] site, supporting the manufacture of the reformulated drug product at the current [ ] site. Addition of a new site [ ] also involves a SUPAC level II equipment change, for which supporting data has not been submitted.

The pivotal bioequivalence study demonstrated bioequivalence between the proposed formulation and the current formulation of the 200 mg strength tablets of PROVIGIL [ ]. Dissolution studies demonstrated similar dissolution profiles between the proposed formulation of the 100 mg and 200 mg strength tablets [ ] that are compositionally proportional. Therefore the Office of Clinical Pharmacology and Biopharmaceutics recommends a biowaiver for the 100 mg strength tablets of the proposed formulation.

Dissolution studies conducted in the approved medium and using the approved methods met the regulatory specification for PROVIGIL tablets for all lots tested. Similarity of the dissolution profiles of specific lots of the current and proposed formulations supports the change in formulation ([ ] and [ ]).

There are no proposed labeling changes related to the Clinical Pharmacology section of the label.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the submitted data in NDA 20-717/S-009 for PROVIGIL acceptable for the [redacted] and [redacted] products. However, there is insufficient data to support the equipment change associated with the [redacted] product. Therefore the OCPB does not find the data submitted for the [redacted] product acceptable.

Please forward the Comments to Sponsor (found in section 3.2) to the Sponsor.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 20-717 (S009)
CSO/ A. Homonnay
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta, C. Sahajwalla

2 Table of Contents

3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

PROVIGIL (modafinil) is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy (NDA 20717). It is available as immediate release tablets (100 mg and 200 mg) and is given once daily. The usual dose is 200 mg/day. The labeling states that doses of 400 mg/day have been well tolerated but that there is no consistent evidence of additional benefit beyond that of the 200 mg dose.

According to the PROVIGIL label, modafinil (a racemic mixture) has an elimination half-life of approximately 15 hours after multiple doses, with steady state reached after 2-4 days of dosing. The enantiomers of modafinil demonstrate linear kinetics after multiple dosing of 200-600 mg once daily in healthy volunteers. The major route of elimination is via hepatic metabolism. Two metabolites, modafinil acid and modafinil sulfone, reach appreciable plasma concentrations, although they do not appear to be involved in the pharmacologic activity of modafinil. Modafinil is metabolized in part via CYP3A4 that appears to be a primary pathway for formation of modafinil sulfone according to the OCPB review of NDA 20-717 (November 1997). According to that review, the formation of modafinil acid does not appear to involve a P450. Modafinil induces CYP3A4. Modafinil inhibits CYP2C19, and in hepatocytes has resulted in concentration-related suppression of CYP2C9.

The Office of Clinical Pharmacology and Biopharmaceutics previously reviewed the proposed documentation that was submitted 7/19/99 and recommended that the formulation changes fall under Level 3 in the Components and Composition section identified under SUPAC (due to adding or deleting an excipient), requiring dissolution documentation and in vivo bioequivalence documentation. It was suggested that the Sponsor could perform a biostudy with the 200 mg strength tablets, and request the approval of the reformulated 100 mg tablets on the basis of dissolution profile testing, as the two strengths appear to be compositionally proportional.

3.2 Current Submission

The purpose of the present submission is to support a new formulation of the drug product for Provigil tablets (100 mg and 200 mg). This formulation change has been made at the [ ] site and at the [ ] site (both are approved sites for current formulation). The supporting documentation includes a bioequivalence study at the [ ] site and Case B dissolution profile comparison for the proposed and current formulations at the [ ] site, as well as a Case B dissolution profile linking the new formulation at the [ ] site and at the [ ] site. Finally the Sponsor has requested addition of an additional site, [ ] for which there is an equipment change in addition to a site change.

The following table summarizes the changes that have been submitted in the present supplement and the documentation that is required. The [ ] and [ ] sites manufacture the new formulation.

Change	SUPAC Change	Required Dissolution/BE Documentation
New Formulation for 100 mg and 200 mg tablets ([ ] site)	Level III change in Components and Composition	• Case B dissolution profile Comparison for proposed and current formulation (Multipoint dissolution profile in compendial medium) • Full BE study (based on compositional proportionality, the 100 mg strength could be evaluated on the basis of dissolution profile testing)
Same Formulation Change as Above ([ ] site)	Linked new formulation at [ ] to [ ] (falls under level III site change)	• Case B dissolution profile • BE documentation not required
Site Change and Equipment Change ([ ] to [ ])	Level III site change Level II equipment change Minor in process change	• Case C dissolution profile (multipoint dissolution profiles in multiple media for proposed and current formulations) • BE documentation not required

The following clinical pharmacology studies have been submitted and reviewed:

- C1538c/411/BE/US – Pivotal bioequivalence study of the highest strength tablets
- Dissolution Documentation

The bioanalytical methods were validated and documented appropriately.

The key findings with respect to the clinical pharmacology and biopharmaceutics of the new formulation of PROVIGIL tablets are as follows:

- Bioequivalence was demonstrated for the proposed aqueous formulation relative to the current [ ] formulation of PROVIGIL 200 mg strength tablets after administration of a single oral dose of 400 mg (2 x 200 mg tablets). The new formulation was the same lot as used in the dissolution studies. The Sponsor has not stated the rationale for using a 400 mg dose, although the reviewer notes that the Sponsor collected samples for analysis of the metabolites as well as for the parent

compound, and the present analytical assay is limited with regard to the sensitivity for measuring the sulfone metabolite.

- Dissolution studies were conducted in the approved medium using the approved methods. The dissolution performance for all lots tested met the regulatory specification for PROVIGIL tablets.

- Dissolution profiles comparing the current commercial formulation ([ ]; full scale commercial lot) and the proposed formulation ([ ]; same lot as used in the bioequivalence study) of the 200 mg strengths were similar using the approved method, as were the dissolution profiles comparing the current commercial formulation ([ ]; full scale commercial lot) and the proposed formulation ([ ]) of the 100 mg strengths. This supports the change in formulation.

- Comparison of the dissolution profiles of the proposed formulation of the 200 mg strength ([ ]; same lot as used in the bioequivalence study) and the proposed 100 mg tablets ([ ]) were similar (as calculated by the reviewer). This supports a biowaiver of the lower strength [ ] tablets.

- Dissolution profiles comparing either strength of the proposed formulation at [ ] and [ ] were similar. This, along with the *in vivo* bioequivalence study for the formulation change at the [ ] site, supports the new formulation to be manufactured at [ ]

- There are no proposed labeling changes related to the Clinical Pharmacology section of the label.

- The equipment change from the [ ] to the [ ] site is a SUPAC Level II change for which the Sponsor has not provided the required dissolution documentation. The product from the [ ] site is therefore not acceptable.

The Office of Clinical Pharmacology and Biopharmaceutics finds that the submitted data in NDA 20-717/S-009 are acceptable only for the [ ] and [ ] sites. The submitted data for the [ ] site are not acceptable.

Please forward the comments below to the Sponsor.

Comments to Sponsor:

1. The change from [ ] to [ ] also involves a SUPAC Level II equipment change. This change requires Case C dissolution documentation involving multi-point dissolution profiles in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. The dissolution profiles of the proposed and currently used formulations should be similar. Please refer to the Guidance for Industry entitled

"Immediate Release Solid Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation" that can be found at http://www.fda.gov/cder/guidance/cmc5.pdf.

2. In the future, to link different strength tablets in an *in vitro* dissolution study, the Sponsor should note that the dissolution test should use only 1 tablet per vessel, rather than dissolving 2 tablets per vessel. This allows for evaluation of the quality of each individual tablet.

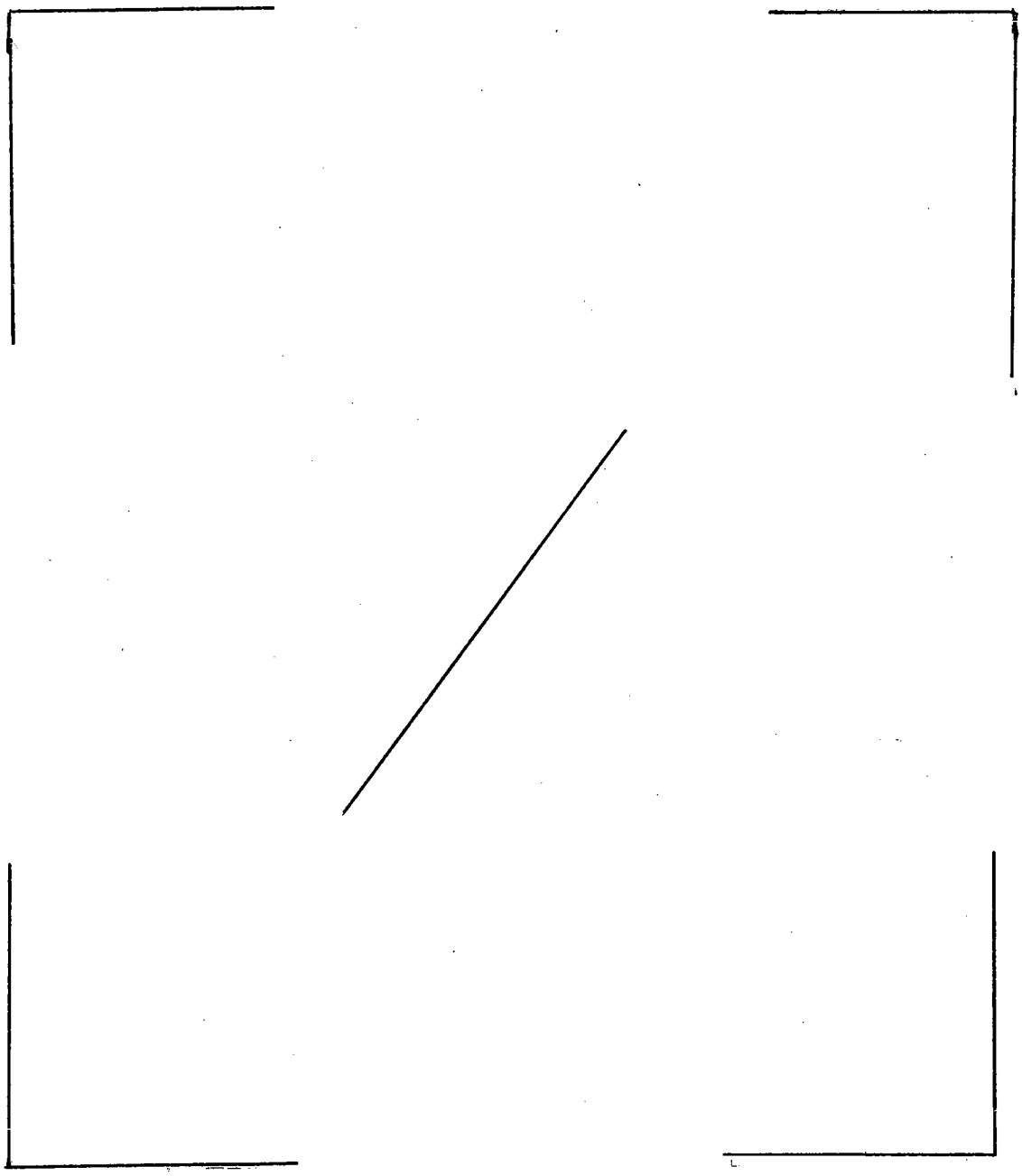
3. In the future, the Sponsor should note that the highest strength tablet (rather than the highest dose) should be used in bioequivalence studies.

