CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019766/S026/S028

STATISTICAL REVIEW(S)

MEMORANDUM

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

Date: JUN 17 1998

From: Joy D. Mele, M.S.
Mathematical Statistician (HFD-715)

Through: Ed Nevius, Ph.D, /S/ 6-16-98
Director, Division of Biometrics 2 (HFD-715)

Subject: ALT/AST responses to simvastatin (Zocor) 80 mg

To: File (NDA 19-766)

The Division of Metabolic and Endocrine (HFD-510) verbally withdrew its request for a statistical consult at the end of May, 1998 on NDA 19-766 Efficacy Supplement 026. At the time of the withdrawal, my review was in the preliminary stages but I had outlined the concerns which were to be the focus of my review; the labeling changes in the Clinical Trials section and liver and muscle safety parameters (with an emphasis on AST and ALT). The former has been addressed in an e-mail to Dr. Orloff (Team Leader in HFD-510) and is included as Appendix 1. The focus of this memo is the transaminase changes (ALT and AST) observed in the Phase III trials of this submission.

In NDA 19-766, the sponsor (Merck Research Laboratories) presented the results of two Phase III, double-blind (DB), controlled, clinical trials (Table 1) to demonstrate the efficacy and safety of simvastatin (Zocor) 80 mg compared to 40 mg (the highest approved dose) for the treatment of primary hypercholesterolemia and dyslipidemia.

Table 1. Controlled Clinical Trials for Simvastatin 80 mg

Study	Design	Entry Criteria	Treatment Group (N)	Duration of DB treatment
117-06 US	Phase III parallel, DB	Meet NCEP guidelines for therapy	40 mg qpm (207) 80 mg qpm (314)	24 weeks
117-07 non-US	Phase III parallel, DB	Meet NCEP guidelines for therapy	40 mg qpm (229) 80 mg qpm (355)	24 weeks

The data from these 2 studies, conducted under identical protocols, is combined for the summaries which follow.

Data for 5 parameters were provided by the sponsor to assess liver and muscle safety; ALT, AST, alkaline phosphate, total bilirubin and CPK. ALT, AST, total bilirubin and CPK levels were measured at baseline, and Weeks 6, 12, 18 and 24; alkaline phosphatase levels were measured at baseline and Weeks 12 and 24. For all 5 parameters, this reviewer summarized the percentage of patients with a value greater than the upper limit of normal at baseline and at each week on study (Table 2). For alkaline phosphatase, total bilirubin and CPK, the treatment groups were comparable at baseline and showed no appreciable changes or treatment differences during double-blind treatment . For AST and ALT, the % of patients with above normal values increases over time and is greater in the 80 mg group than the 40 mg group at each timepoint. Comparisons of change from baseline by week for ALT and AST showed statistically significant differences between the groups (80>40) at each week ($p<.01$, ANOVA).

Table 2. Percent of patients with values above the upper limit of normal at baseline and by week on study

	AST		ALT		Alk Phos		Total Bilirubin		CPK	
Week	40 mg	80mg	40 mg	80 mg	40 mg	80 mg	40 mg	80 mg	40 mg	80 mg
Baseline	5%	6%	5%	5%	8%	6%	6%	5%	9%	10%
6	12%	12%	12%	15%	NA	NA	6%	5%	12%	12%
12	13%	15%	15%	18%	9%	8%	6%	7%	15%	13%
18	14%	20%	15%	20%	NA	NA	6%	6%	13%	13%
24	14%	20%	15%	23%	10%	9%	6%	8%	12%	13%

The sponsor reported a statistically significant treatment difference in the % of patients with marked elevations in transaminases (> 3x ULN) as shown in Table 3 below.

Table 3. Sponsor's Results
% of Patients with elevations >3 x ULN at anytime on treatment

	40 mg (n=433)	80 mg (n=664)	p-values
ALT	1.4%	3.9%	.015
AST	0.9%	2.7%	.039

On the following page, I have presented boxplots (Figures 1 and 2) for ALT and AST at baseline (Week 0) and at Weeks 6, 12, 18 and 24. Only observed data is included in these plots; that is, data is not carried forward to impute missing data. For both dose groups and both measures, there is a clear upward shift in the distribution of the data over time with greater changes seen for the 80 mg dose but, as previously evidenced by Table 3, only a small number of patients show changes in ALT/AST levels above 3xULN.

