ORIGINAL

Synthon
Pharmaceuticals, Inc.

August 1, 2006

VIA FEDERAL EXPRESS

Mary Parks, M.D.
Division Director
Division of Metabolism and Endocrinology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705
Tel: 301.796.2290

RE: NDA 21-961
Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Synthon Pharmaceuticals, Inc.
Response to FDA's July 11, 2006 Letter Regarding "Not Approvable Letter"

Dear Dr. Parks:

Reference is made to the Division of Metabolism and Endocrinology Drug Products' (the "Division's") May 25, 2006 "Not Approvable Letter" regarding NDA 21-961 (the "Not Approvable Letter," copy enclosed as Exhibit 1), Synthon Pharmaceuticals, Inc.'s ("Synthon's") May 30, 2006 response to the Not Approvable Letter and request for an "End of Review" meeting ("Synthon's Response," copy (cover letter only) enclosed as Exhibit 2), and the Division's July 11, 2006 letter concerning Synthon's Response (the "Division's Response," copy enclosed as Exhibit 3).

Synthon's Response contained not only a response to the conclusions drawn by the Division of Scientific Investigations ("DSI") concerning Synthon's bioequivalence study, but also a specific request for an "End of Review Meeting" to discuss the merits of DSI's recommendation. We believed that such a meeting would be the appropriate place to discuss whether the inspectional observations concerning [redacted] (the site where Synthon's bioequivalence study was performed) justified DSI's conclusion that the bioequivalence study data are invalid. In fact, FDA's regulations state that the "End of Review" meeting is intended for just such a purpose. See 21 C.F.R. § 314.103(c)(1). Thus, it was with great disappointment that Synthon received the Division's Response on July 11, 2006, which confirmed the "Not Approvable" status of the NDA and stated that

b(4)

the Division was "happy to discuss the details of another bioequivalence study with [Synthon] at [the] meeting scheduled for 17 July 2006."

In subsequent discussions with the Division, it became apparent that the Division was not prepared to discuss the validity of the data in Synthon's bioequivalence study and that any discussion during the meeting that was scheduled for July 17th would be limited to the design of a *new* study. Because Synthon believed, and continues to believe, that its original bioequivalence study is valid, we do not intend to perform another duplicative study at this time. Therefore, we agreed with the Division's conclusion that the meeting scheduled for July 17th would not be productive in terms of discussing the merits of DSI's recommendation. On July 13, 2006, we withdrew our meeting request via email (copy enclosed as Exhibit 4).

Having exhausted our administrative remedies at the Division level, Synthon now intends to seek formal dispute resolution pursuant to FDA's regulations and applicable Guidance documents. See 21 C.F.R. §§ 10.75, 314.103; Guidance for Industry Formal Dispute Resolution: Appeals above the Division Level (the "Dispute Resolution Guidance"). Formal Dispute Resolution is limited to a review of the administrative record that was reviewed by the Division. Therefore, it is important that the Division have a chance to review all of the relevant information in the administrative file prior to the filing of the appeal. See Dispute Resolution Guidance at p. 3 ("[N]o new information should be submitted as part of a request for reconsideration or appeal.")

Currently, the last document in the administrative file for our NDA is the Division's Response of July 11th. That document includes an Appendix (the "Appendix") setting forth allegations concerning Synthon's bioequivalence study that had not been previously communicated to Synthon or [redacted] Neither the Form 483s issued to [redacted] nor the Not Approvable Letter sent to Synthon mention several of the matters referenced in the Appendix. Furthermore, neither of the FDA investigators who inspected [redacted]'s facility mentioned these new allegations to [redacted] Therefore, we are compelled to respond to these new allegations at the Division level before taking the matter on appeal through formal dispute resolution. We would like to initiate the dispute resolution process as quickly as possible, while also providing the Division with sufficient time to review our responses to these new allegations. Therefore, if we do not receive notification of the approval of the NDA within ten business days of the Division's receipt of this letter, we will assume that the Not Approvable decision remains in effect and we will proceed with our appeal.

b(4)

Response to the New DSI Allegations in the Appendix to the Division's July 11, 2006 Letter

The Appendix to the Division's Response is divided into two separate sections that attempt to respond to Synthon's Response concerning the bioequivalence study. We address each of these two sections in the discussion below. However, a general comment concerning a particularly distressing aspect of the Appendix is in order before proceeding

to the details. The Appendix is clearly an attempt to defend the untenable position in which DSI finds itself with regard to the simvastatin orally disintegrating tablets bioequivalence study. Synthon's original response to the Not Approvable Letter provided a concise rebuttal to all of the original DSI allegations with supporting documentation demonstrating the integrity of the data. Yet, DSI did not attempt to respond directly to our responses, except to merely restate the original allegations. Instead DSI brings up new alleged deficiencies (e.g., a new requirement for handwritten dates for each individual study activity) that had never before been communicated to Synthon or [redacted]. In so doing, DSI sets up a situation where Synthon and [redacted] are chasing a perpetually moving target with respect to the "requirements" for a valid bioequivalence study. Even if [redacted] adopted all of the changes to its procedures that were suggested during the November 2005 inspection, it would still be the subject of an FDA Form 483 because it missed the latest "requirements" articulated in the Appendix. It is hard to imagine a situation that is more "arbitrary and capricious" than this sort of *post hoc* rationalization that results in vague "requirements" that have significant impact for regulated companies. DSI's actions in this matter are not only unfair, they are intellectually dishonest and inconsistent with law. b(4)

Comments on Response # 1 in the Appendix:

Synthon's assertion that the actual drug administration times were documented on the drug dispensing envelopes remains unrefuted. As does the fact that the envelopes constitute primary "raw" data that are included in the applicable Case Report Forms ("CRF") in accordance with the protocol. Thus, there is no longer a question as to whether the actual drug administration times were documented.

With regard to verification of the dose prior to administration, Synthon's Response document stated that the initials on the dispensing envelope also served as verification that the dispensing physician confirmed the dose prior to administration. Rather than directly challenging the accuracy of this statement (presumably because there was no basis for doing so), DSI attempts to cast doubt on this explanation by alleging that it is a contradiction of Synthon's "original statement."[1] In fact, no such contradiction exists. Synthon has consistently explained that the initials on the dispensing envelope provide evidence that the correct drug was administered at the correct time. The physician removed the drug from the sealed envelope, checked the identification of the subject via the information on the subject's arm band, visually confirmed the dose, dosed the subject, and documented these activities by initialing and writing the time on the envelope. These activities were verified by a nurse who also initialed the envelope. As we have previously stated, Synthon and [redacted] are not opposed to implementing the minor clerical changes that DSI is requesting. However, we strongly disagree with the b(4)

[1] DSI does not identify the "original statement" that "contradicts" Synthon's current explanation and Synthon is unaware of any such "contradiction." In any event, DSI has yet to adequately refute Synthon's statement that the physician had to confirm the dosage form when the dose was removed from the envelope in order to properly administer the study drug.

conclusion that such minor documentation formatting issues can support the total invalidation of the bioequivalence study.

Perhaps the most egregious aspect of DSI's new allegations is the attempt to discredit the data contained on the drug dispensing envelope. As noted above, the dosing time is clearly documented on the envelopes. Likewise, there is no reasonable basis for concluding that the physician did not simultaneously confirm the dose using the industry standard terms of "test" and "reference" drug products. Unable to refute the facts, DSI turns to a new tactic to discredit the data on the envelopes -- they were not hand dated. DSI states that "[b]ecause the initials on the envelopes were not dated contemporaneously by the responsible individuals (dates on the unit dose envelopes were pre-printed), the initials fail to reflect documentation at the time of dosing." This is an entirely new and puzzling allegation. If it is so important to have the physician and nurse hand write the dates on the envelopes, why did DSI wait until this late stage in the process to let Synthon and [redacted] know that a study can be totally invalidated by the omission of what DSI apparently considers to be essential data? Furthermore, if it is so important to have each study activity hand-dated in this manner, why is it that the rest of the pharmaceutical industry seems to have neglected to do so on every study that our outside expert has reviewed? See Declaration of [redacted]. (enclosed as Exhibit 5). Preprinting dates for bioequivalence studies is common industry practice due to the large number of activities that occur on a single study day in these types of studies. It is overly burdensome and unnecessary to require investigators to hand-write the same date each time they collect every piece of study data – especially when all of the data is collected on the same day. Thus, the type of hand-dating that DSI is requiring for Synthon is not the standard in the pharmaceutical industry and, to the best of our knowledge, FDA has not required this type of documentation for other pharmaceutical companies. b(4)