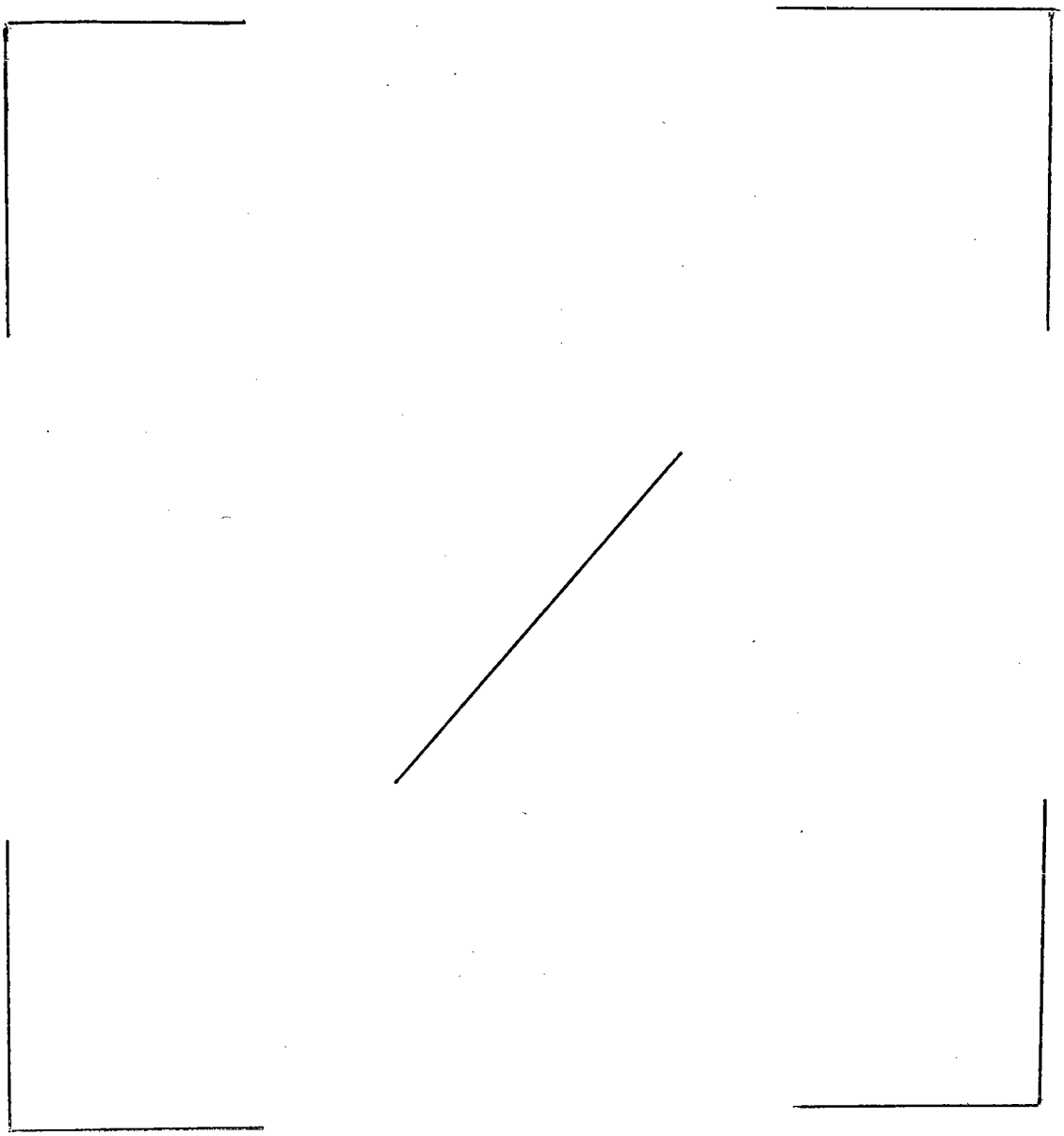
4 Appendices

4.1 Bioanalytical Methodology

Bioanalytical Method for Modafinil and Metabolites in NDA 20-717

A high performance liquid chromatographic (HPLC) assay was developed and validated for determination of modafinil and its metabolites, modafinil acid and modafinil sulfone, in human plasma. [





In conclusion, the bioanalytical method used for analysis of plasma samples in the clinical studies in this NDA 20-717 supplement is considered adequately documented and validated.

4.2 Bioequivalence Study

AN OPEN-LABEL, RANDOMIZED, TWO-WAY CROSSOVER STUDY TO COMPARE THE RELATIVE BIOAVAILABILITY AND BIOEQUIVALENCE OF TWO ORAL TABLET FORMULATIONS OF PROVIGIL

Study Investigators and Site:

[redacted]

Protocol Number: C1538c/411/BE/US

OBJECTIVES:

To evaluate the bioavailability of a new aqueous formulation (Formulation B, test) relative to the current [redacted] formulation (Formulation A, reference) of PROVIGIL (modafinil) 200 mg strength tablets after administration of a single 400 mg oral dose.

FORMULATIONS:

Table 1. Products used in C1538c/411/BE/US

	Package Lot Number	Dose Form Lot Number	Date of Manufacture (Dates of Study)
Test Product (T) Modafinil 200 mg tablets [redacted]	823203	1538-FL19-2	3/10/98 (1/99-7/20/99)
Reference Product (R) Modafinil 200 mg tablets [redacted]	729501	087645	10/8/97 (1/99-7/20/99) Expiry Date: [redacted] months

The batch size for the test product was [redacted] and the [redacted] was [redacted] into multiple tablet strengths that included [redacted] tablets for the 200 mg strength. The proposed commercial batch size is [redacted]. Stability data for the test product suggests stability (by HPLC assay and dissolution testing) at [redacted] months.

STUDY DESIGN:

This study was an open-label, randomized, 2-period, 2-treatment, 2-sequence crossover study, as shown in Table 1, below. For Treatment A, subjects received modafinil Formulation A 400 mg (2x200 mg) as a single dose (reference, R). For Treatment B, subjects received modafinil Formulation B 400 mg (2x200 mg) as a single dose (test, T). There was a minimum interval of 7 days and no more than 21 days between

administration of each formulation. The 200 mg strength is the highest marketed strength of PROVIGIL. The 400 mg dose is the highest dose in the labeled dose range.

Table 2. Treatment Sequence in C1538c/411/BE/US

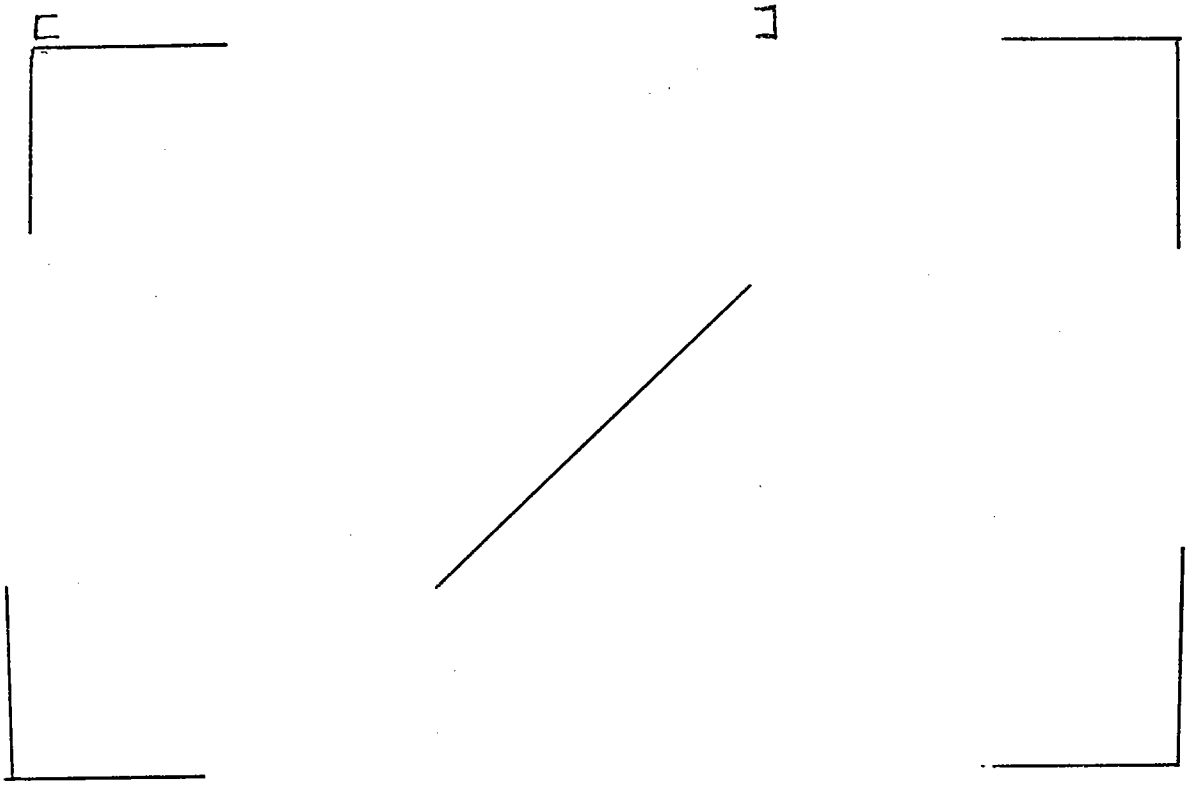
Sequence Number	Treatment Period 1	Treatment Period 2
1	A (R)	B (T)
2	B (T)	A (R)

Inclusion criteria included healthy nonsmoking males, 18 to 45 years of age (inclusive). Exclusion criteria included prior experience with modafinil, use of prescribed systemic or topical medication within 4 weeks of the start of dosing or any systemic or topical nonprescription medications within 2 weeks of the start of dosing, treatment agents such as barbiturates, phenothiazines, or cimetidine known to alter major organs or systems within 4 weeks of the start of dosing, history of alcohol, narcotic, or drug abuse, had clinically significant excessive consumption of coffee, tea, or other caffeine-containing beverages or food within 14 days prior to the first dose.

After overnight fast, subjects were administered a single 400 mg (2x200 mg tablets) oral dose of modafinil with 180 ml of water on each of two dosing occasions. Subjects continued to fast until 4 hours following the dose, except for 200 ml water at 1 hour before and 2 and 4 hours after dosing. Caffeine intake was restricted to 1 cup of tea or coffee with meals while subjects were in the clinic. Subjects remained in the clinic for at least 24 hours after dosing, and returned to the clinic for the last three assessments. Blood samples were collected for drug assay at predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 36, 48, and 60 hours of dosing.