In conclusion, the data shows that transaminase levels steadily increase over time and that these changes are dose-related.

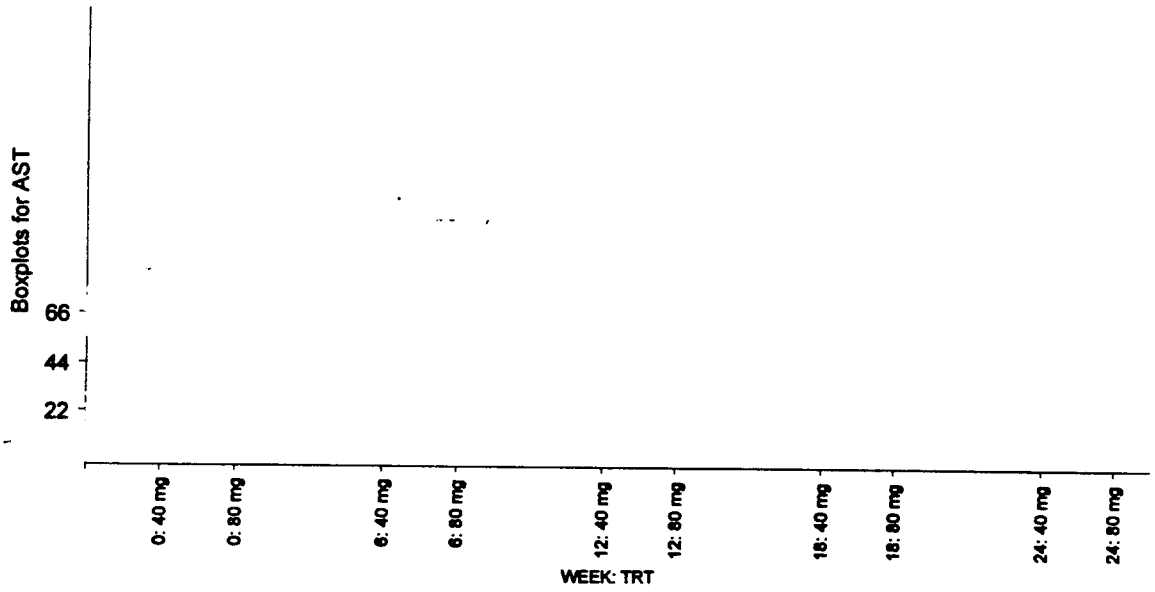

Figure 1 AST levels (mIU/mL) by week and treatment group[1]