Another puzzling aspect of the Appendix is the admonition to, "[p]lease recall that the sponsor's monitor signed the dispensing records in North Carolina after the study was completed." The exact meaning and purpose of this statement is unclear. The referenced document is actually entitled, "Drug Inventory and Dispensing Record." This form is not a primary source document. Rather, it is a secondary document that is used to confirm the inventory of all doses used in the bioequivalence study. Importantly, this document is intended to be completed and signed by the monitor *after* the study is complete because a final inventory cannot be undertaken until all doses have been administered. In this case, the study monitor verified the final inventory during a site visit on April 5, 2005. The monitor then completed the Drug Inventory and Dispensing Record on April 21, 2005, after returning to the U.S. Synthon and [redacted] explained this entire procedure to the FDA investigator during the May 2006 inspection and provided ample supporting correspondence. Synthon agreed to have the monitor sign the Drug Inventory and Dispensing Record while on site for all future bioequivalence studies. Yet, once again, there is no basis for concluding that the time at which this secondary document was signed has any impact on the validity of the study data. b(4)

As to the documentation for the packaging of the dispensing envelopes, the Appendix contains no meaningful new allegations, but rather states the truism that SOPs only reflect intent and must be backed up by documentation of actual activity. We agree. This is precisely why [redacted] has two initials and the investigator's signature and handwritten date on the Drug Packaging Record. We acknowledge that the Drug Packaging Record does not contain a notarized affidavit that the applicable SOP was followed. However, we believe it is reasonable and consistent with industry practice and agency policy to conclude that the signatures on the document are confirmation that persons signing the document followed the applicable SOP. b(4)

Likewise, we continue to respectfully disagree with DSI's allegation that there is no assurance that the drugs were packaged correctly. The Drug Packaging Record was signed and dated by the principal investigator on the date the packaging occurred. This signature attests that the drug packaging was completed and witnessed by the physician and nurse. DSI now states, "[t]he sponsor states that the dosing envelopes were verified by [redacted] staff at the time of packaging. This cannot be assured, as the analysts[2] who initialed 'Performed by' and 'Checked by' did not date their initials." Once again, this "observation" is a distinction without any meaning. The initials are not dated because the packaging operation is all performed on the same day and the document contains the *signature* (not initials) of the principal investigator *with a handwritten date.* How many handwritten dates are required in order to provide sufficient evidence that the packaging was performed on the date that is written on the document? Apparently, [redacted] is expected to have dates written for each initial on the page, but the rest of the FDA-regulated industry is allowed to take a more common-sense approach. Synthon and [redacted] are left wondering how they are to expected to learn the unwritten "rules" that can result in their studies being found lacking integrity. [redacted] asked the FDA investigator how one "knows the proper procedure" during the May 2006 inspection of [redacted] Surprisingly, the investigator replied that [redacted] must learn the FDA's requirements "through inspections." See Declaration of [redacted] (enclosed as Exhibit 6). To an extent we agree with this approach -- Synthon and [redacted] expect to learn about the agency's preferred approaches through the inspectional process. But, the Appendix takes this approach to its extreme in that Synthon's bioequivalence study is being invalidated based solely on failing to follow unwritten "rules" that can only be discerned after numerous FDA inspections. b(4)

Comments on Response # 2 in the Appendix:

The second "response' in the Appendix does not contain any significant new information. For the most part, it is a rehash of the same positions that Synthon refuted in its response to the Not Approvable letter. As noted previously, the fact that the dosing times were recorded on the dispensing envelopes and that those envelopes constitute "raw" data in the CRF remains unrefuted. DSI, however, continues to focus on the use of "preprinted"

[2] It should be noted that "analysts" did not perform the packaging. Packaging was performed by a physician and checked by a nurse/technician.

times on the "Drug Administration Record" and the "Sample Time Record."[3] Synthon acknowledges that the times were preprinted on these forms and we continue to believe that the use of preprinted times was appropriate and consistent with industry practice. The use of preprinted times does not reduce the accuracy of the data, in fact it has the opposite effect. Preprinting times on the forms allows for the easy documentation of deviations and reduces the risk of transcription errors.

Similarly, Synthon acknowledges that some documents were preprinted with the date upon which multiple activities were to occur. In those instances, the dates were preprinted on the day before the planned studies. This reflects the realty of single-dose bioequivalence studies where a large number of planned activities occur on a single day. Thus, the industry norm is to have certain information (including the date) preprinted for logistical reasons. For example, the date is preprinted on the "Drug Administration Record" and the "Sample Time Record" for the approximately 400 separate activities to occur on a single given day. However, this does not mean that the documents do not bear a handwritten date. On the contrary, the principal investigator signs and dates (**not preprinted**) each record to attest to the validity of the activity and to the initials of the staff performing the function. We are not aware of any statute, regulation or guidance that requires, or even recommends, that the principal investigator initial and date every activity during a bioequivalence study.

Lastly, the Appendix states that "[t]he record included deviations from scheduled times for less than 3% of blood draws."[4] This statement seems to imply that the deviation rate for sampling times was lower than what one would have expected for this type of study. Yet, we find the deviation rate to be consistent with what one would expect for a well-run clinical site that has highly trained phlebotomist/nurses[5] using indwelling venous catheters, which allow for timely blood draws in healthy subjects.

As we have stressed throughout the correspondence concerning this matter, Synthon and [redacted] are committed to full cooperation as to implementing DSI's preferred bioequivalence study methods. In fact, [redacted] has committed to changing its procedures in response to FDA's recommendations. However, Synthon and [redacted] now find themselves in a quagmire, as DSI is changing their requirements in each new response. If it is critical that sponsors use only the DSI preferred approach, FDA is likewise compelled to inform sponsors of those requirements in the form of formal regulations, or at least very specific Guidance documents. Yet, no such regulatory guidance exists. In this regulatory vacuum, regulated entities must be permitted to employ any appropriate means of ensuring the integrity of the study data. Synthon

b(4)

[3] The Appendix to the Division's Response incorrectly refers to the "Dose Administration Record" and the "Sampling Time Record." The correct titles of the document are the "Drug Administration Record" and the "Sample Time Record," respectively.

[4] Please note that the actual deviation rate for blood sample time in this bioequivalence study was 3.14%, not "less than 3%."

[5] Contrary to DSI's statements, we note that "analysts" were not used to draw blood samples. Trained phlebotomist/nurses performed all blood draws.

contends that the data supplied for its bioequivalence study more than adequately met this requirement. DSI has yet to refute that contention. As noted above, unless we receive notification of the approval of the NDA within ten business days of the Division's receipt of this letter, we will assume that the Not Approvable status remains in effect and we will pursue appropriate dispute resolution.

Thank you for your attention to this matter.

Respectfully submitted,

Michael H. Hinckle
Vice President & General Counsel

Enclosure(s)

cc: Eric Colman, M.D., FDA (courtesy copy)
Margaret Simoneau, FDA (courtesy copy)

[ ]

b(4)

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On Original

Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Synthon Pharmaceuticals, Inc. Response to
FDA's July 11, 2006 Letter Regarding "Not Approvable Letter"

LIST OF EXHIBITS

b(4)

Simoneau, Margaret A

From: Richard Almond [ralmond@synthon.com]
Sent: Tuesday, June 20, 2006 4:51 PM
To: Simoneau, Margaret A
Cc: Mike Hinckle; Wayne Stargel
Subject: NDA 21-961, Simvastatin Orally Disintegrating Tablets
Attachments: SOP — 20-03.pdf b(4)

Hi Margaret,

Please refer to Synthon Pharmaceutical, Inc.'s (Synthon) NDA 21-961 for Simvastatin Orally Disintegrating Tablets, the FDA's 5/25/06 Not Approvable Letter and to Synthon's 5/30/06 meeting request packet.

As I explained to you earlier, the original meeting request packet contained an incorrect version of an SOP written in —— Please replace the —— SOP in exhibit 8 of the meeting packet send 5/30/06 with the ——. SOP attached ot this email, this is the correct version. Also, please be aware that the English version of SOP 20-02, also in exhibit 8 of the meeting request packet, indicates that it is version 02, when it is the correct version 03. b(4)

Please forward this information to the appropriate people that will be attending the July 17, 2006 meeting.

Thanks for your help, and please call if you have any questions,

Best Regards,
Rich Almond

Rich Almond, MBA, RAC
Manager, Regulatory Affairs
Synthon Pharmaceuticals, Inc.
9000 Development Drive
Research Triangle Park, NC 27709
Phone: (919) 536-1325
Fax: (919) 493-6104

4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Simoneau, Margaret A

Subject:	NDA 21-961 Simvastatin ODT/End of Review INDUSTRY Meeting to discuss the Not-Approval Action Letter of 5.25.06
cation:	CDER WO 1309 conf rm Bldg22
Start:	Mon 7/17/2006 12:00 PM
End:	Mon 7/17/2006 1:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Parks, Mary H; Colman, Eric C; Hill, John; Chung, Sang; Autor, Deborah; Viswanathan, CT; Salewski, Joseph
Optional Attendees:	Ahn, Hae Young
Resources:	CDER WO 1309 conf rm Bldg22

Note:

INTERNAL MEETING IS JUNE 29, 2006 @ 1 PM

2 pages
Total 7 pages

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-961

Synthon Pharmaceuticals, Inc.
Attention: Michael H. Hinckle, J.D.
Vice President and General Counsel
9000 Development Drive
P.O. Box 110487
Research Triangle Park, NC 27709

Dear Mr. Hinckle:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

The Divisions of Scientific Investigations and Metabolic and Endocrine Products have reviewed your 30 May 2006 submission and response to the 25 May 2006 not approvable letter for NDA 21-961.