ASSAY:

The study included determination of plasma concentrations of the parent and metabolites modafinil acid and modafinil sulfone. However, since these metabolites are not considered to contribute to the pharmacologic activity of modafinil, their concentrations have not been evaluated in the present review, since measurement of only parent drug is generally recommended in this case (Draft Guidance for Industry: "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations", July 2002).



RESULTS:

Demographics

Twenty-four male subjects were enrolled in the study. Twenty-two subjects completed the entire study and were eligible for pharmacokinetic analysis. One subject was discontinued due to death from accidental injury and a second subject was discontinued due to a protocol violation. Demographics of the subjects completing the study are shown below.

Table 4. Demographics of Subjects Completing the Study

Mean Age (Range)	Weight (mean ± SD)	Race
31 (22-45)	76.8 ± 11.1 kg	Asian 1 Black 2 Caucasian 17 Hispanic 2

Pharmacokinetics

Pharmacokinetic parameters were determined using noncompartmental analysis. The plasma concentration time course and the pertinent pharmacokinetic parameters for modafinil are shown in Figure 1 and Tables 5 and 6, below.

Figure 1. Mean Plasma Concentration Time Course for Modafinil after Administration of Test (open circles) or Reference (solid squares) Formulations (as provided by Sponsor).

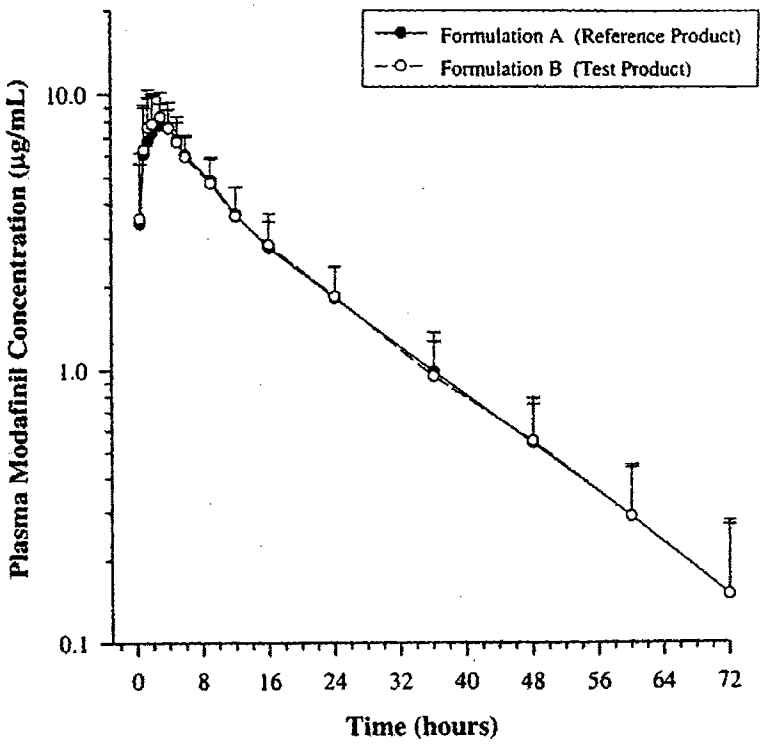


Table 5. Pharmacokinetic Parameters (Arithmetic Mean) for Modafinil (Study C1538c/411/BE/US)

	Test (Formulation B) (% CV) n=22	Reference (Formulation A) (% CV) n=22
Modafinil		
t_{max} (h)[a,b]	3.0 (1.00-5.00)	2.0 (1.00-6.00)
C_{max} (µg/mL)	9.2 (22)	9.2 (22)
AUC $_{0-t}$ (µg*h/mL)	133.3 (23)	132.4 (22)
AUC $_{0-\infty}$ (µg*h/mL)	137.3 (24)	136.5 (22)
λ_z (hr^{-1})	0.05 (17)	0.05 (15)
$t_{1/2}$ (hr)	13.6 (16)	13.6 (15)

[a] median (range)
[b] calculated by reviewer

Table 6. Bioequivalence Assessment for Study C1538c/411/BE/US

	Geometric Mean		Ratio of Geometric Means[a]	90% CI for the Ratio of Geometric Means
	Test (Formulation B)	Reference (Formulation A)		
Modafinil				
C_{max} (µg/ml)	9.0	9.0	0.99	(0.90, 1.09)
AUC $_{0-t}$ (µg*h/mL)	130.0	129.5	1.00	(0.96, 1.05)
AUC $_{0-\infty}$ (µg*h/mL)	133.8	133.4	1.00	(0.96, 1.04)

[a]calculated by reviewer

Reanalysis of the data by the reviewer was in agreement with that provided by the sponsor regarding the pharmacokinetic parameters for modafinil as well as the bioequivalence of the test and reference compounds.

The 90% confidence intervals on the geometric means of the C_{max}, AUC $_{0-t}$, and AUC_{0-24} ratios are within the bioequivalence interval of 0.8 to 1.25 for modafinil.

Safety

Treatment-emergent adverse events were reported in 54% of subjects following administration of Formulation A (reference) and in 45% following administration of Formulation B (test). The adverse effect profiles for the test and reference products were similar, except that a larger percentage of subjects reported nervousness after Formulation A (reference, 13%) than after Formulation B (test, 0%). The most common adverse events that were considered possibly or probably related to study medication were headache, asthenia, nausea, nervousness, dizziness, insomnia, confusion, and paresthesia.

CONCLUSIONS:

This study demonstrated bioequivalence between the new aqueous formulation (Formulation B, test) relative to the current [ ] formulation (Formulation A, reference) of PROVIGIL (modafinil) 200 mg strength tablets manufactured at the [ ] site after administration of a single 400 mg oral dose.

The 400 mg dose of modafinil used in the present study utilized 2 x 200 mg tablets (the highest strength tablet). The dose of 400 mg is within the labeled dose range, although the label states that there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose. The Sponsor has not identified the reason for using the 400 mg dose, although this dose would have allowed for greater characterization of the pharmacokinetics of the sulfone metabolite than would a lower dose, using the present analytical assay. In the future, the Sponsor should note that the highest strength tablet should be used in bioequivalence studies.

Since modafinil is neither a substrate nor an inhibitor of CYP1A2, the inclusion of caffeine in the present study is unlikely to have had an impact on the pharmacokinetic results. However, xanthine or caffeine-containing foods and beverages are generally

restricted in these types of studies from prior to the study period until after the last blood sample is collected. In addition, the sponsor should note that in BA and BE studies study drug is generally administered with 240 ml of water. The Sponsor should take this into consideration in future studies.

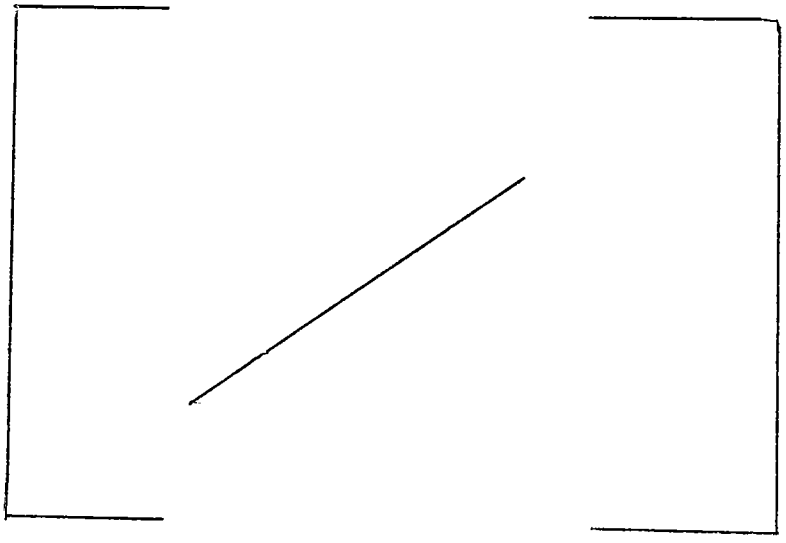
4.3 Dissolution Studies

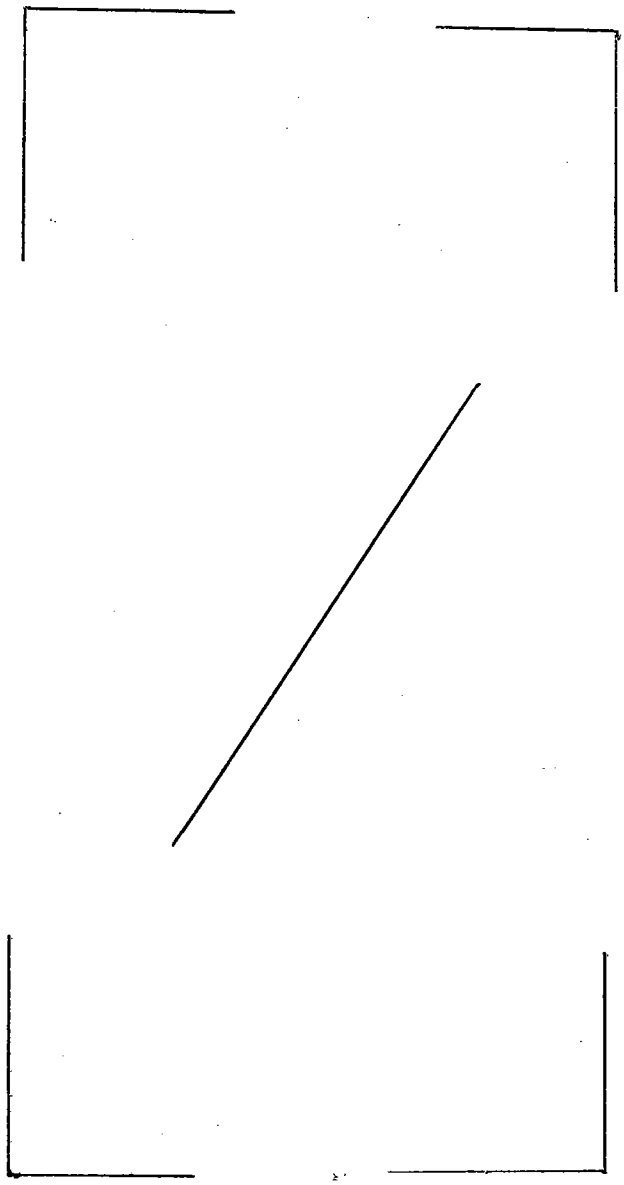
PROVIGIL DISSOLUTION - *IN VITRO* COMPARATIVE RESULTS

Rationale for Evaluation Methodology

The Sponsor has submitted *in vitro* dissolution studies to support a new formulation (proposed aqueous formulation compared to current [ ] formulation) of the 100 mg and 200 mg strengths of the drug product for PROVIGIL Tablets. In addition, the site for manufacturing, testing, packaging, and labeling of the reformulated product has changed such that [ ] will be removed as a site, the new formulation will be made at the [ ] site (a current site), and [ ] will be added as a new site (a level III site change). The Sponsor has submitted *in vitro* dissolution studies as documentation that link the new formulation at the [ ] site and the [ ] site, as well as dissolution studies to support a level III site change for the [ ] site.