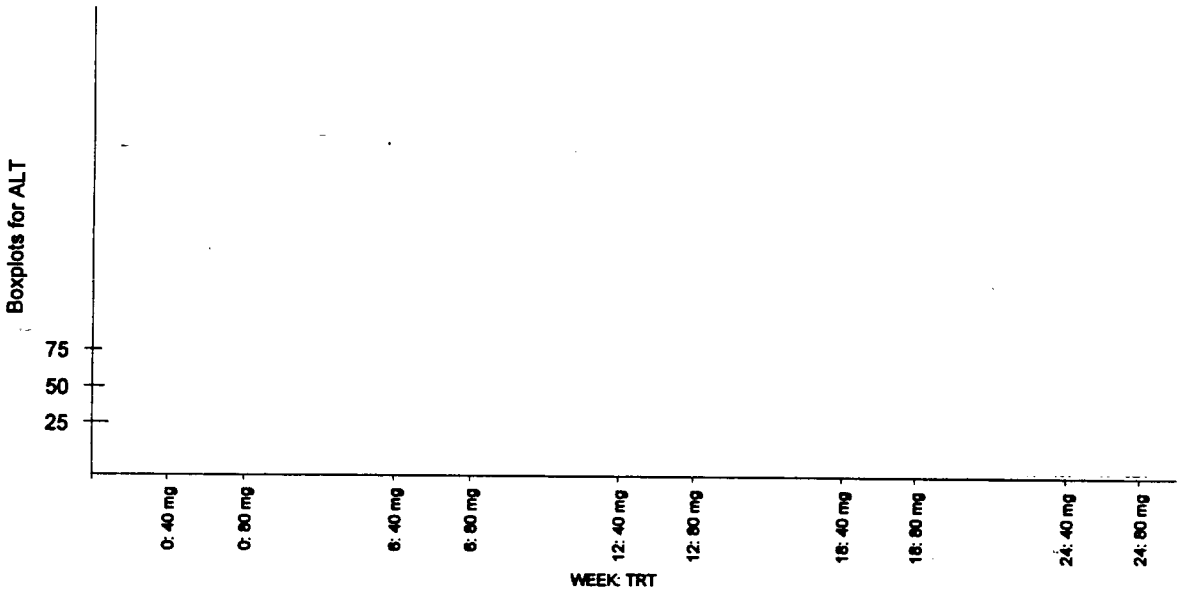

Figure 2 ALT levels (mIU/mL) by week and treatment group

1 The lower solid line indicates the 25th percentile and the upper solid line, the 75th percentile. The symbol between the dark solid lines represents the median. The grid lines represent the ULN, 2xULN and 3xULN.

Joy D. Mele, M.S.
Mathematical Statistician

Concur:
Dr. Sahlroot /S/ 6/16/98

cc:
Orig. NDA 19-766
HFD-510
HFD-510/DOrloff, SShen, MSimoneau, SSobel
HFD-715/DOB 2 File, Chron, ENevius, TSahlroot, JMele

Mele/827-6376/DOB2/Word-zoc80_tf.mem.doc /June 9. 1998
This memorandum contains 4 pages of text plus 1 appendix.

Appendix 1.

Copy of **e-mail** from Joy Mele sent to David Orloff (Team Leader, Division of Metabolic and Endocrine Drug Products) with cc's to Ed Nevius (Division Director, Division of Biometrics 2), Todd Sahlroot (Team Leader, Division of Biometrics 2) and Shaio Shen (Medical Officer, Division of Metabolic and Endocrine Drug Products) on May 29, 1998.

David,

When I began my review of this application, I looked at the labeling changes first and I had several concerns that I planned to address in my review. Since the request for a statistical review has been withdrawn, I feel obligated to pass them onto you via this e-mail.

The changing to the wording in the paragraph preceding Table 1 is puzzling – if it continues to refer to the same study, how did the interpretation change so much?

The sponsor has replaced a table of results from a dose response study (Table 1) with a table of data from several studies. Several independent studies with only a few doses in each cannot demonstrate dose-response – baseline issues, non-randomized groups, etc. — and therefore the table should not be labeled as demonstrating dose-response.

The paragraph that follows the table is full of ambiguous comments that, from a cursory inspection of their references, have not been substantiated by the data.

The draft guidelines for labeling suggest that certain basic principles be followed, such as: include baseline data, include all comparator groups, include only endpoint data essential to the claim ... and it goes on. I think that many of the sponsor's changes are purely promotional in nature and appear not to be helpful to a prescribing physician (the latter is our goal, I think). For example, the new table – the old table had 8 week data, the new one; 6-24 week data – how could a physician use this table to judge who to treat with what starting dose (no baseline data, also notice they have added the word "usual" in the dosage section to describe the starting dose), when to titrate or if the drug was working as expected (at what timepoint?).

I would be happy to give you a copy of the draft guidelines.

Joy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019766/ S026/S028

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date: 08-JUL-98
From: Robert M. Shore, Pharm.D.
To: M. Simoneau, HY. Ahn
Re: NDA 19-766/SE2-026
Zocor 80 mg

Merck Research Laboratories (MRL) submitted NDA 19-766/SE2-026 (Zocor 80 mg tablet) on 04-AUG-97. The recommendation from the OCPB Review was as follows:

CC: NDA 19-766/SE2-026 (orig., 1 copy), HFD-510(Orloff, Simoneau, Galliers), HFD-870(Ahn, Shore, ChenME)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 19-766/SE2-026	**SUBMISSION DATE: 04-AUG-97, 21-OCT-97, 12-DEC-97 27-MAY-98, 12-JUN-98, 26-JUN-98**
BRAND NAME:	**Zocor®**
GENERIC NAME:	**simvastatin 80 mg oral tablet**
REVIEWER:	**Robert M. Shore, Pharm.D.**
SPONSOR:	**Merck Research Laboratories, West Point, PA**
TYPE OF SUBMISSION:	**Efficacy Supplement for 80 mg tablet**

TERMS AND ABBREVIATIONS:

90%CI ..... 90% confidence interval
AUCa-b ..... area under the plasma-concentration-time curve from time a to time b
RMSE.. ..... Root mean square error
Cmax... ..... Maximum concentration
DMEDP ..... Division of Metabolic and Endocrine Drug Products
CV..... ..... Coefficient of variation
GM..... ..... Geometric mean
SD..... ..... Single dose
MD .... Multiple dose
GMR.... ..... Geometric mean ratio
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics

SYNOPSIS:

The current approved maximum daily dose of simvastatin (Zocor) is 40 mg. This submission seeks approval for an increase in this dose to 80 mg daily and approval of a new 80 mg tablet. One pivotal *in vivo* bioequivalence study was submitted which demonstrated acceptable bioequivalence between 2x40 and 1x80 mg Zocor tablets. Dose proportionality for simvastatin has already been established up to 120 mg (as per current labeling). Dissolution data for the 80 mg tablet are similar to the 40 mg tablet.

Pharmacokinetic parameters generated from the original NDA studies (late 1980s) and those generated from studies submitted in this supplement are inconsistent. The newer studies have resulted in pharmacokinetic parameters the older parameters. According to the sponsor, the used has been the same; it is a Although the data generated *within* a study are valid, there is concern about

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II

(OCPB/DPE-2) has reviewed NDA 19-766/SE2-026 submitted 04-AUG-97, 21-OCT-97, 12-DEC-97, 27-MAY-98, 12-JUN-98, and 26-JUN-98. The used by the sponsor has come under

Table of Contents Page

(Appendices and/or Attachments available from DPE-II upon request)

BACKGROUND:

Zocor (simvastatin) is an HMG-CoA reductase inhibitor used to treat hyerlipidemia. Currently, Zocor is available in 5, 10, 20, and 40 mg immediate release oral tablets. The pharmacokinetics of simvastatin are linear up to doses of 120 mg, as per the approved labeling. The sponsor seeks approval of an 80 mg dose and an 80 mg tablet.

PROTOCOL INDEX

Protocol Number	Title	Page
120	An Open, Randomized, Single-Dose, 2-Period, Complete-Block, Crossover, Pharmacokinetic Study Comparing Simvastatin 2 x 40-mg Conventional Tablets to Simvastatin 80-mg Tablets	p. 26

VOLUMES REVIEWED: 1.1, 1.6-1.11.

DRUG FORMULATION:

Table 1 lists the ingredients for the Zocor 40mg and 80mg tablets. The 80mg tablet is proportionally and compositionally similar to the 40mg tablet.

Table 1. Zocor Formulation.

Formulation Strength:	40.0 mg	80.0 mg
Simvastatin		
Starch		
Lactose,		
Butylated Hydroxyanisole		
Magnesium Stearate		
Hydroxypropyl Methylcellulose		
Hydroxypropyl Cellulose		
Titanium Dioxide		
Talc		
Total Tablet Weight		

DISSOLUTION:

ANALYTICAL METHODOLOGY:

Reviewer Comments

1. The assay used in the study 120 (pivotal bioequivalence) is acceptable. However, the sponsor should be encouraged to develop a less variable and more specific assay.

Table 2. Pharmacokinetic Parameter Summary From Studies in Original NDA and SE2-026.

Study Number	Dose mg	Range of Pharmacokinetic Means			
		AUC total (ng eq.hr/mL)	Cmax total (ng eq/mL)	AUC Active (ng eq.hr/mL)	Cmax Active (ng eq/mL)
011-01 (N=16) original NDA	4x10 2x20 1x40				
016-01 (N=18) Original NDA	1x40 2x20				
006-01 (N=18) Original NDA	4x20 (normalized to 40 mg)	333 (167)	69 (35)	128 (64)	22 (11)
Range for 40mg dose:					
115* (N=12) Supplement	2x40 (normalized to 40 mg)	550 (275)	123 (62)	160 (80)	24 (12)
120* (N=23) PIVOTAL BE STUDY Supplement	2x40 1x80 (normalized to 40 mg)	612 (306) 632 (316)	167 (84) 172 (86)	214 (107) 219 (110)	45 (23) 44 (22)
111 (N=18) MD Study Supplement	2x20 2x40 (normalized to 40 mg)	316 636 (318)	75 165 (83)	120 263 (132)	21 50 (25)
Range for 40mg dose:					

* Geometric means
BE: Bioequivalence
MD: Multiple dose

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Bioequivalence

Protocol 120 was the pivotal bioequivalence study between 2x40mg and 1x80mg tablets. Twenty-three subjects received a single dose of 2x40mg (reference) and 1x80mg (test) Zocor tablets in a crossover study. Figure 1 presents the mean plasma concentration data.