A single bioequivalence study was submitted as the sole source of clinical data supporting the approval of NDA 21-961 as a 505(b)(2) application. For the reasons provided in the Appendix, we do not believe you have submitted any new information to assure the accuracy of the drug treatment administration, dosing times, and pharmacokinetic blood sampling times. As no other data were provided to allow us to conclude that simvastatin ODT was bioequivalent to the reference listed product, Zocor®, we continue to believe that the not approvable action taken on NDA 21-961 was appropriate.

Moving forward, we would be happy to discuss the details of another bioequivalence study with you at our meeting scheduled for 17 July 2006.

If you have any questions, call Margaret Simoneau, Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Appendix

Synthon's Comments from 30 May 2006 Submission:

- **The drug identification on the labels of the dispensing envelopes was more than adequate to assure the accuracy and integrity of the biostudy.**

- **The signatures on the dispensing envelopes serve as adequate documentation that the investigator and study nurse visually confirmed the identity of the tablets prior to administration.**

Response: We do not agree that the labels of the dispensing envelopes were adequate. Contrary to the sponsor's assertion, the labeling of the unit dose envelopes were identified as "1 Simvastatin 80 mg tablet" for both the innovator and test product. Although each envelope label was marked "T" or "R" following the study number, there was no record to indicate that either the physician or the technician verified the actual tablet administered at the time of administration. Also, we disagree with the sponsor's claim that the initials on the dosing envelopes constitute confirmation of the identity of the tablets at the time of drug administration. Because the initials on the envelopes were not dated contemporaneously by the responsible individuals (dates on the unit dose envelopes were pre-printed), the initials fail to reflect documentation at the time of dosing. Also, the sponsor's current explanation for the purpose of the initials contradicts their original statement that the initials served to verify the accuracy of the dose administration time. Please recall that the sponsor's monitor signed the dispensing records in North Carolina after the study was completed.

We disagree with the sponsor that there is a high degree of assurance that the drugs were packaged correctly. The sponsor states that [redacted]'s Drug Packaging and Labeling SOP ensures that the correct drug is placed in the correct envelope. However, the procedures in the SOP only reflect intent; source documentation of the actual events is necessary to demonstrate whether the procedures were followed. In this context, the "Drug Packaging Record" does not assure that the dispensing procedures described in [redacted]'s SOP were followed. Furthermore, the packaging information (i.e. preparation and quantity) for each unit dose envelope was not individually initialed and dated by the persons responsible for packaging and verifying the unit doses; instead, the source record contains only one "performed by" and one "checked by" initial for packaging of unit doses for 18 different subjects. The sponsor states that the dosing envelopes were verified by [redacted]'s staff at the time of packaging. This cannot be assured, as the analysts who initialed "Performed by" and "Checked by" did not date their initials. Furthermore, the packaging record does not assure that the unit dose packaging information for each subject was recorded at the time each unit dose was packaged. [redacted]'s SOP for Packaging and Labeling of Study Drugs for Pharmacokinetic Studies states that the packaging information is recorded after all unit doses are packaged. Specifically the SOP states: "Filling drug into envelopes is carried out for each sequence separately. Then an appropriate record is made to Drug Packaging Record form."

b(4)

Synthon's Comment from 30 May 2006 Submission:

- **The actual times of dosing and pharmacokinetic blood sampling were accurately recorded.**

Response: Contrary to the sponsor's assertion, the **actual** times were **not** recorded in the CRFs "Dose Administration Record" and "Sampling Time Record". The only times entered in the CRF records were the scheduled times; in fact, both —— and the sponsor confirmed that these times were preprinted. The record included deviations from scheduled times for less than 3% of blood draws. For all the scheduled drug administration times and a majority of scheduled sampling times, the "Time deviation" columns of the records were documented by a straight line, without the analysts' dates and initials for the individual entries. Although multiple analysts were involved in blood sampling, the records fail to identify the responsible analyst for each blood sampling. Instead, all the analysts involved signed at the bottom of the page, without dating their initials. Because of the failure of the analysts to date their initials, the data in the "Dose Administration Record" and "Sampling Time Record" cannot be verified as contemporaneously recorded. Furthermore, the dates on the CRF records cannot be assured to be recorded on the day the event occurred. b(4)

The —— SOP 46-01 for Recording Dates and Time specifically states: "the responsible person of the pharmacology department enters the dates into the CRFs for upcoming study period on the day prior to planned drug administration. At the same time, the study period number, numbers and initials of the volunteers are entered in the CRFs." b(4)

Both the sponsor and —— state that the time of drug administration was documented on the drug dispensing envelopes and initialed by the physician responsible for dosing and study nurse. However, since the initials on the envelopes were not dated, it is not possible to verify whether the times were recorded on the day of drug administration. The date on the envelope was preprinted and therefore does not constitute contemporaneous documentation. b(4)

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

/s/

Eric Colman
7/11/2006 03:29:27 PM
Eric Colman for Mary Parks

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NEW CORRESP

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JUL 10 2006

CDER White Oak DR 1

RECEIVED

JUL 07 2006

CDER CDR

July 6, 2006

VIA FEDERAL EXPRESS

Mary Parks, M.D.
Division Director
Division of Metabolic and Endocrine Drug Products
US Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705
Tel: 301.796.2290

DUPLICATE

DUPLICATE

RE: NDA # 21-961 / Amendment 012
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
Documentation of receipt of patent notice

Dear Dr. Parks:

We have enclosed one original and two copies of Amendment 012 to Synthon Pharmaceuticals, Inc.'s ("Synthon's") new drug application ("NDA") for simvastatin orally disintegrating tablets (NDA No. 21-961). The amendment is being submitted pursuant to 21 C.F.R. § 314.52(e) and includes documentation of the receipt by the appropriate NDA holder and patent owner of Synthon's notice of patent invalidity or noninfringement for patents included in Synthon's paragraph IV certification pursuant to Synthon's NDA Amendment 011.

Synthon has delivered the notice via Federal Express to the following address (the NDA holder and patent owner):

Merck & Co., Inc.
One Merck Drive
Whitehouse Station, NJ 08889-0100 USA
Attn: Legal Department

The addressee received the notice on July 5, 2006. Therefore, in accordance with FDA's regulations, 21 C.F.R. § 314.52(f), July 6, 2006 is the first day of the 45-day period provided for in Section 505 (c)(3)(C) of the Federal Food, Drug, and Cosmetic Act.

Documentation confirming receipt of the notice by the aforementioned addressee is included in the enclosed amendment in the form of a copy of the Federal Express delivery verification. A completed Form FDA 356h is also included in the amendment.

Should you have any questions concerning this amendment or any other aspect of Synthon's application, please contact me at 919-493-6006.

Sincerely,

Michael H. Hinckle
Vice President & General Counsel

Enclosure(s)

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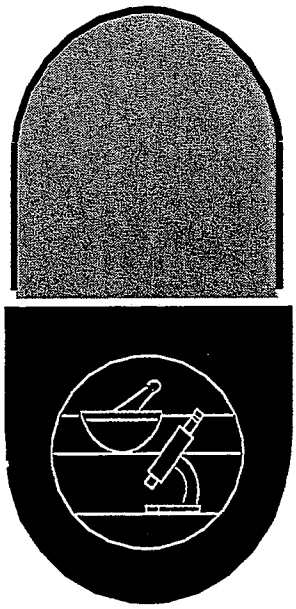
On Original

Orange Book Reference for Patent Information on Zocor®

CUMULATIVE SUPPLEMENT 5
MAY 2005



APPROVED DRUG PRODUCTS

WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

25th EDITION

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs

2005

Proprietary Name Search Results from "OB_Rx" table for query on "Zocor."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
019766		No	SIMVASTATIN	TABLET; ORAL	10MG	ZOCOR	MERCK
019766		No	SIMVASTATIN	TABLET; ORAL	20MG	ZOCOR	MERCK
019766		No	SIMVASTATIN	TABLET; ORAL	40MG	ZOCOR	MERCK
019766		No	SIMVASTATIN	TABLET; ORAL	5MG	ZOCOR	MERCK
019766		Yes	SIMVASTATIN	TABLET; ORAL	80MG	ZOCOR	MERCK

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through May, 2005
Patent and Generic Drug Product Data Last Updated: July 01, 2005

Search results from the "OB_Rx" table for query on "019766."