The [ ] step during manufacturing has been changed. This involves an equipment change to allow for either [ ] and [ ]) or the [ ] ([ ]). The Table below (as provided by Sponsor) compares the equipment used in the manufacturing process at each site. The accompanying Figure below (as provided by Sponsor) outlines the manufacturing process, comparing the [ ] [ ] Based on these comparisons, the Office of Clinical Pharmacology and Biopharmaceutics, after consultation with the Office of New Drug Chemistry, has determined that this change involves a SUPAC Level II equipment change and a minor process change (since the same [ ] [ ]





Proposed changes in formulation were previously reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (September 1999) that concluded that the changes corresponded to SUPAC Level III changes in Components and Composition due to deleting or adding an excipient. Therefore it was recommended that dissolution documentation would require a multi-point dissolution profile on at least 12 individual dosage units in the NDA approved medium at 15, 30, 45, 60, and 120 minutes, with dissolution profiles being similar between the biobatches of reformulated and current products.

The following table summarizes the proposed changes and the documentation that is required to support those changes.

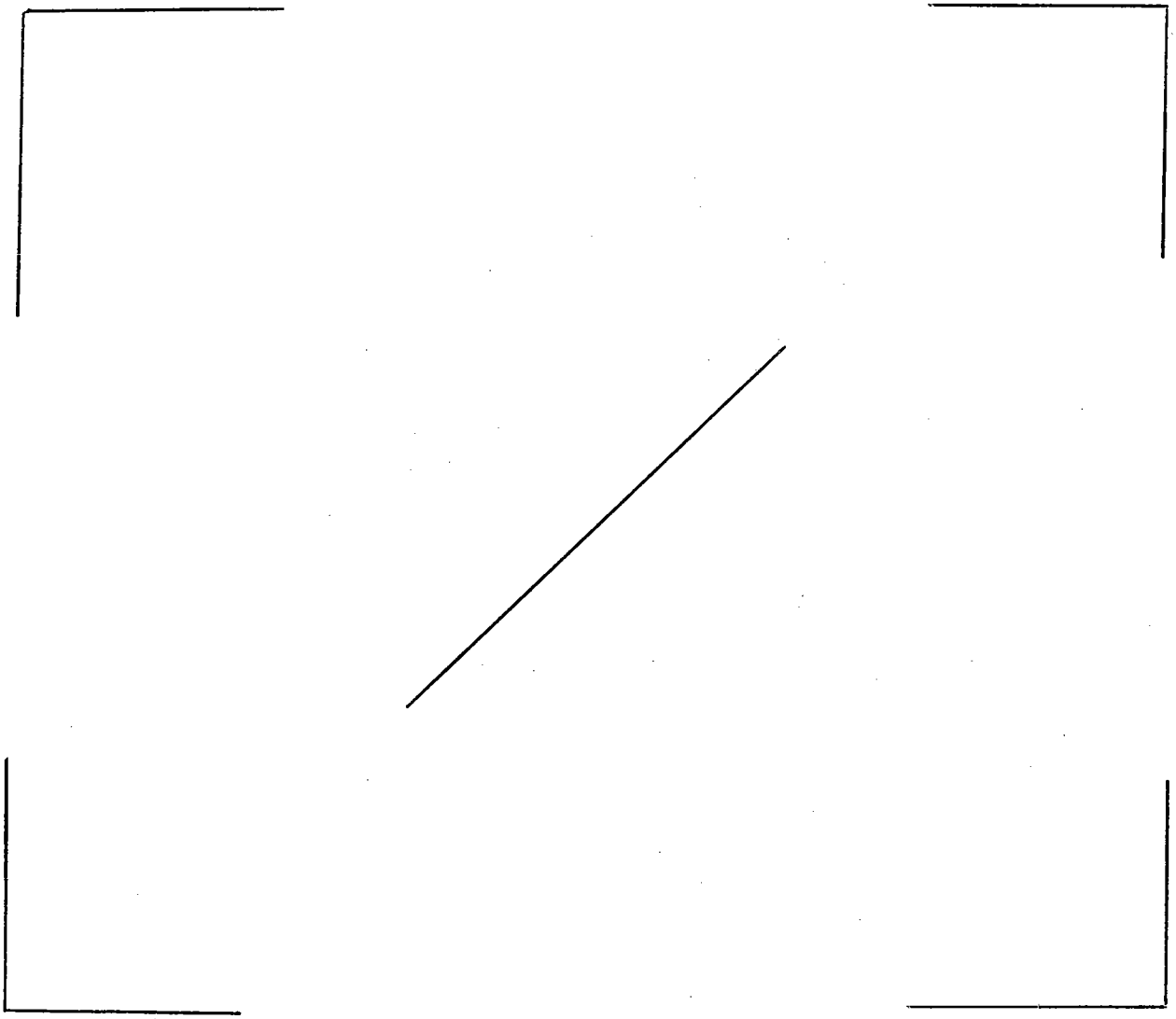
Change	**SUPAC Change**	**Required Dissolution/BE Documentation**
New Formulation for 100 mg and 200 mg tablets ([ ] site)	Level III change in Components and Composition	• Case B dissolution profile Comparison for proposed and current formulation (Multipoint dissolution profile in compendial medium) • Full BE study (based on compositional proportionality, the 100 mg strength could be evaluated on the basis of dissolution profile testing)
Same Formulation Change as Above ([ ] site)	Linked new formulation at [ ] to [ ] (falls under level III site change)	• Case B dissolution profile • BE documentation not required
Site Change and Equipment Change ([ ] to [ ])	Level III site change Level II equipment change Minor in process change	• Case C dissolution profile (multipoint dissolution profiles in multiple media for proposed and current formulations) • BE documentation not required

Lot Summary

Lot #	Strength	Manufacturer (Date of Manufacture)	Description
730003	100 mg	[ ] (10/6/97)	Current Commercial Formulation; Full Scale Commercial Lot
806902	200 mg	[ ] (2/10/98)	Current Commercial Formulation; Full Scale Commercial Lot (*not the same as used in the bioavailability study*)
809001	100 mg	[ ] (3/10/98)	Proposed Formulation
823203	200 mg	[ ] (3/10/98)	Proposed Formulation (*same as used in the bioavailability study*)
F1125B004	100 mg	[ ] (3/5/02)	Proposed Formulation
F1126B002	200 mg	[ ] (3/4/02)	Proposed Formulation
2J3003	100 mg	[ ] (10/9/02)	Proposed Formulation
2J3004	200 mg	[ ] (10/9/02)	Proposed Formulation

Composition of Current and Proposed Formulations

The tablet below shows the composition of the current and proposed formulations of both the 100 mg and 200 mg strength tablets. The changes in formulation involve addition or deletion of excipients. In addition, it can be seen that the 100 mg and 200 mg strength tablets are compositionally proportional.



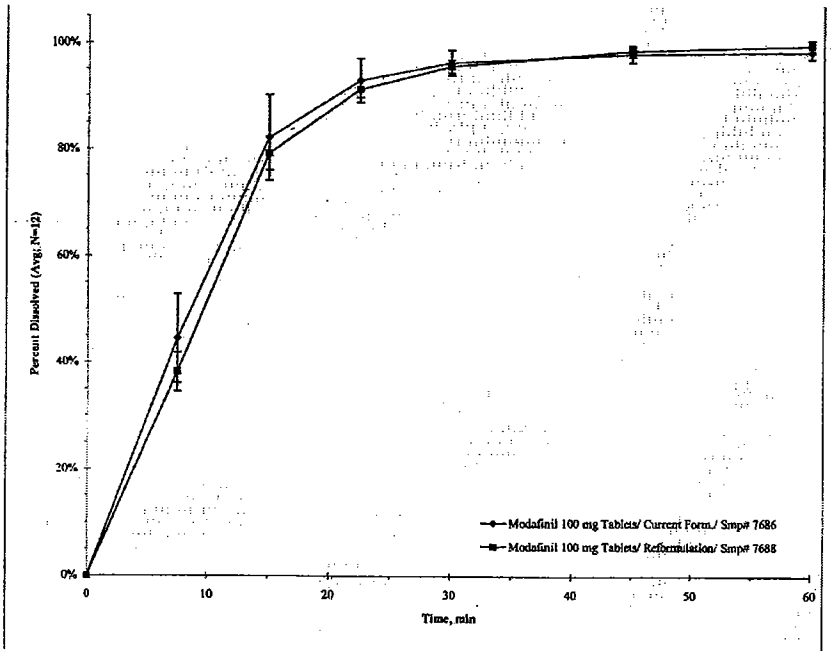
Approved Dissolution Method and Specification

The approved dissolution method (NDA 20-717) is USP Dissolution Apparatus II, paddle speed of 50 rpm, in 900 ml 0.1 N HCl dissolution medium. The Specification is not less than[ ]% in 45 minutes.

Dissolution of Proposed vs. Current Formulation ([ ])

The current and proposed formulations ([ ]) of the 100 mg strength (lots 73003 and 809001) were evaluated using an *in vitro* dissolution comparison in 5 media (water; 0.1 N HCl; pH 2.0, 50 mM KCl; pH 6.4 50 mM phosphate; and pH 7.4, 50 mM phosphate). The dissolution conditions were Apparatus II, paddle speed of 50 rpm, 900 ml of medium, at 37 C. Dissolution profiles were generated for 12 tablets of each formulation. Sampling time points were 7.5, 15, 22.5, 30, 45, and 60 minutes.

Both products were more than / % dissolved by 22.5 minutes, allowing for consideration of measurements at the first 3 time points. The % CV (as calculated by reviewer) was less than 20% at 7.5 minutes and less than 10% at all other time points, allowing for the use of mean data. The comparative dissolution profiles in 0.1 N HCl are shown in the Figure below. The f_1 and f_2 values using a 3-point calculation (as calculated by Sponsor) in 5 different media are shown in the table below.