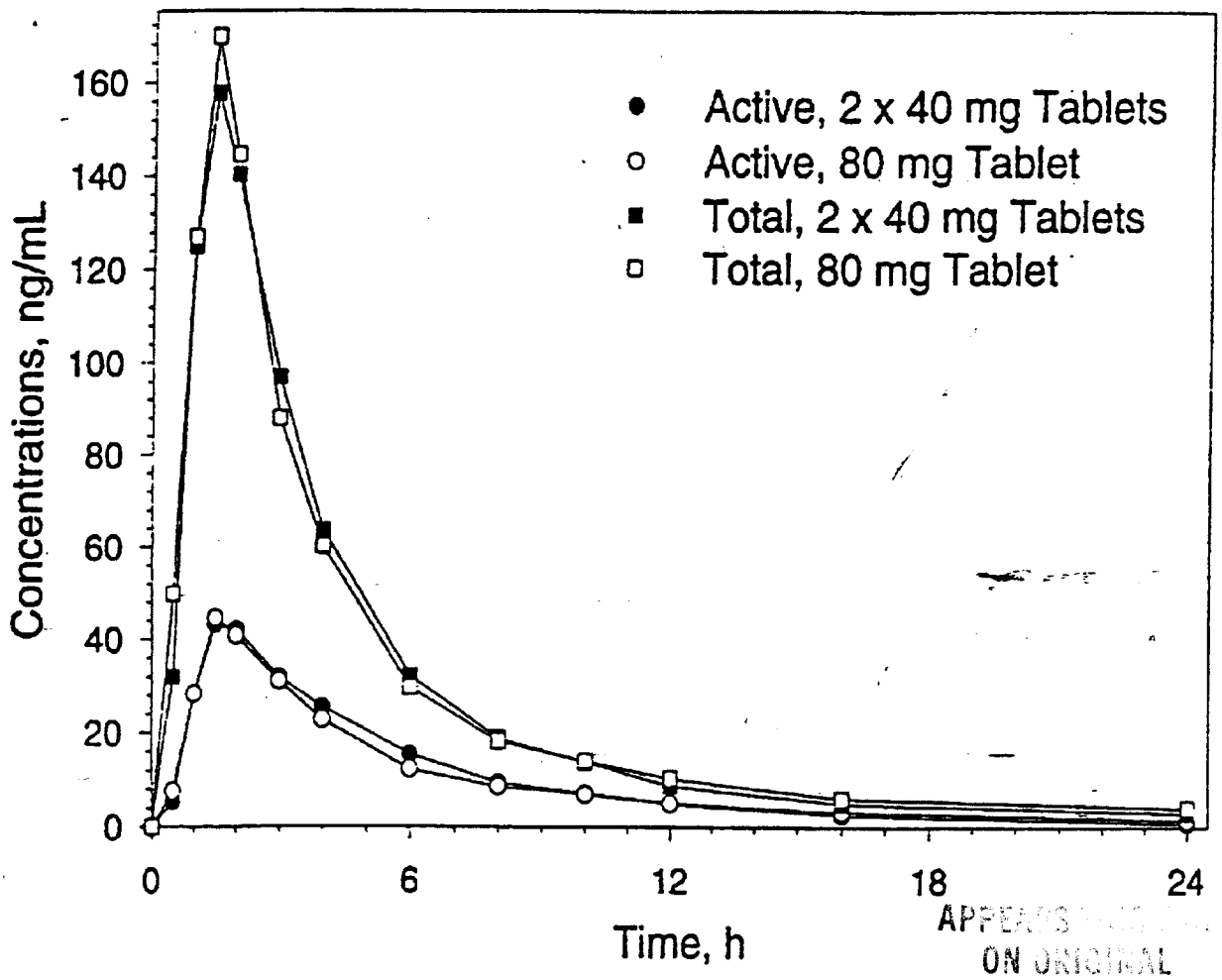

Figure 1. Mean plasma concentrations of active and total HMG-CoA inhibitors following a single dose of 2x40mg and 1x80mg tablets of Zocor (N=23).