Active Ingredient:	SIMVASTATIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ZOCOR
Applicant:	MERCK
Strength:	5MG
Application Number:	019766
Product Number:	001
Approval Date:	Dec 23, 1991
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	SIMVASTATIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ZOCOR
Applicant:	MERCK
Strength:	10MG
Application Number:	019766
Product Number:	002
Approval Date:	Dec 23, 1991
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	SIMVASTATIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ZOCOR
Applicant:	MERCK
Strength:	20MG
Application Number:	019766
Product Number:	003
Approval Date:	Dec 23, 1991
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	SIMVASTATIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ZOCOR
Applicant:	MERCK
Strength:	40MG
Application Number:	019766

Appears This Way On Original

Product Number:	004
Approval Date:	Dec 23, 1991
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	SIMVASTATIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ZOCOR
Applicant:	MERCK
Strength:	80MG
Application Number:	019766
Product Number:	005
Approval Date:	Jul 10, 1998
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through April, 2005
Patent and Generic Drug Product Data Last Updated: May 24, 2005

Patent and Exclusivity Search Results from query on Appl No 019766 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019766	001	4444784	DEC 23,2005			U-59
019766	001	4444784*PED	JUN 23,2006			U-59

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019766	001	I-350	OCT 18,2005
019766	001	PED	APR 18,2006
019766	001	I-390	APR 16,2006

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

View a list of all patent use codes
View a list of all exclusivity codes

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Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through April, 2005
Patent and Generic Drug Product Data Last Updated: May 24, 2005

Patent and Exclusivity Search Results from query on Appl No 019766 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019766	002	4444784	DEC 23,2005			U-59
019766	002	4444784*PED	JUN 23,2006			U-59

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019766	002	I-350	OCT 18,2005
019766	002	I-390	APR 16,2006
019766	002	PED	APR 18,2006

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

View a list of all patent use codes
View a list of all exclusivity codes

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Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2005
Patent and Generic Drug Product Data Last Updated: September 20, 2005

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
I-350	TREATMENT OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA IN ADOLESCENT BOYS AND GIRLS AT LEAST ONE YEAR POSTMENARCHAL, AGES 10 TO 17 YEARS, WITH A RECOMMENDED DOSING RANGE OF 10 TO 40MG ONCE DAILY

View a list of all exclusivity codes

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Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-59	METHOD OF TREATING HYPERCHOLESTEROLEMIA

View a list of all patent use codes

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Orange Book Data - **Monthly**
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Orange Book Data Updated Through July, 2005
Patent and Generic Drug Product Data Last Updated: September 20, 2005

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
PED	PEDIATRIC EXCLUSIVITY

View a list of all exclusivity codes

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FDA/Center for Drug Evaluation and Research
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Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2005
Patent and Generic Drug Product Data Last Updated: September 20, 2005

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Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
I-390	USE IN PTS AT HIGH RISK CORONARY EVENTS DUE TO EXISTING CORONARY HEART DISEASE,DIABETES,PERIPHERAL VESSEL DISEASE,STROKE HISTORY,OTHER CV DISEASE TO REDUCE RISK TOTAL MORTALITY BY REDUCING CORONARY DEATH,REDUCE NONFATAL MI & STROKE.....

View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2005
Patent and Generic Drug Product Data Last Updated: September 20, 2005

Synthon
Pharmaceuticals, Inc.

Paragraph III Certification

In accordance with section 505(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), Synthon Pharmaceuticals, Inc. ("Synthon") hereby provides its Patent Certification for our New Drug Application for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets. Synthon's NDA is submitted under FDCA § 505(b)(2) and incorporates by reference the FDA's previous finding of safety and efficacy for the Zocor® drug product described in approved NDA # 19-766.

Synthon hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 4,444,784 held by Merck & Co., Inc. will expire on December 23, 2005, but that, for the purposes of this Patent Certification, such expiration date has been extended to June 23, 2006 pursuant to FDCA § 505A. In accordance with FDCA § 505(b)(2)(A)(iii) and 21 C.F.R. § 314.50(i)(1)(i)(3), Synthon is hereby requesting approval of its NDA no earlier than June 23, 2006.

Synthon Pharmaceuticals, Inc.

Kamali Chance
Kamali Chance, MPH, Ph.D., RAC
Director of Regulatory Affairs

July 19, 2005
Date

9000 Development Drive • P.O. Box 110487 • Research Triangle Park, North Carolina 27709
Phone +1 (919) 493-6006 • Fax +1 (919) 493-6104

1.3.3 Submission of Patent Information

Synthon Pharmaceuticals, Inc. hereby certifies that there are no relevant patents that claim the proposed drug substance (simvastatin), drug product (Simvastatin 10 mg, 20 mg, 40 mg, 80 mg orally disintegrating tablets), or any method of use of such drug product. A completed FDA Form 3542a is provided in Exhibit 1 to this Section.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER

NAME OF APPLICANT / NDA HOLDER
Synthon Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
None

ACTIVE INGREDIENT(S)	STRENGTH(S)
Simvastatin	10mg, 20mg, 40mg, 80mg

DOSAGE FORM
Orally Disintegrating Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

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

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Michael H. Hinckle	7/22/05

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

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Michael H. Hinckle, Esq., Synthon Pharmaceuticals, Inc., Vice President & General Counsel	
Address 9000 Development Drive P.O. Box 110487	City/State Research Triangle Park, North Carolina
ZIP Code 27709	Telephone Number (919) 493-6006
FAX Number *(if available)* (919) 493-6104	E-Mail Address *(if available)* mhinckle@synthon-usa.com

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INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

1.3.1 Basis for New Drug Application

Synthon Pharmaceuticals, Inc.'s (Synthon's) proposed new drug product, Simvastatin orally disintegrating tablets is a new dosage form of the blood lipid-lowering drug product Zocor® tablets, NDA # 019766, held by Merck & Co., Inc. After oral ingestion, simvastatin, which is an inactive lactone is hydrolysed to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which catalyses an early step in the biosynthesis of cholesterol limiting the rate of the total reaction. The active moiety, simvastatin, is identical for Synthon's proposed new drug product, Simvastatin orally disintegrating tablets and Zocor® tablets marketed by Merck & Co., Inc.

In accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. § 314.54, this NDA relies, in part, on FDA's finding of safety and effectiveness for the approved Zocor® drug product as well as the safety and efficacy information contained in the scientific literature. Hence, there was no need to duplicate the clinical trials necessary to demonstrate the well-established safety and efficacy of simvastatin. A comparative bioavailability study performed by Synthon demonstrates that Synthon's Simvastatin orally disintegrating tablets is "bioequivalent" to the approved Zocor® drug product. A detailed discussion of the bioequivalence study, statistical analyses, and the study protocol are provided in Volume 1, Module 5 of this application.

Because of proven bioequivalence, the package insert for Simvastatin orally disintegrating tablets is the same as the approved labeling for Zocor® tablets with certain modifications which are listed below and also can be found in a side by side, annotated label comparison in Volume 1, Module 1, Section 6.3.1 of this application.

According to information published in the list of Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), 25th Edition, cumulative Supplement 05 (May, 2005), U.S. Patent No. 4,444,784 is the only patent listed by Merck & Co., Inc. for Zocor® drug product (see Exhibit 1 to this section). This patent expires on December 23, 2005, but has received an additional six months of Orange Book listing pursuant to a grant of "pediatric exclusivity." Therefore, for the purposes of the patent certification required under FDCA § 505(b)(2)(A) and 21 C.F.R. § 314.50(i), the Orange Book patent "expiration" date for the relevant listed patent is June 23, 2006. Synthon is filing a patent certification to this listed patent pursuant to FDCA § 505(b)(2)(A)(iii) (i.e., a "Paragraph III Certification"). Therefore, Synthon acknowledges that this

NDA cannot receive final approval prior to June 23, 2006. Paragraph III Certification is provided in Volume 1, Module 1, Section 1.3.2, Exhibit 1.

Additionally, Zocor® is the subject of two unexpired periods of market exclusivity associated with new indications. These exclusivity periods cover: (1) "treatment of heterozygous familial hypercholesterolemia in adolescent boys and girls at least one year postmenarchal, ages 10 to 17 years, with a recommended dosing range of 10 to 40 mg once daily" and (2) "use in patients at high risk of coronary events due to existing coronary heart disease, diabetes, peripheral vessel disease, stroke history, or other cardiovascular disease to reduce risk and total mortality by reducing coronary death, reduce nonfatal myocardial infarction, stroke, etc." These periods of exclusivity expire on April 18, 2006 (including the applicable pediatric exclusivity extension) and April 16, 2006, respectively. In accordance with FDCA § 505(c)(3)(D)(iii) and/or (iv), Synthon acknowledges that this NDA cannot be granted final approval prior to the expiration of all of the aforementioned periods of exclusivity, i.e., April 18, 2006. The exclusivity statement is provided in Volume 1, Module 1, Section 3.2, Exhibit 2.