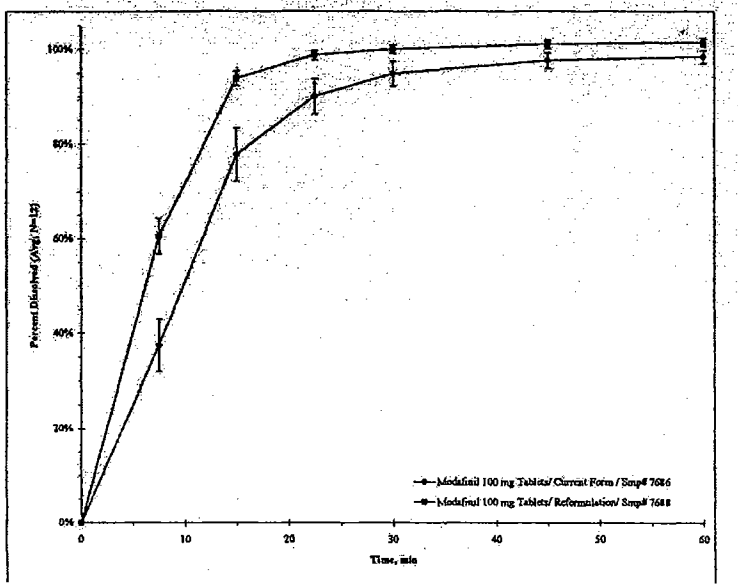


Dissolution of 100 mg modafinil tablets (current and reformulated) in 0.1 N HCl

Dissolution Comparison of Current and Proposed 100 mg Strength

Dissolution Medium	f_1 Parameter	f_2 Parameter
0.1 N HCl	5.0	68.7
Water	18.8	38.5
pH 2.0	4.9	70.2
pH 6.4	3.9	74.2
pH 7.4	7.0	60.6

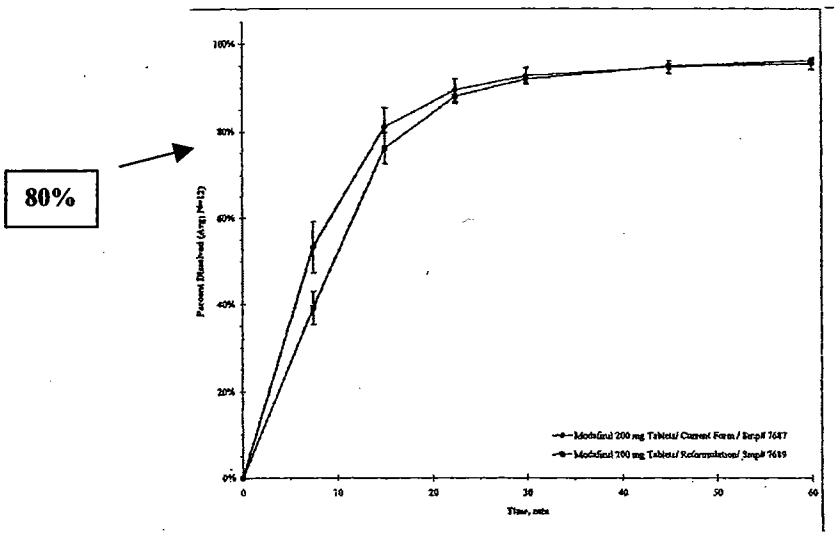
The results show that the two formulations of the 100 mg strengths were similar (f1 = 0-15, f_2 = 50-100) in the NDA approved medium (0.1 N HCl) and in pH 2.0, pH 6.4, and pH 7.4 medium, whereas the profiles obtained in water were not similar. (However, the 100 mg and 200 mg strengths have similar dissolution profiles in the approved medium and they are compositionally proportional). The profiles in water are shown below.



Dissolution of 100 mg modafinil tablets (current and reformulated) in water

The current and proposed formulations of the 200 mg strength (lots 806902 and 823203) were similarly evaluated. With this strength as well, both products were more than ✓ % dissolved by 22.5 minutes, allowing for consideration of measurements at the first 3 time points. The % CV was less than 20% at 7.5 minutes and less than 10% at all other time points, allowing for the use of mean data. The comparative dissolution profiles in 0.1 N

HCl are shown in the Figure below. The f_1 and f_2 values using a 3-point calculation (as calculated by Sponsor) in 5 different media are shown in the table below.



Dissolution Profiles of Modafinil 200 mg Tablets (Current and Reformulated) in 0.1 N HCl

Dissolution Comparison of Current and Proposed 200 mg Strength

Dissolution Medium	f_1 Parameter	f_2 Parameter
0.1 N HCl	9.1	53.0
Water	5.9	66.4
pH 2.0	5.9	67.2
pH 6.4	4.7	68.0
pH 7.4	6.5	62.5

The results show that the two formulations of the 200 mg strengths were similar (f1 = 0-15, f_2 = 50-100) in all media evaluated.

Dissolution of 100 mg vs. 200 mg Proposed Formulation at [ ]

This *in vitro* dissolution study was conducted to support a request for a biowaiver for the lower strength of the [ ] reformulated tablet. *In vivo* bioequivalence was evaluated for the current and reformulated [ ] tablets of the 200 mg strengths. As can be seen in the compositional tables above, the 100 mg and 200 mg strengths are proportionately similar in composition. The Sponsor has compared the previously generated dissolution profile for the 200 mg strength reformulated [ ] tablet (shown above) with an *in vitro* dissolution profile for the 100 mg strength reformulated tablet that was performed using 2 tablets per vessel. Since only 1 tablet per vessel should be used, this information was not used to compare the 100 and 200 mg strength tablets. However, the reviewer has

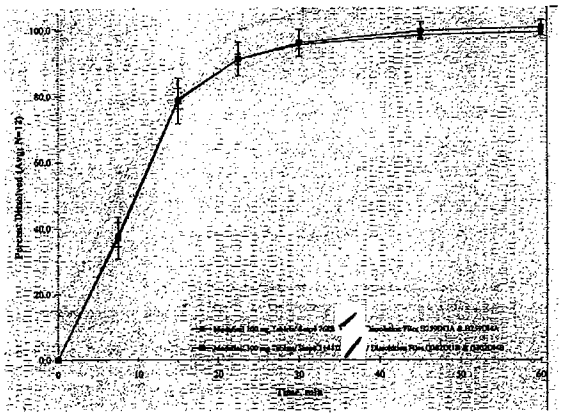
used the data from the appropriately conducted dissolution studies described above (comparing the current and reformulated products) to compare the profiles of the 100 mg strength and 200 mg strength tablets of the reformulated [ ] formulation.

As discussed above, mean data could be used, with consideration of measurements at the first 3 time points. The mean values at the first three time points (7.5, 15, and 22.5 minutes) were 38.3, 79.3, and 91.3 for the 100 mg tablets and were 39.2, 76.3, and 87.9 for the 200 mg tablets. The f1 and f2 values (as calculated by the reviewer) using a 3-point calculation in the approved medium, 0.1 N HCl, are 77.26 and 3.49, respectively. These results show that the profiles of the 100 mg strength and the 200 mg strength can be considered similar. Thus a biowaiver for the 100 mg strength of the proposed [ ] formulation can be granted.

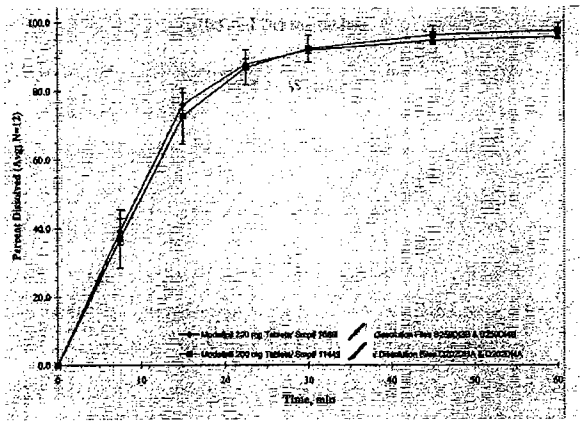
Dissolution of Proposed Formulation at [ ] vs. [ ]

Dissolution of both strengths (100 mg and 200 mg) of the proposed formulation were evaluated to compare two manufacturing sites: [ ] and [ ] that also used different manufacturing processes. This is a level III site change as well as a level II equipment change. The latter requires that dissolution testing be conducted at multiple points in the multiple media. The Sponsor has only evaluated dissolution for the [ ] product in the approved medium, and therefore this evaluation is not acceptable.

The following paragraph reviews the dissolution test that was conducted. The following dissolution conditions were used: Apparatus II at 50 rpm, 900 ml of medium at 37° C in 0.1 N HCl. Twelve tablets of each batch were evaluated. Sampling time points were 7.5, 15, 22.5, 30, 45, and 60 minutes. Both strengths of tablets manufactured at either site were more than [redacted]% dissolved by 22.5 minutes, allowing for consideration of measurements at the first 3 time points. The % CV was less than 10% at all time points for both strengths of the [ ] formulation. For the [ ] 100 mg strength the CV was less than 20% at 7.5 minutes and less than 10% at all other time points. For the [ ] 200 mg strength formulation the CV was 23.1% at 7.5 minutes. However it was 11.3% at 15 minutes, and less than 10% at the remaining time points. The comparative dissolution profiles in 0.1 N HCl are shown in the Figures below. The f_1 and f_2 values using a 3-point calculation (as calculated by Sponsor) were 0.9 and 95.0, respectively for the 100 mg strength tablets and 3.2 and 79.5, respectively for the 200 mg tablets. These profiles in 0.1 N HCl can be considered similar.



Dissolution of 100 mg strength tablets of [ ] vs. [ ] (as provided by Sponsor)

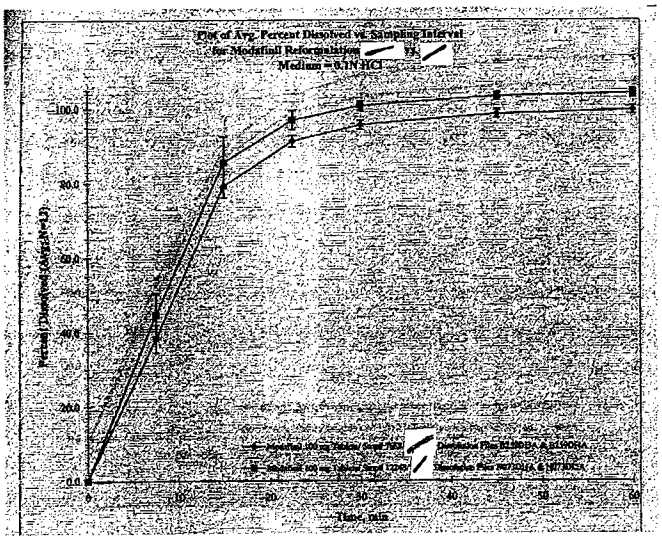


Dissolution of 200 mg strength tablets of [ ] vs. [ ] (as provided by Sponsor)

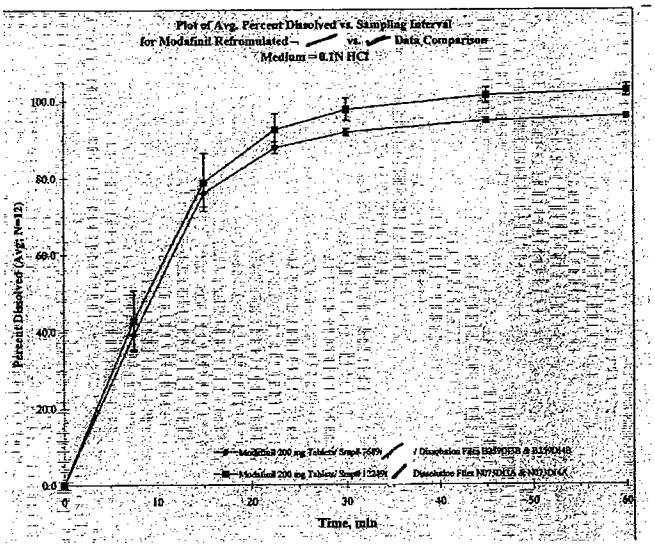
Dissolution of Proposed Formulation at [ ] vs. [ ]

Dissolution of both strengths (100 mg and 200 mg) of the proposed formulation were evaluated to compare two manufacturing sites: [ ] and [ ]. This is a level III site change for which dissolution testing may be conducted at multiple points in the compendial medium. The dissolution conditions were identical to those described above: Apparatus II at 50 rpm, 900 ml of medium at 37° C in 0.1 N HCl. Twelve tablets of each batch were evaluated. Sampling time points were 7.5, 15, 22.5, 30, 45, 52.5, and 60 minutes.