Tables 3 and 4 indicate the pharmacokinetic and bioequivalence parameters of the inhibitors. Currently, to declare two products bioequivalent, the 90%CI for the geometric mean ratio should be within the interval (0.8-1.25).

Table 3. Active inhibitors (N=23)

Parameter	Treatment	GM (CV%)	GMR	90%CI
AUC (ng.eq.hr/mL)	2 x 40 mg	214.1 (48)	1.02	0.92, 1.14
	1 x 80 mg	218.8 (37)		
Cmax (ng.eq/mL)	2 x 40 mg	45.2 (80)	0.96	**0.79**, 1.17
	1 x 80 mg	43.6 (64)		
Tmax (hr)	2 x 40 mg	2.0*	* Median Tmax.	
	1 x 80 mg	1.5*		

Table 4. Total inhibitors (N=23)

Parameter	Treatment	GM (CV%)	GMR	90%CI
AUC (ng.eq.hr/mL)	2 x 40 mg	611.7 (37)	1.03	0.94, 1.13
	1 x 80 mg	631.7 (34)		
Cmax (ng.eq/mL)	2 x 40 mg	166.8 (77)	1.03	0.83, **1.28**
	1 x 80 mg	172.2 (65)		
Tmax (hr)	2 x 40 mg	2.0*	* Median Tmax.	
	1 x 80 mg	1.5*		

The following similarities can be seen for both active and total inhibitors:
1) The point estimate of the ratio for AUC and Cmax is close to 1 (0.96-1.03);
2) For AUC, the 90%CI are almost identical and within the interval (0.8-1.25);
3) For Cmax, the 90%CI extend slightly beyond the (0.8-1.25) interval;
4) The variability in Cmax tends to be larger than that of AUC.

Although the 90%CI for Cmax is wide and indeterminant regarding bioequivalence, it seems to be symmetric i.e., the point estimate is close to 1, indicating that, on average, the bioavailability of the formulations is similar. Tmax values, for both active and total inhibitors, of 1.5 to 2.0 hr are similar to values of 1.3 to 2.4 hr currently reported in the labeling.

According to the sponsor, 'the only difference between the clinical batches...and the intended commercial process is scale' (Submission 12-DEC-97 BB). Although SUPAC is aimed at post-approval changes, it can be applied to pre-approval changes, too. SUPAC-IR (November 1995) indicates that

> 'For solid oral dosage forms [Pilot Scale] is generally taken to be, at a minimum, that of whichever is larger'.

The commercial batch size is to be tablets; the batch used in this pivotal bioequivalence study (protocol 120) was tablets and the batches used in the pivotal clinical studies were tablets. Therefore, according to SUPAC-IR, this pilot batch was of inadequate size to characterize a full commercial batch.

Reviewer Comments

1. Given 1) the similar dissolution profiles, 2) bioequivalence of the AUC parameters, and 3) variability of the Cmax parameters with their slightly extended bioequivalence confidence intervals, the 80 mg tablet can be accepted as bioequivalent to 2x40 mg tablet.

C. Intra-individual Variability

As calculated from the RMSE generated with the ANOVA analysis of study 120 (data not shown), intra-subject variability was estimated to have been approximately 20% for both AUC parameters and 40% for both Cmax parameters.

II. Pharmacokinetics

A. Single vs. Multiple Dose Administration

This submission did not include a study in which simvastatin pharmacokinetics were determined under both SD and MD conditions. However, a comparison of studies 111 and 120 (Table 2) shows that the pharmacokinetic parameters after SD or MD are comparable; there appears to be little if any accumulation.

COMMENTS TO BE SENT TO SPONSOR

1) The enzyme inhibition assay shows great variability between studies. The sponsor, as per the Recommendation, should develop an assay with less variability.

2) The sponsor should be aware that, in future studies with solid oral dosage forms, 'Pilot Scale' batches should generally be, at a minimum, one-tenth that of full production, or tablets whichever is larger (SUPAC-IR Nov. 95).