Active Ingredient

The active ingredient used in the manufacture of Synthon's Simvastatin orally disintegrating 10 mg, 20 mg, 40 mg and 80 mg tablets is simvastatin. The active ingredient used in the manufacture of Zocor® tablets is also simvastatin. Thus, Synthon's Simvastatin orally disintegrating tablets drug product contains the "same" active ingredient as the Zocor® drug product.

Route of Administration, Strength and Dosage Form

The route of administration is oral for both Synthon's Simvastatin orally disintegrating tablets and Zocor® tablets. The dosage form of Synthon's drug product is immediate release orally disintegrating tablets while the Zocor® tablets are standard immediate release tablets. Synthon proposes to market its product in 10 mg, 20 mg, 40 mg and 80 mg strengths, whereas Zocor® is marketed in 5 mg, 10 mg, 20 mg, 40 mg and 80 mg strengths.

Bioequivalence

The bioequivalence study comparing Synthon's Simvastatin orally disintegrating 80 mg tablets with Zocor® 80 mg reference listed drug were performed by the [redacted] located in the [redacted] and the bioanalytical testing was completed by [redacted]

b(4)

[redacted] These studies demonstrate that Synthon's drug product is bioequivalent to the Zocor® 80 mg tablets. Final reports for these studies are provided in Volumes 1 - 6, Module 5 of this submission. A request for a waiver of evidence of *in vivo* bioequivalence for Simvastatin orally disintegrating 10 mg, 20 mg and 40 mg tablets, based on formulation proportionality and *in vitro* dissolution testing is provided in Volume 1, Module 1, Section 3.9, pages 1-6 of this application. b(4)

Potential Clinical Benefits

Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate an early step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

Clinical Use

Hypercholesterolaemia

Simvastatin is used to reduce increased plasma total and LDL cholesterol in patients with primary hypercholesterolaemia (type IIa) or combined hyperlipidaemia (type IIb) in combination with dietary measures when no adequate effect is obtained with dietary measures and other non-pharmacological measures alone (e.g. fitness training and weight loss).

Coronary Heart Disease

Simvastatin is used for the secondary prevention of coronary heart disease in patients with elevated plasma cholesterol levels (>5.5 mmol/l). Prophylaxis with simvastatin is indicated if total cholesterol-serum concentration is 5.5 mmol/l (212 mg/dl) or higher despite lipid-lowering diet and other non-pharmacological measures and should be carried out in conjunction with diet and other non-pharmacological measures (e.g. physical training and weight reduction).

Simoneau, Margaret A

From: Richard Almond [ralmond@synthon.com]
Sent: Thursday, July 06, 2006 9:42 AM
To: Simoneau, Margaret A
Cc: Kim Bartakovits
Subject: End of Review Meeting for SVT-ODT (NDA 21-961)

Hi Margaret,

The following is a list of people who will be attending the NDA 21-961 "End of Review" meeting scheduled for 12:00 pm on July 17, 2006:

[redacted]	[redacted]
Wayne Stargel, Pharm.D.	VP Medical Affairs, Synthon
[redacted]	[redacted]
Michael Hinckle, J.D.	VP General Counsel, Regulatory Affairs, Synthon USA
Gary Yingling, J.D.	Kirkpatrick & Lochart, Nicholson, Graham, LLP – Regulatory Counsel
Richard Almond	Manager, Regulatory Affairs, Synthon USA

b(4)

Could you please forward to me a list of people from FDA that confirmed they will attend. I believe last time we spoke a few people were still tentative.

Thanks,

Rich Almond

Rich Almond, MBA, RAC
Manager, Regulatory Affairs
Synthon Pharmaceuticals, Inc.
9000 Development Drive
Research Triangle Park, NC 27709
Phone: (919) 536-1325
Fax: (919) 493-6104

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E M O R A N D U M

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

DATE: July 5, 2006

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director - Bioequivalence
Division of Scientific Investigations (DSI)

SUBJECT: DSI Review of Sponsor's May 30, 2006 Response to FDA's May 25, 2006 "Not Approvable Letter" for NDA 21-961 (Simvastatin Orally Disintegrating Tablets) Sponsored by Synthon Laboratories Inc.

TO: Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Drug Products (DMEP)

This memorandum is limited to Sponsor's response to DMEP's May 25, 2006 "Not Approvable Letter", particularly their response to inspectional findings for the following bioequivalence study. The inspectional findings were relayed to DMEP verbally and by electronic mail on May 17 and 23, 2006, respectively, and DSI's review of the inspectional findings was provided in a separate memo to DMEP dated June 7, 2006.

Synthon Protocol CSP.US01.SVT.ODT80.001
"Randomized, Two-period, Crossover, Bioequivalence Study on Simvastatin 80 mg ODT (Synthon Pharmaceuticals, Ltd., USA) versus ZOCOR® 80 mg Tablets (Merck & Co., Inc., USA) in Healthy Volunteers under Fasting Conditions."
[redacted] *Study No* [redacted] *226-04)*

b(4)

Background

At the request of DMEP, the DSI conducted a **for cause** audit of the clinical portion of Study CSP.US01.SVT.ODT80.001 at [redacted] at [redacted] between May 15 and 18, 2006. This was a for cause audit, since the first FDA inspection of [redacted] in November, 2005 conducted by an FDA investigator from the New York District Office (NYK-DO) found significant deficiencies. DSI's evaluation of the FDA investigator's findings resulted in the rejection of a bioequivalence study for a generic drug application.

The current audit found that the accuracy of the drug treatment administration, dosing times, and pharmacokinetic blood sampling times cannot be assured, confirming the findings of the earlier inspection of this facility by the NYK-DO FDA investigator. Based on the significant deficiencies in study conduct, DSI recommended to DMEP that Study

CSP.US01.SVT.ODT80.001 not be accepted for Agency review (Refer to DSI review dated 6/7/06). DMEP concurred with DSI's recommendation and sent a "Not Approvable Letter" to the sponsor. In their May 25, 2006 response to DMEP, the sponsor responded to the inspectional findings and maintained that "the observations do not rise to the level of justifying the rejection of the biostudy data". In addition, [redacted], the clinical site, also responded to inspectional findings in their letter dated June 15, 2006 to DSI. b(4)

DSI's Review of Synthon's May 25, 2006, Letter to DMEP and [redacted] Response June 15, 2006, to DSI:

Following our review of the responses, DSI concludes that the information provided by the sponsor and [redacted] do not resolve the significant deficiencies identified during the inspection. It remains that the source documentation fails to confirm the identity of the treatments administered to the study subjects at the time of dosing.

The sponsor's claim that the "DSI conclusion that only the DSI approach is adequate and other appropriate method cannot provide reliable results" and "any study not conducted using the exact administrative procedures preferred by an individual Agency Investigator would be suspect and, indeed, unacceptable" is without merit. There is no specialized DSI approach or individual preference but only verification of accuracy based on the source records. In this context, the design and documentation of records for the current study were not adequate to assure proper study conduct. Especially, the sponsor clinical monitor's completion and signature of the "Drug Inventory and Dispensing Record" in North Carolina, a month or more after study completion for a study conducted in [redacted] is unethical and demonstrates a fundamental lack of compliance. Please note that these deficiencies in study conduct were initially observed by an FDA field investigator and not by DSI in relation to a different Synthon application for OGD. The current inspection was conducted by DSI to independently verify whether the findings from the first inspection equally affected the simvastatin NDA. Thus two independent investigators are now in agreement that these deficiencies exist in Synthon's studies. b(4)

DSI's review of the sponsor's specific responses follows:

Synthon's Response

- **The drug identification on the labels of the dispensing envelopes was more than adequate to assure the accuracy and integrity of the biostudy.**
- **The signatures on the dispensing envelopes serve as adequate documentation that the investigator and study nurse visually confirmed the identity of the tablets prior to administration.**

DSI Review: DSI does not find that the labels of the dispensing envelopes were adequate and this remains as a deficiency. Contrary to the sponsor, the labeling of the unit dose envelopes, were identified as "1 Simvastatin 80 mg tablet" for both the innovator and test product. Although each envelope label was marked "T" or "R" following the study number, there was no record to indicate that either the physician or the technician verified the actual tablet administered at the time of administration. Also, DSI disagrees with the sponsor that the initials on the dosing envelopes constitute confirmation of the identity of the tablets at the time of drug

administration. Because the initials on the envelopes were not dated contemporaneously by the responsible individuals (dates on the unit dose envelopes were pre-printed), the initials fail to reflect documentation at the time of dosing. Also, the sponsor's current explanation for the purpose of the initials contradicts their original statement that the initials served to verify the accuracy of the dose administration time. Please recall that the sponsor monitor's signing the Dispensing records in North Carolina after the study completion.