Both strengths of tablets manufactured at either site were more than / % dissolved by 22.5 minutes, allowing for consideration of measurements at the first 3 time points. The % CV was less than 10% at all time points for both strengths of the [ ] formulation. For both strengths of the [ ] formulation, the CV was less than 20% at 7.5 minutes and less than 10% at all other time points. The comparative dissolution profiles in 0.1 N HCl are shown in the Figures below. The f_1 and f_2 values using a 3-point calculation (as calculated by Sponsor) were 8.8 and 60.3, respectively for the 100 mg strength tablets and 5.5 and 70.2, respectively for the 200 mg tablets. Thus the profiles of either strength formulated at the [ ] and [ ] sites can be considered similar.



Dissolution of 100 mg strength tablets of [ ] vs. [ ] (as provided by Sponsor)



Dissolution of 200 mg strength tablets of [ ] vs. [ ] (as provided by Sponsor)

CONCLUSIONS:

Due to reformulation of modafinil 100 mg and 200 mg strength tablets, as well as changes in the site of manufacture and manufacturing equipment, *in vitro* dissolution studies were performed. The dissolution performance for all lots tested met the regulatory specification for Provigil tablets. (It should be noted that the lot of the current commercial formulation used in the dissolution tests was not the same lot as used in the bioequivalence study). The results show that for the [ ] product, the *in vitro* dissolution performance is comparable between the current (full scale commercial lots) and reformulated (proposed) tablets of either strength and that dissolution of the reformulated 100 mg and 200 mg strength tablets is comparable. The results also show that *in vitro* dissolution of both strengths of tablets manufactured at the [ ] site is comparable to that of tablets from the [ ] site. The required dissolution documentation for the equipment change ([ ] site) was not submitted, and therefore the product from the [ ] site cannot be considered to be adequately evaluated.

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

/s/

Sally Yasuda
7/16/03 02:04:48 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/16/03 02:15:48 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-717 (SCF-009) amendment
Brand Name:	Provigil
Generic Name:	Modafinil
Type of Dosage Form:	Oral Tablets
Strengths:	100 mg, 200 mg
Indications:	Narcolepsy
Type of Submission:	CMC Supplement, Additional Supporting Dissolution Data to Support [ ] Site
Sponsor:	Cephalon Inc.
Submission Dates:	July 17, 2003, July 18, 2003
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

Executive Summary

This review evaluates additional data submitted by the Sponsor on July 17, 2003 to support a SUPAC level II equipment change for the addition of a new site ([ ]).

Dissolution studies in multiple media (Case C dissolution) demonstrated similar dissolution profiles for the aqueous formulation from the [ ] site and the [ ] site for both the 100 mg and 200 mg strength tablets. The full review is found in the Appendix. The similarity of the dissolution profiles supports the SUPAC level II equipment change and level III site change for the [ ] site.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the additional data supporting the equipment change (and addition of new site) associated with the [ ] product acceptable.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 20-717 (S009)
CSO/ A. Homonnay
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta, C. Sahajwalla

Appendix
PROVIGIL DISSOLUTION - IN VITRO COMPARATIVE RESULTS

Rationale for Evaluation Methodology

The Sponsor has submitted *in vitro* dissolution studies to support a level II equipment change in the manufacturing process, comparing the product manufactured at [ ] to Patheon for a new formulation (proposed aqueous formulation) of the 100 mg and 200 mg strengths of the drug product for PROVIGIL Tablets. The [ ] step during manufacturing has been changed. This involves an equipment change to allow for either [ ] [ ] The Office of Clinical Pharmacology and Biopharmaceutics, after consultation with the Office of New Drug Chemistry, has determined that this change involves a SUPAC Level II equipment change and a minor process change (since the same [ ] [ ]). This change requires Case C dissolution documentation involving multi-point dissolution profiles in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the [ ] and [ ] products. (See OCPB review dated 7/16/03).

The Sponsor has submitted in vitro data comparing the [ ] formulation with the proposed aqueous formulation ([ ]), and data comparing the aqueous formulation ([ ]) with the aqueous formulation ([ ]). The data regarding the aqueous formulations will be reviewed here.

Dissolution of Proposed Formulation at [ ] vs. [ ]

Lot Summary

Lot #	Strength	Manufacturer (Date of Manufacture)	Description
809001	100 mg	[ ] (3/10/98)	Proposed Formulation *
823203	200 mg	[ ] (3/10/98)	Proposed Formulation* (*same as used in the bioequivalence study*)
F1125B004	100 mg	[ ] (3/5/02)	Proposed Formulation
F1126B002	200 mg	[ ] (3/4/02)	Proposed Formulation

* Proposed aqueous formulation at [ ] site was considered acceptable (see OCPB review of 7/16/03).

Dissolution profiles

The following paragraph reviews the dissolution test that was conducted. The following dissolution conditions were used: Apparatus II at 50 rpm, 900 ml of medium at 37° C. Twelve tablets of each batch were evaluated. Sampling time points were 7.5, 15, 22.5, 30, 45, and 60 minutes. Testing was performed in five media (0.1 N HCl; water; pH 2.0, 50 mM KCl; pH 6.4, 50 mM phosphate; and pH 7.4, 50 mM phosphate). The Sponsor states that dissolution studies were not conducted in pH 4.5 media due to interference by the buffer with the assay.

The 100 mg strength tablets manufactured at either site were more than ✓% dissolved by 22.5 minutes in pH 2.0, 50 mM KCl medium, allowing for consideration of measurements at the first 3 time points. In the other 4 media, 100 mg strength tablets manufactured at either site were more than ✓% dissolved by 30 minutes, allowing for consideration of measurements at the first 4 time points. The 200 mg strength tablets manufactured at either site were more than ✓% dissolved by 22.5 minutes in all media except 0.1 N HCl in which they were more than ✓% dissolved by 30 minutes. This allows for consideration of the first 3 times points for all media except 0.1 N HCl, for which the first 4 time points are considered.

The F1 and F2 parameters, as provided by the Sponsor, are shown in the table below.

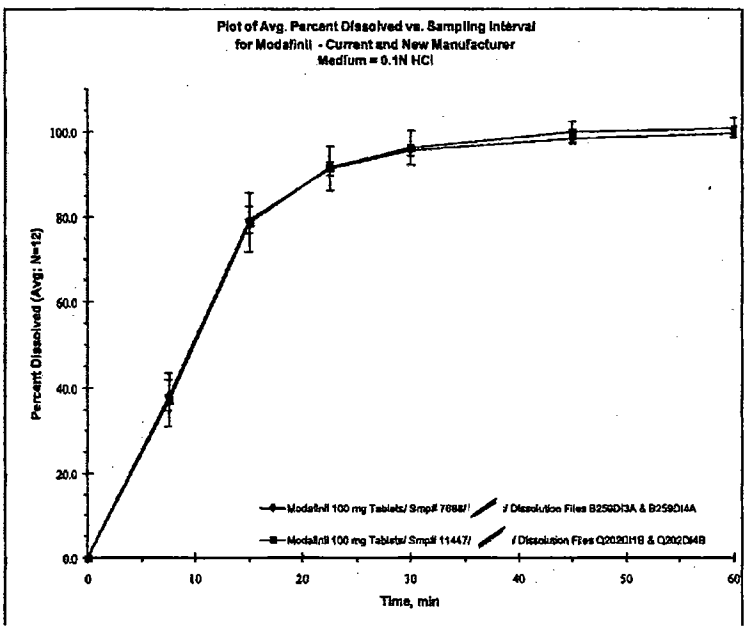
Table 1. F1 and F2 Parameters for Modafinil 100 and 200 mg tablets - Aqueous Formulation Produced at [ ] vs. Aqueous Formulation Produced at [ ] (as provided by Sponsor)

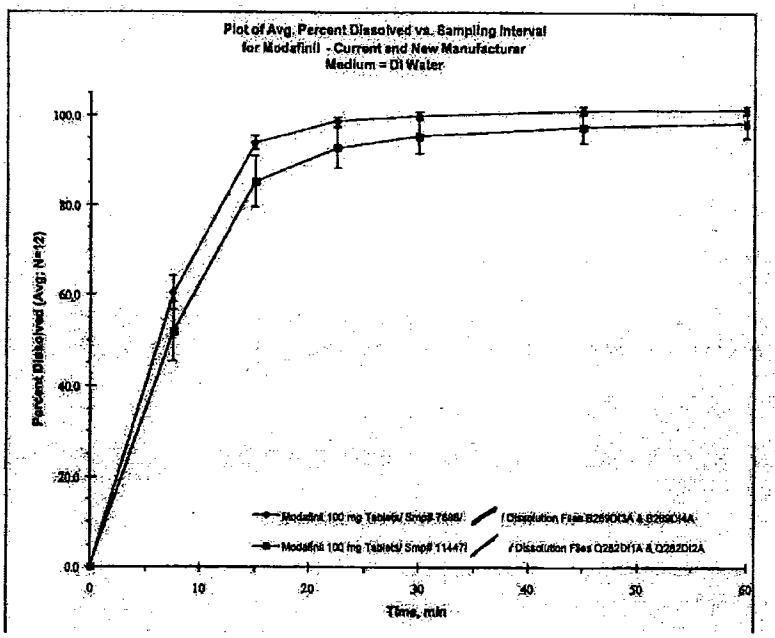
	100 mg Tablet		200 mg Tablet	
Dissolution Medium	F1 Parameter	F2 Parameter	F1 Parameter	F2 Parameter
0.1N HCl	0.9	95.0	3.2	79.5
Water	9.0	55.4	0.6	97.1
pH 2.0, 50 mM KCl	7.7	59.8	3.1	77.4
pH 6.4, 50 mM Phosphate	5.4	66.9	3.1	78.3
pH 7.4, 50 mM Phosphate	11.4	50.9	1.5	90.8