01-JUL-98

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 30-JUN-98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 9/11/98

Simonean

CC: NDA 19-766/SE2-026 (orig.,1 copy), HFD-510(Shen, Orloff), HFD-340 (Viswanathan), HFD-850(Lesko, Huang), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: AE

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 19-766/SE2-026	**SUBMISSION DATE:**	**12-JUN-98**
BRAND NAME:	**Zocor®**	
GENERIC NAME:	**simvastatin 80 mg oral tablet**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Merck Research Laboratories, West Point, PA**	
TYPE OF SUBMISSION:	**BB: Response to Questions**	

SUBMISSION:

This submission was a response to a question that this reviewer posed to the sponsor. According to the review (dated 15-MAY-91) of the original NDA for Zocor, a number of single-dose studies were conducted. The pharmacokinetic parameters of simvastatin were summarized in the review. Upon comparison with parameters generated in more recent studies, submitted in SE2-026 on 04-AUG-97, this reviewer noticed that the more recent parameters were greater than the original parameters. Dr. Silverman, on 05-JUN-98 was asked to address this discrepancy.

Table 1 summarizes the results of the original and more recent studies. It has already been established that the pharmacokinetics of simvastatin are linear up to a dose of 120 mg. As indicated, the range of mean pharmacokinetic values from the original NDA studies is lower than that for the supplement's studies. There is only slight overlap of the results for Cmax Active.

Table 1. Pharmacokinetic Parameter Summary From Studies in Original NDA and SE2-026.

		Range of Pharmacokinetic Means			
Study Number	Dose mg	AUC total (ng eq.hr/mL)	Cmax total (ng eq/mL)	AUC Active (ng eq.hr/mL)	Cmax Active (ng eq/mL)
011-01 (N=16) original NDA	4x10 2x20 1x40				
016-01 (N=18) Original NDA	1x40 2x20				
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Range for 40mg dose:					
115* (N=12) Supplement	2x40 (normalized to 40 mg)	550 (275)	123 (62)	160 (80)	24 (12)
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111 (N=18) MD Study Supplement	2x20 2x40 (normalized to 40 mg)	316 636 (318)	75 165 (83)	120 263 (132)	21 50 (25)
Range for 40mg dose:					

* Geometric means
BE: Bioequivalence
MD: Multiple dose

The response submitted by Merck indicated that "The variation and discrepancy in pharmacokinetic parameters between different studies is well recognized for the statins." At least from the NDA and supplement data, there *does* seem to be some general range of values into which the parameters fall - it's just that the original and supplement studies do not fall into the *same* range. If the sponsor has data from other studies, or literature values, that show such marked discrepancies of pharmacokinetic parameters between studies, these data should be submitted for review.

In addition, the response indicated that 'There have been no changes in the composition of drug product" and that "The only difference in the analytical method used for the current studies in this application is that the enzyme inhibition assay used to analyze the plasma samples has been optimized to make it more sensitive; however, we do not believe that this accounts for the noted variation in the test results." These could have been possible explanations for the differences but, according to the sponsor, are not .

COMMENTS TO BE SENT TO SPONSOR

1) Table 1 should be forwarded to the sponsor.

2) The response does not explain the discrepant results between the original NDA and supplement studies. As per Table 1, the range of pharmacokinetic values obtained from the original NDA studies is below that obtained in the more recent studies. It is not the variation of the results that is concerning, but that the range of mean estimates do not agree. If the sponsor has data from other studies, or literature values, that show such marked discrepancies of pharmacokinetic parameters between studies, these data should be submitted for review. The sponsor has already indicated that neither the formulation nor the assay have changed in a way that would explain this discrepancy.

Robert M. Shore, Pharm.D. /S/ 22-JUN-98
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 6/23

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 6/23/98

CC: NDA 19-766/SE2-026 (orig.,1 copy), HFD-510(Shen, Orloff), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: AE

Simoneau

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date of Telecon:	05-JUN-98
From:	Robert M. Shore, Pharm.D.
Re:	NDA 19-766/SE2-026 Zocor® simvastatin 80 mg tablet
Participants:	Robert M. Shore (FDA); Dr. Robert Silverman (Merck)

This submission seeks approval for an 80 mg dose of Zocor; the current maximum dose is 40 mg. Included in the supplement is data from studies submitted in the original NDA in the early 1990s. Two recent studies (protocols 111 and 120) that are in the current submission contain pharmacokinetic data that is discrepant with the older data. Specifically, the older AUC and Cmax values tend to be much lower than the newer data, for the same dose. I requested some explanation for this difference.

CC: NDA 19-766/SE2-026 (orig., 1 copy), HFD-510(Simoneau, Orloff), HFD-870 (Shore, Ahn)