DSI disagrees with the sponsor that there is a high degree of assurance that the drugs were packaged correctly. The sponsor states that ——— s Drug Packaging and Labeling SOP ensures that the correct drug is placed in the correct envelope. However, the procedures in the SOP only reflect intent; source documentation of the actual events is necessary to demonstrate whether the procedures were followed. In this context, the "Drug Packaging Record" does not assure that the dispensing procedures described in ———s SOP were followed. Specifically, the packaging information (i.e. preparation and quantity) for each unit dose envelope was not individually initialed and dated by the persons responsible for packaging and verifying the unit doses; instead the source record contains only one "performed by" and one "checked by" initial for packaging of unit doses for 18 different subjects. The sponsor's states that the dosing envelopes were verified by ——— s staff at the time of packaging. This cannot be assured, as the analysts who initialed "Performed by" and "Checked by" did not date their initials. Furthermore, packaging record does not assure that the unit dose packaging information for each subject was recorded at the time each unit dose was packaged. ———s SOP for Packaging and Labeling of Study Drugs for Pharmacokinetic Studies states that the packaging information is recorded after all unit doses are packaged, specifically the SOP states, b(4)

> **"Filling drug into envelopes is carried out for each sequence separately. Then an appropriate record is made to Drug Packaging Record form."**

Synthon Response

- **The actual times of dosing and pharmacokinetic blood sampling were accurately recorded.**

DSI Review: Contrary to the sponsor, the **actual** times were **not** recorded in the CRFs "Dose Administration Record" and "Sampling Time Record". The only times entered in the CRF's records were the scheduled times; in fact, both ——— and the sponsor confirmed that these times were preprinted. The record included deviations from scheduled times for less than 3% of blood draws. For all the scheduled drug administration times and a majority of scheduled sampling times, the "Time deviation" columns of the records were documented by a straight line, without the analysts' dates and initials for the individual entries. Although multiple analysts were involved in blood sampling, the records fail to identify the responsible analyst for each blood sampling. Instead, all the analysts involved signed at the bottom of the page, without dating their initials. Because of the failure of the analysts to date their initials, the data in the "Dose Administration Record" and "Sampling Time Record" cannot be verified as contemporaneously recorded. Furthermore, the dates on the CRF records cannot be assured to be recorded on the day the event occurred. ———SOP 46-01 for Recording Dates and Time specifically states b(4)

"the responsible person of the pharmacology department enters the dates into the CRFs for upcoming study period on the day prior to planned drug administration. At the same time, the study period number, numbers and initials of the volunteers are entered in the CRFs."

Both the sponsor and [redacted] state that the time of drug administration was documented on the drug dispensing envelopes and initialed by the physician responsible for dosing and study nurse. However, since the initials on the envelopes were not dated, it is not possible to verify whether the times were recorded on the day of drug administration. The date on the envelope was preprinted and therefore does not constitute contemporaneous documentation. b(4)

In summary, the sponsor has not provided any new information to assure the accuracy of the drug treatment administration, dosing times, and pharmacokinetic blood sampling times.

Sriram Subramaniam, Ph.D.

DSI Final Classification:
OAI – [redacted] b(4)

cc:
HFD-45/RF
HFD-48/Subramaniam/Himaya/cf
HFD-510/Colman/Simoneau
HFD-870/Chung/Ahn
Draft: SS 6/29/06
Edit: JAO 6/30/06
DSI:5659; O:\BE\EIRCOVER\21961synsim.res
FACTS ID 730511

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

/s/

Sriram Subramaniam
7/5/2006 03:33:34 PM
PHARMACOLOGIST
Dr. Viswanathan signed the paper copy on 7/5/06.

N-000 C

NEW CORRESP

DUPLICATE

Synthon
Pharmaceuticals, Inc.

June 30, 2006

VIA FEDERAL EXPRESS

Mary Parks, M.D.
Division Director
Division of Metabolic and Endocrine Drug Products
US Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705
Tel: 301.796.2290

RE: NDA # 21-961 / Amendment 011
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
Amendment of Patent Certification to Include Newly Listed Patents

Dear Dr. Parks:

Reference is made to New Drug Application ("NDA") #21-961 for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg, submitted by Synthon Pharmaceuticals, Inc. ("Synthon") on July 28, 2005. Pursuant to Section 505(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act (the "Act"), Synthon hereby amends the aforementioned NDA to include a "Paragraph IV" patent certification for U.S. Patent Nos. RE36481 and RE36520 (certification enclosed as Exhibit 2). These patents were "re-listed" in FDA's "Orange Book" as a result of a recent court decision.

The notice required under Section 505(b)(3)(A) of the Act has been sent via Federal Express to Merck & Co., Inc., which is the patent owner of both patents and the holder of the relevant approved New Drug Application (i.e., NDA 19-766). As required by Section 505(b)(3)(B), the required notice was sent to Merck on the same day that this amendment was sent to FDA.

Synthon will further amend its NDA with verification of the date upon which Merck received the required notice. Pursuant to Section 505(c)(3)(C), this amendment will delay the effective date of Synthon's NDA approval ***only*** if Merck sues Synthon for patent infringement before the expiration of 45 days after the date upon which Merck receives the aforementioned notice. If no lawsuit is filed within the prescribed 45-day period, this certification will not result in any delay in the approval of Synthon's NDA. If a lawsuit is filed, Synthon will amend its NDA to notify FDA of the filing of the suit.

9000 Development Drive • P.O. Box 110487 • Research Triangle Park, North Carolina 27709
Phone +1 (919) 493-6006 • Fax +1 (919) 493-6104

Should you have any questions or comments concerning this amendment, please do not hesitate to contact me at (919) 493-6006.

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

Appears This Way
On Original

Synthon
Pharmaceuticals, Inc.

June 30, 2006

Paragraph IV Patent Certification

Synthon Pharmaceuticals, Inc. certifies that, in its opinion and to the best of its knowledge, U.S. Patent Nos. **RE36481** and **RE36520** are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the Simvastatin Orally Disintegrating Tablets for which New Drug Application No. 21-961 was submitted:

Paragraph IV Statement

Synthon Pharmaceuticals, Inc. hereby states, in accordance with Sections 505(b)(3) of the Federal Food, Drug, and Cosmetic Act ("the Act") and 21 C.F.R. § 314.50(i)(1)(i)(A)(4), that it has given or is giving on even date herewith notices containing the information required by Section 505(b)(3)(D) of the Act and 21 C.F.R. § 314.52(c) to the following persons by Federal Express with receipt verification:

1. The owner of each of the following patent numbers:

   RE36481 and RE36520 (or the representative of each owner designated to receive the notice); and

2. The holder of approved NDA number 19-766 (or the representative of the holder designated to receive the notice).

Synthon Pharmaceuticals, Inc.

Michael H. Hinckle
Vice President & General Counsel

9000 Development Drive • P.O. Box 110487 • Research Triangle Park, North Carolina 27709
Phone +1 (919) 493-6006 • Fax +1 (919) 493-6104

Simoneau, Margaret A

Subject:	NDA 21-961 Simvastatin Orally Disintegrating Tablet/End of Review INTERNAL MEETING/Discussion of Agency's Not-Approval Action Letter of 5.25.06
cation:	CDER WO 3376 conf rm Bldg22;
Start:	Thu 6/29/2006 1:00 PM
End:	Thu 6/29/2006 2:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Resources:	CDER WO 3376 conf rm Bldg22

Called to Sponsor's date 6/9/06

NOTE:

1. Brief document is May 30, 2006 (copies to be delivered)
2. For the INTERNAL MEETING, A CALL-IN NUMBER will be made available. Sponsor has requested a face-to-face meeting instead of a teleconference.

Appears This Way
On Original

3 parts

Simoneau, Margaret A

Subject:	NDA 21-961 Simvastatin Orally Disintegrating Tablet/End of Review INTERNAL MEETING/Discussion of Agency's Not-Approval Action Letter of 5.25.06
cation:	CDER WO 3376 conf rm Bldg22;
Start:	Thu 6/29/2006 1:00 PM
End:	Thu 6/29/2006 2:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Parks, Mary H; Colman, Eric C; Hill, John; Chung, Sang; Viswanathan, CT; Autor, Deborah; Famulare, Joseph; Colman, Eric C
Optional Attendees:	Ahn, Hae Young; Salewski, Joseph; Purucker, Mary E; Silverman, Steven
Resources:	CDER WO 3376 conf rm Bldg22

Total 7

Amy Egan
Kate Johnson

NOTE:

1. Brief document is May 30, 2006 (copies delivered)
2. For the INTERNAL MEETING, A CALL-IN NUMBER is available.

PARTICIPANT ACCESS INFORMATION

AUDIO PARTICIPANT ACCESS

CALL DATE:	JUN-29-2006 (Thursday)
CALL TIME:	01:00 PM EASTERN TIME
DURATION:	1 hr
LEADER:	MS MARGARET SIMONEAU
USA Toll Free Number:	888-324-9563

PASSCODE: 49629

For security reasons, the passcode and the leader's name will be required to join your call.