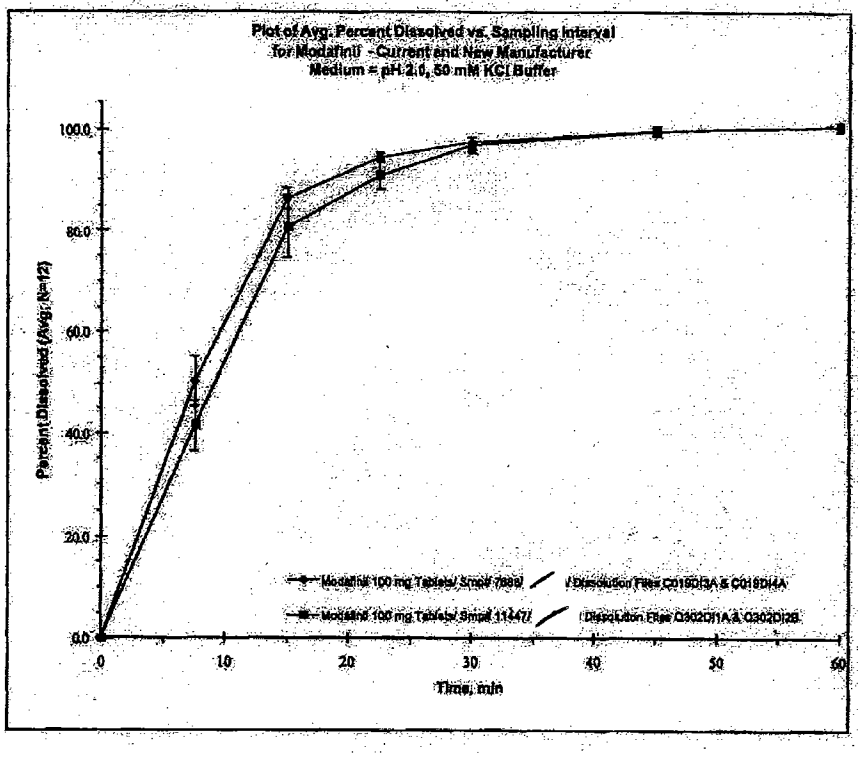
For profile similarity, F1 < 15 and F2 > 50

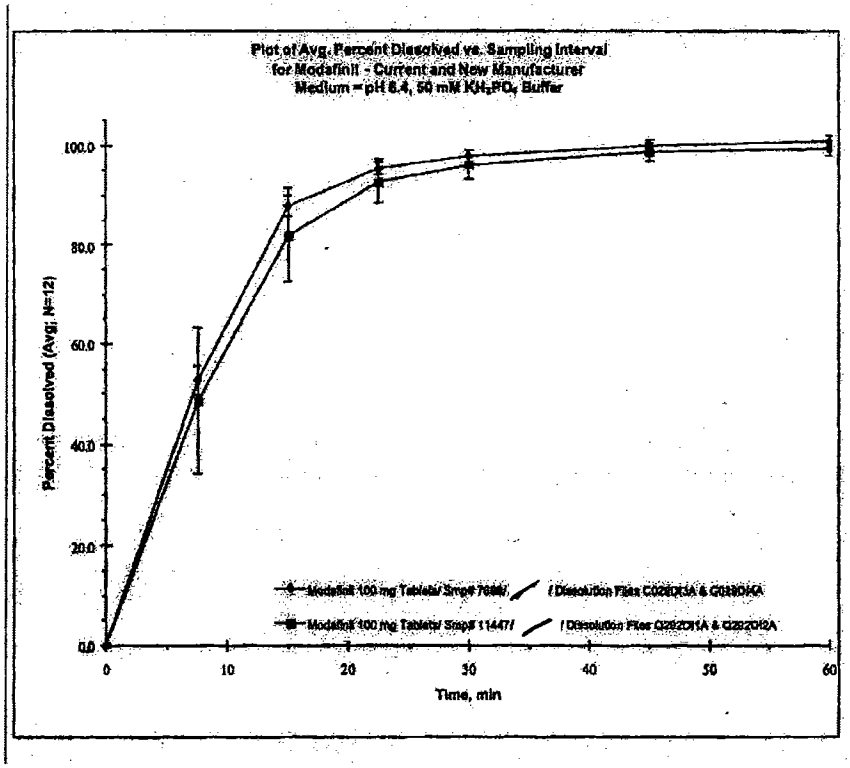
The reviewer has re-analyzed the dissolution profiles provided by the Sponsor. (Note for the [ ] 100 mg tablets in pH 2.0, the reviewer has calculated the mean at 7.5 minutes to be 43.4 rather than 41.6 as reported by the Sponsor). For the 100 mg tablets, the % CV was less than 20% at early time points and less than 10% at all other times for both the [ ] and [ ] tablet in all media except pH 6.4. In that medium the [ ] 7.5 minute time point had a CV of 29.9%, although it significantly reduced to 11.5% at 15 minutes. Therefore for the 100 mg strengths mean data were used by the reviewer for determination of difference and similarity factors. For the 200 mg tablets the % CV was less than 20% at early time points and less than 10% at all other times for both the [ ] and [ ] tablets in all media except 0.1 N HCl and pH 6.4. For the [ ] product in those media, the % CV was greater than 20% at 7.5 minutes which significantly reduced to 11.3% and 10.5% at 15 minutes for the 0.1 N HCl and pH 6.4, respectively. Therefore for the 200 mg strengths, mean data were used by the reviewer for determination of difference and similarity factors. The results were generally in agreement with those reported by the Sponsor, with all f2 values between 50-100 and all f1 values < 15.

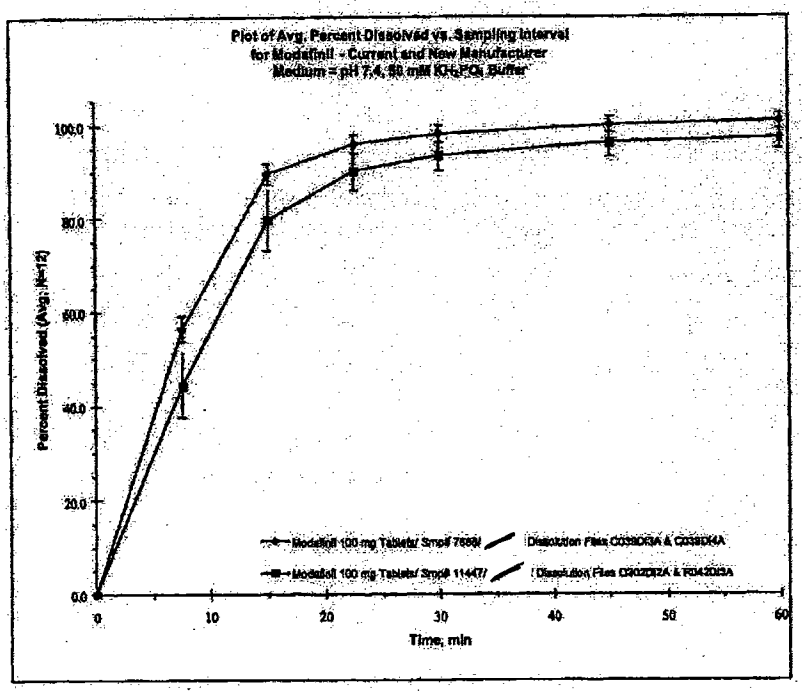
The comparative dissolution profiles are shown in the figures below.



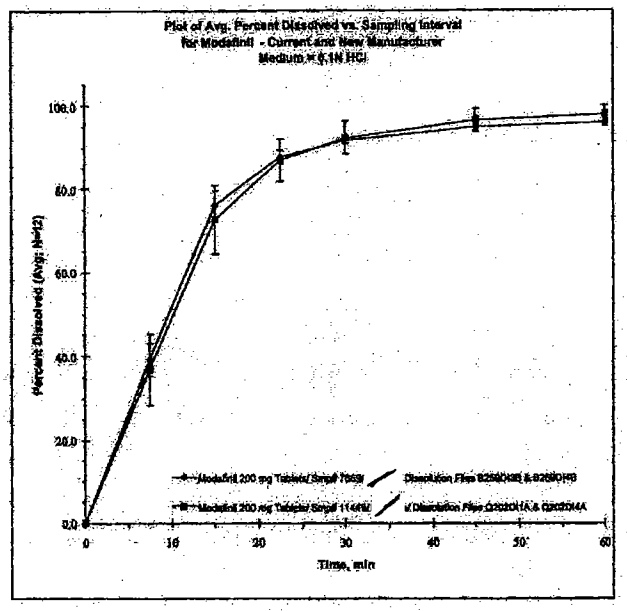


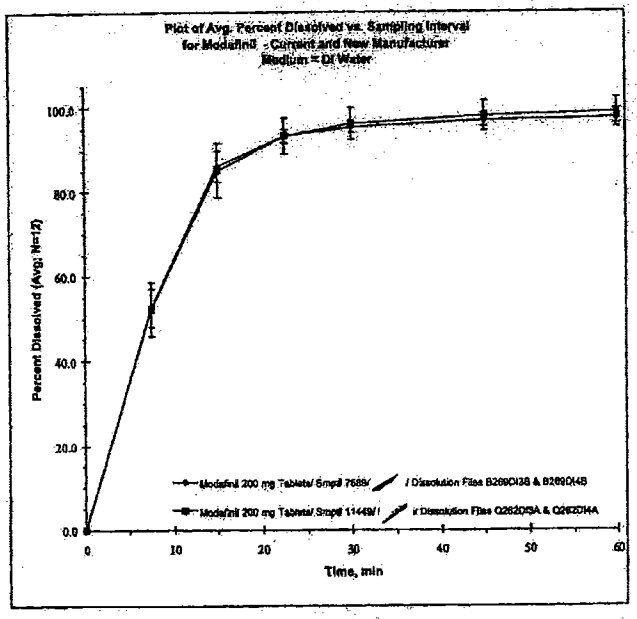

Plot of Avg. Percent Dissolved vs. Sampling Interval
for Modafinil - Current and New Manufacturer
Medium = pH 2.0, 50 mM KCl Buffer
Percent Dissolved (Avg; N=12)
100.0
80.0
60.0
40.0
20.0
0.0
0
10
20
30
40
50
60
Time, min
Modafinil 100 mg Tablets/ Smpl# 7889
/ Dissolution Files C0160I3A & C0180I4A
Modafinil 100 mg Tablets/ Smpl# 11447/
/ Dissolution Files C0302D1A & C0302D2B