MEMORANDUM

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

DATE: June 7, 2006

FROM: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering NDA 21-961
Simvastatin Orally Disintegrating Tablets
Sponsored by Synthon Laboratories Inc.

TO: Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Drug Products (DMEP)

At the request of DMEP, the Division of Scientific Investigations conducted a **for cause** audit of the clinical portion of the following bioequivalence study:

Synthon Protocol CSP.US01.SVT.ODT80.001
"Randomized, Two-period, Crossover, Bioequivalence Study on Simvastatin 80 mg ODT (Synthon Pharmaceuticals, Ltd., USA) versus ZOCOR® 80 mg Tablets (Merck & Co., Inc., USA) in Healthy Volunteers under Fasting Conditions." b(4)
(*Study No* [redacted] *226-04*)

This report is a follow-up to DSI's discussion of the inspectional findings with Dr. Eric Colman and Ms. Margaret Simoneau of DMEP via telecon on 5/17/06 and e-mail dated 5/23/06.

The clinical portion of Study CSP.US01.SVT.ODT80.001 was conducted at [redacted] at [redacted] The analytical portion was conducted at [redacted] The audit was initiated, as the first FDA inspection of [redacted] in November, 2005 found significant problems with clinical conduct resulting in DSI's recommendation to reject a bioequivalence study for a generic application. b(4)

A Form 483 was issued to [redacted] following the inspection (5/15-18/06). The current inspection confirmed the significant

discrepancies uncovered in the earlier inspection of this facility. As the significant findings at [redacted] affected the acceptability of the study, the inspection at [redacted] was cancelled. The significant findings of the current inspection and an evaluation of them follows: b(4)

Clinical Site: [redacted]

a. **Failure to include the correct name of the dispensed medication (dosage form) on the dispensing envelope prior to dosing. All dosing envelopes, whether they were intended to contain reference material (ZOCOR, 80 mg tablet) or the test article (Simvastatin 80 mg tablet) were labeled "Simvastatin 80 mg tablet". (Item 2, Form 483)**
b. **Failure to include the batch numbers of the medications on the dispensed envelope. (Item 3, Form 483)**
c. **Failure to visually confirm the identity of the medication at the time of drug administration and to document the results of the confirmation. (Item 4, Form 483)**

The study personnel failed to confirm the identity of the medication at the time of drug administration; there was no documentation to indicate that the intended medications were the actual medications administered.

The labels on the unit dose envelopes, irrespective of whether they were intended to contain test or reference, were identified as "1 Simvastatin 80 mg tablet" (Exhibit 1). Further, the envelope label did not include the name of the dispensed medication (e.g. Zocor) or the lot number. Although each envelope label had preprinted letter "T" or "R" following the study number and the test and reference tablets were distinctive in size, shape and scoring, there was no record to indicate that either the physician or the technician verified the actual tablet administered at the time of administration. While initials were recorded on each unit dose envelope, the date when the initials were recorded was not assured as the clinical staff did not date their initials, and hence fails to reflect documentation at the time of dosing. The dates on the envelopes were preprinted.

Therefore, due to the lack of documentation of the treatments administered to the subjects at the time of dosing, **the accuracy of dosing cannot be verified.**

d. **Although the simvastatin study was conducted at the [redacted] site at [redacted] the Drug Inventory and Dispensing Record was signed as verified by the sponsor clinical monitor in North Carolina, U.S on April 21, 2006 after the study completion. (Item 12, Form 483)**
The sponsor's "Drug Inventory and Dispensing Record" (Exhibit 2) was left in place as part of the source records at [redacted] (the clinical site), although it was not completed at the time of the study. Instead, it was completed in North Carolina, a month or more after study completion. This is unethical and fraudulent. b(4)

e. **The CRF fails to include signatures or initials to document individual dosing and dosing verification for study subjects. (Item 6, Form 483)**
The treatments recorded for each subject in the Drug Administration Records (Exhibit 3) represent only intended treatments, as they were preprinted prior to drug administration. According to the site, the only information recorded during dosing was the column entitled "Time Deviation." Also, instead of initialing and dating the dosing record on a line-by-line basis for individual subjects, the records are signed only at the bottom of the document, with the purported intent of confirming dosing for all the subjects covered by the records.

f. **Repackaging records of test and reference medications fail to indicate that individual checks were made. (Item 5, Form 483)**
Each page of the "Drug Packaging Record" (Exhibit 4) documents packaging for about 18 different study subjects. However, the record only includes one "performed by" and one "checked by" signature at the bottom each page to document unit doses for all the subjects listed in the page. Packaging of each unit dose was not individually initialed and dated to confirm dispensing according to the randomization schedule. Also, it is not known when the information was recorded on Drug Packaging Record. [redacted] s drug packaging SOP [redacted] PHA 20-02, indicates that the information on the packaging record was entered after the drug was packaged and not at the time each unit dose envelope was filled. b(4)

g. **Failure to record the actual time of blood draw from the subjects. Only intended draw times are prefilled. (Item 7, Form 483)**
The blood draw times in the "Sampling Time Records" (Exhibit 5) represent only the intended draw times, as the entries were preprinted. According to the site, the only information recorded during blood sampling was the column entitled "Time Deviation." This column only records deviations from the scheduled times, with no initial and date for individual entries. It should be noted that majority of the collection times did not deviate from scheduled times; time deviations were reported for 3% of the collection times.

Similarly, dosing times in the Drug Administration Record (Exhibit 3) only serve as the intended dosing times as the entries were preprinted. As stated in Item e, only the column entitled "Time Deviation" was completed during dosing. Although the unit dose envelopes contain hand-written times following the designation "Admin. Time", the date when the time was recorded on the envelope cannot be assured, as the clinical staff who initialed the labels failed to date their initials. The dates on the labels were preprinted.

Therefore, **the accuracy of the dosing and sampling times cannot be assured** due to the absence of records of the actual times and the technicians' initials and dates to confirm the times.

h. **Failure to maintain adequate and accurate records of receipt and to check for the conditions of study medications such as intact safety seals, unopened bottles, description of the content..etc. (Item 8, Form 483)**
The records do not indicate how ——— received the study drugs (i.e. mode of transport). Also, the records do not indicate whether the drugs were in sealed bottles and whether seals were intact upon receipt. b(4)

i. **Failure to maintain laboratory records to indicate the blood processing procedures and the time elapsed in such process. (Item 9, Form 483)**
Thus, the time elapsed between blood sample collection and frozen storage in unknown. Because of the interconversion between simvastatin and its β-hydroxyacid metabolite in plasma and the absence of information to indicate the duration of study sample storage at bench-top, the accuracy

of reported concentrations of simvastatin and its metabolite achieved in the studies cannot be assured.

j. **Failure to exclude subject 20 from simvastatin study since the subject vomited within 6 hours following dosing (for SVTA). (Item 10, Form 483)**

k. **The sponsor monitor has signed and approved the drug packaging record, drug administration, sample time record and dispensing envelope templates that were used in the studies. These forms fail to provide for individual check, correct name of the medications and actual blood collection times. (Item 11, Form 483)**
The templates for the records used by [redacted] for the studies were approved by the sponsor. b(4)

Conclusion:

The Division of Scientific Investigations recommends that Study CPA 226-04 **not be accepted** as the accuracy of treatments administered (Observations a-f), dosing times and pharmacokinetic blood sampling times (Observation g) cannot be assured.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

DSI Final Classification:
OAI - [redacted] b(4)

cc:
HFD-45/RF
HFD-48/Subramaniam/Himaya/cf
HFD-510/Colman/Simoneau
HFD-870/Chung/Ahn
Draft: SS
Edit: JAO
DSI:5659; O:\BE\EIRCOVER\21961syn.sim
FACTS ID 730511

15/05 2006 13:24 FAX +420 377 540 432 [redacted] 002

EXHIBIT 1

b(4)

CONTAINS PROPRIETARY INFORMATION NOT TO BE DISCLOSED TO A THIRD PARTY

CONFIDENTIAL

FOR CLINICAL TRIAL
Principal Investigator [redacted]
STUDY 099/226/05 PERIOD 1
Subj. No. 1 Initials [redacted]
1 simvastatin 80 mg tablet: 099/226/05/R
Date 12. 03. 05 Admin. Time 7:00
Technician Supervisor [redacted]

b(4)

FOR CLINICAL TRIAL
Principal Investigator : [redacted]
STUDY 099/226/05 PERIOD 2
Subj. No. 1 Initials [redacted]
1 simvastatin 80 mg tablet: 099/226/05/T
Date 26. 03. 05 Admin. Time 7:00
Technician [redacted] Supervisor [redacted]

b(4)

CONFIDENTIAL

CONTAINS PROPRIETARY INFORMATION NOT TO BE DISCLOSED TO A THIRD PARTY

Synthon Pharmaceuticals, Ltd.