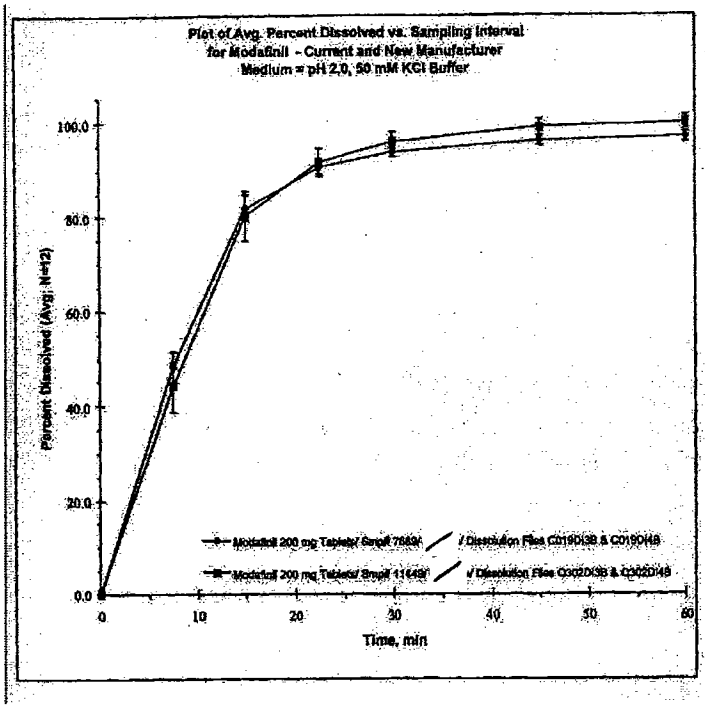

Plot of Avg. Percent Dissolved vs. Sampling Interval
for Modafinil - Current and New Manufacturer
Medium = pH 6.4, 50 mM KH2PO4 Buffer
Percent Dissolved (Avg; N=12)
100.0
80.0
60.0
40.0
20.0
0.0
0
10
20
30
40
50
60
Time, min
Modafinil 100 mg Tablets/ Smpl# 7889/
/ Dissolution Files C0280I3A & C0380I4A
Modafinil 100 mg Tablets/ Smpl# 11447/
/ Dissolution Files C0282D1A & C0282D2A

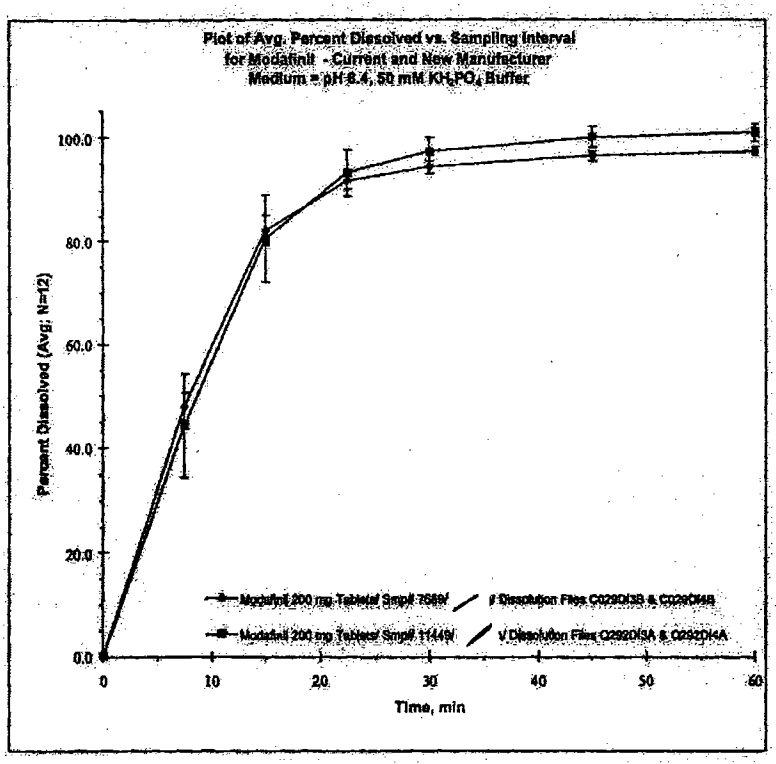


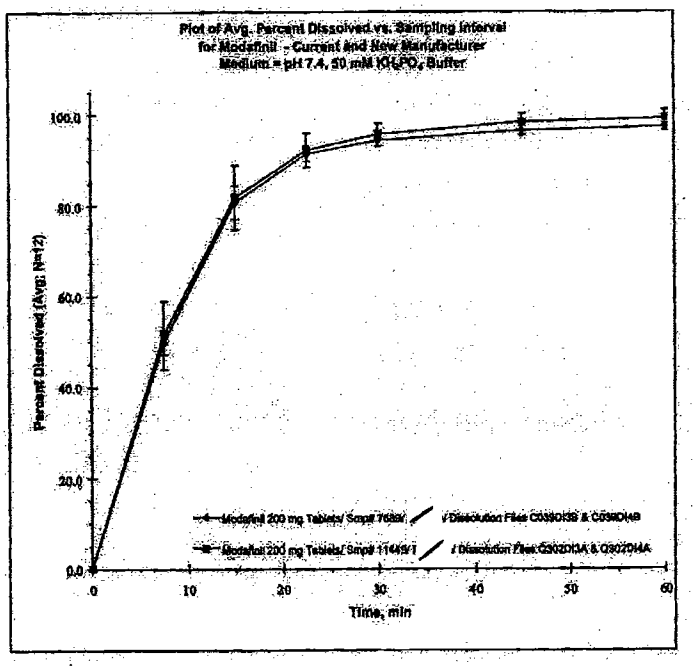
Appears This Way
On Original


Plot of Avg. Percent Dissolved vs. Sampling Interval
for Modafinil - Current and New Manufacturer
Medium = 0.1N HCl
Percent Dissolved (Avg; N=12)
100.0
80.0
60.0
40.0
20.0
0.0
0
10
20
30
40
50
60
Time, min
Modafinil 200 mg Tablets/ Smpl# 7689/
Dissolution Files B269DI3B & B269DI4B
Modafinil 200 mg Tablets/ Smpl# 11449/
Dissolution Files Q262DI3A & Q262DI4A


Plot of Avg. Percent Dissolved vs. Sampling Interval
for Modafinil - Current and New Manufacturer
Medium = DI Water
Percent Dissolved (Avg; N=12)
100.0
80.0
60.0
40.0
20.0
0.0
0
10
20
30
40
50
60
Time, min
Modafinil 200 mg Tablets/ Smpl# 7689/
Dissolution Files B269DI3B & B269DI4B
Modafinil 200 mg Tablets/ Smpl# 11449/
Dissolution Files Q262DI3A & Q262DI4A


Plot of Avg. Percent Dissolved vs. Sampling Interval
for Modafinil - Current and New Manufacturer
Medium = pH 2.0, 50 mM KCl Buffer
Percent Dissolved (Avg; N=12)
100.0
80.0
60.0
40.0
20.0
0.0
0
10
20
30
40
50
60
Time, min
Modafinil 200 mg Tablets/ Smpl# 7689/ / Dissolution Files C019DI3B & C019DI4B
Modafinil 200 mg Tablets/ Smpl# 11449/ / Dissolution Files C302DI3B & C302DI4B


Plot of Avg. Percent Dissolved vs. Sampling Interval
for Modafinil - Current and New Manufacturer
Medium = pH 6.4, 50 mM KH2PO4 Buffer
Percent Dissolved (Avg; N=12)
100.0
80.0
60.0
40.0
20.0
0.0
0
10
20
30
40
50
60
Time, min
Modafinil 200 mg Tablets/ Smpl# 7689/ / Dissolution Files C029DI3B & C029DI4B
Modafinil 200 mg Tablets/ Smpl# 11449/ / Dissolution Files C292DI3A & C292DI4A



Based on the f1 and f2 values, the profiles of the aqueous formulations of the [ ] and [ ] products of either strength can be considered similar.

CONCLUSIONS:

To fulfill the requirements of the SUPAC level II equipment change from the [ ] to the [ ] sites, the Sponsor has submitted dissolution profiles (Case C dissolution) of the proposed aqueous formulation to compare the [ ] with the [ ] tablets. Comparisons have been made in multiple media for both strengths of tablets. The results show that the *in vitro* dissolution performance is comparable for either strength of the [ ] and [ ] tablets.

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

/s/

Sally Yasuda
7/18/03 12:22:45 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/18/03 12:32:08 PM
BIOPHARMACEUTICS

ENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-717/S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Homonnay Weikel, Anna M

From: Yasuda, Sally
Sent: Friday, May 30, 2003 1:33 PM
To: Homonnay Weikel, Anna M
Subject: CMC Supplement for reformulation of Provigil Tablets

Anna Marie,

I am the Clin Pharm/Biopharm reviewer for this CMC supplement. I have several questions for the Sponsor to answer so that I can complete my review. They are attached in the Word file - could you please forward them to the Sponsor? I would like to have the response (including SAS transport files with the data from the BE study) by June 16th.

If you have any questions, please let me know.

Thank you very much,


Questions to Sponsor.doc

Sally Yasuda

Sally Usdin Yasuda, MS, PharmD
Reviewer, DPE-I
Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation & Research
Office of Clinical Pharmacology & Biopharmaceutics
Room 3019, HFD-860, WOC2
1451 Rockville Pike
Rockville, MD 20852

phone (301)594-5680
fax (301)480-3212
email yasudas@cder.fda.gov

Analytical Method

1. For determining selectivity in the analytical method, how many lots of control plasma did this represent?

2. Please provide information on the stability of stock solutions of modafinil and its metabolites in N,N-DMF as well as internal standard.

3. Please provide information on dilution integrity for modafinil and its metabolites.

4. For both the analytical method validation and the analytical run, were samples for calibration curves and QC samples spiked blank plasma samples? For the calibration curves, was there a blank and a zero sample for each run?

5. For the BE study, please provide standard operating procedures (SOPs) that were in place for sample preparation, the analytical procedure, for acceptance of the bioanalytical run, and acceptance criteria for subject samples, including sample dilution, as well as for repeat analysis and reintegration of data.

BE StudyC1538c/411/BE/US

1. Were the standard curves provided in PK-2.1.1 run on the same days as the samples?

2. Please provide details of the analytical runs including data and time of analysis for the samples, any deviation from the established method, as well as raw data, and documentation for any repeat analysis. Please also provide several randomly selected chromatograms.

3. Please provide information on the products used in the BE study including dates of manufacture and expiration date (or stability data if expiration date not available), as well as information on the batch size for the test product and proposed commercial batch size.

4. Please provide electronic data sets (SAS transport files) for the BE study to include subject, sequence, period, treatment, AUC and Cmax, as well as data sets containing subject, sequence, period, and treatment with the raw data for plasma concentrations.

Dissolution Study

Please provide more information on the lots used in the dissolution studies – specifically did they represent a recent commercial lot (for the reference), or batches from the bioavailability studies?

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

/s/

Anna-Marie Homonnay
6/5/03 09:29:07 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-717/S-009

Cephalon, Inc.
Attention: Paul Kirsch
Senior Director, Regulatory Affairs
145 Brandywine Parkway
West Chester, PA 19380

Dear Mr. Kirsch:

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

Name of Drug Product: Provigil® (modafinil) Tablets

NDA Number: 20-717

Supplement number: S-009

Date of supplement: March 28, 2003

Date of receipt: March 31, 2003

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 May 31, 2003, in accordance with 21 CFR 314.101(a).

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
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/

Anna-Marie Homonnay
4/11/03 11:37:10 AM