Drug Inventory and Dispensing Record

See Form Instructions

Investigator Name: [redacted]	Test Article Identification: Zocor® 80 mg tablets	Lot Number: N5746	Dispensing Unit: 1 tablet	No of Units Rec'd: 90	Date Received: 10.03.2005
Protocol Number: CSP US01.SVT.ODT80.001	Abbreviated Protocol Title: Randomized, Two-period, Crossover, Bioequivalence Study on Simvastatin 80 mg ODT (Synthon Pharmaceuticals, Ltd., USA) versus Zocor® 80 mg tablets (Merck Co., Inc., USA) in Healthy, Volunteers under Fasting Conditions				

Subject Initial				Dispensing Record			*Units Returned by Subject		Verified by Synthon Clinical Monitor	
F	M	U	Enrollment Number	Subject Number (circled for study only)	Date	Units Dispensed (tablets, caps, etc.)	Date	Number of Units	Date	Clinical Monitor Initials
[redacted]			-	1	12.03.2005	1	NA	NA	21.04.05	
			-	2	12.03.2005	1	NA	NA	21.04.05	
			-	3	12.03.2005	1	NA	NA	21.04.05	
			-	4	12.03.2005	1	NA	NA	21.04.05	
			-	7	12.03.2005	1	NA	NA	21.04.05	
			-	8	12.03.2005	1	NA	NA	21.04.05	
			-	9	12.03.2005	1	NA	NA	21.04.05	
			-	10	12.03.2005	1	NA	NA	21.04.05	
			-	11	12.03.2005	1	NA	NA	21.04.05	
			-	12	12.03.2005	1	NA	NA	21.04.05	
			-	14	12.03.2005	1	NA	NA	21.04.05	
			-	16	12.03.2005	1	NA	NA	21.04.05	
			-	17	12.03.2005	1	NA	NA	21.04.05	
			-	21	12.03.2005	1	NA	NA	21.04.05	
			-	22	12.03.2005	1	NA	NA	21.04.05	
			-	26	12.03.2005	1	NA	NA	21.04.05	
			-	31	12.03.2005	1	NA	NA	21.04.05	
			-	37	14.03.2005	1	NA	NA	21.04.05	
			-	38	14.03.2005	1	NA	NA	21.04.05	
			-	40	14.03.2005	1	NA	NA	21.04.05	
			-	41	14.03.2005	1	NA	NA	21.04.05	
			-	42	14.03.2005	1	NA	NA	21.04.05	

Received by Clinical Pharmacy

Signature: [redacted] Date:

Principal Investigator's Signature: [redacted] 21.03.05 Date

* These units are NOT to be redispensed to any study subject. Return them to the Clinical Monitor.

b(4)

Exhibit 2

Synthon Pharmaceuticals, Ltd.

Drug Inventory and Dispensing Record

See Form Instructions

Investigator Name:	Test Article Identification: Simvastatin 80 mg ODT	Lot Number: 311840340	Dispensing Unit: 1 tablet	No of Units Rcvd: 90	Date Received: 10.03.2005
Protocol Number: CSP.US01.SVT ODT80.001	Abbreviated Protocol Title: Randomized, Two-period, Crossover, Bioequivalence Study on Simvastatin 80 mg ODT (Synthon Pharmaceuticals, Ltd., USA) versus Zocor® 80 mg tablets (Merck Co., Inc., USA) in Healthy, Volunteers under Fasting Conditions.				

Subject Initial				Dispensing Record			*Units Returned by Subject		Verified by Synthon Clinical Monitor	
FI	MI	LI	Enrollment Number	Subject Number (contains test article only)	Date	Units Dispensed (capsules, tablets, etc.)	Date	Number of Units	Date	Clinical Monitor Initials
[redacted]			-	5	12.03.2005	1	NA	NA	21.04.05	
			-	6	12.03.2005	1	NA	NA	21.04.05	
			-	13	12.03.2005	1	NA	NA	21.04.05	
			-	15	12.03.2005	1	NA	NA	21.04.05	
			-	18	12.03.2005	1	NA	NA	21.04.05	
			-	19	12.03.2005	1	NA	NA	21.04.05	
			-	20	12.03.2005	1	NA	NA	21.04.05	
			-	23	12.03.2005	1	NA	NA	21.04.05	
			-	24	12.03.2005	1	NA	NA	21.04.05	
			-	25	12.03.2005	1	NA	NA	21.04.05	
			-	27	12.03.2005	1	NA	NA	21.04.05	
			-	28	12.03.2005	1	NA	NA	21.04.05	
			-	29	12.03.2005	1	NA	NA	21.04.05	
			-	30	12.03.2005	1	NA	NA	21.04.05	
			-	32	12.03.2005	1	NA	NA	21.04.05	
			-	33	12.03.2005	1	NA	NA	21.04.05	
			-	34	12.03.2005	1	NA	NA	21.04.05	
			-	35	12.03.2005	1	NA	NA	21.04.05	
			-	36	12.03.2005	1	NA	NA	21.04.05	
			-	39	14.03.2005	1	NA	NA	21.04.05	
			-	44	14.03.2005	1	NA	NA	21.04.05	
			-	46	14.03.2005	1	NA	NA	21.04.05	

Received by Clinical Pharmacy

Signature: [redacted] Date:

Principal Investigator's Signature: [redacted] 22.03.05 Date

* These units are NOT to be redispensed to any study subject

Return them to the Clinical Monitor

b(4)

Exhibit 2

15/05 2006 13:25 FAX +420 377 540 432 EXHIBIT 3 003

[redacted] Study Code:	[redacted]226-04 Page
[redacted] Study Code:	099/226/05
Sponsor's Code:	CSP.US01.SVT.ODT80.001

b(4)

[redacted] 1 (Study Period) 14.03.05 (Date) 1/4 (Page)

Subj. No.	Subj. Initials	Preparation (R/T)	Scheduled time of administration	Time deviation (min)
37	[redacted]	R	7:00	[redacted]
38		R	7:02	[redacted]
39		T	7:04	[redacted]
40		R	7:06	[redacted]
41		R	7:08	[redacted]
42		R	7:10	[redacted]
43		R	7:12	[redacted]
44		T	7:14	[redacted]
45		R	7:16	[redacted]
46		T	7:18	[redacted]
47		T	7:20	[redacted]
48		T	7:22	[redacted]
49		T	7:24	[redacted]
50		R	7:26	[redacted]
51		T	7:28	[redacted]
52		T	7:30	[redacted]
53		R	7:32	[redacted]
54	[redacted]	T	7:34	[redacted]

b(4)

[redacted] (Technician)

CONTAINS PROPRIETARY INFORMATION NOT TO BE DISCLOSED TO A THIRD PARTY

T: Simvastatin 80 mg ODT (Synthon Pharmaceuticals, Ltd., USA)
batch No.: 3118403V3
Dose: 80 mg of simvastatin in one tablet with 240 mL of water 0 min post-dosing

R: Zocor® 80 mg tablets (Merck & Co., Inc., USA)
batch No.: N5746
Dose: 80 mg of simvastatin in one tablet with 240 mL of water

CONFIDENTIAL

14.03.05 (Date) [redacted] (Administration supervised by)

15/05 2006 13:25 FAX +420 377 540 432 [redacted] EXHIBIT 4

[redacted] Study Code: [redacted] 226-04 Page b(4)
Study Code: 099/226/05

Drug Packaging Record

1 (Study Period) 11.03.05 (Date) (Page)

Číslo Dobr. Subj. No.	Přípravek (R/T) Preparation (R/T)	Množství (tbl) Quantity (tbl)	Poznámky Comments
1	R	1	
2	R	1	
3	R	1	
4	R	1	
5	T	1	
6	T	1	
7	R	1	
8	R	1	
9	R	1	
10	R	1	
11	R	1	
12	R	1	
13	T	1	
14	R	1	
15	T	1	
16	R	1	
17	R	1	
18	T	1	

CONTAINS PROPRIETARY INFORMATION NOT TO BE DISCLOSED TO A THIRD PARTY

CONFIDENTIAL

b(4)

[redacted] (Performed by): [redacted]

[redacted] (Checked by): [redacted]

T: Simvastatin 80 mg ODT (Synthon Pharmaceuticals. Ltd., USA)
batch No.: 3118403V3
Dose: 80 mg of simvastatin in one tablet

R: Zocor® 80 mg tablets (Merck & Co., Inc., USA)
batch No.: N5746
Dose: 80 mg of simvastatin in one tablet

b(4)

11.03.05 [redacted] [redacted]

(Date) (Clinical Investigator's Signature)

EXHIBIT 5

[redacted] Study Code: [redacted]226-04 Page 000207

Sponsor's Code: Study Code: 099/226/05 CSP.US01.SVT.ODT80.001

b(4)

/ Sample Time Record

1 (Study Period) 12.08.05 (Date) 1/24 (Page)

Sample No.		1		2		3		4		Comments
Interval		Prior	Dose	7:10	Dev.''	7:20	Dev.''	7:30	Dev.''	
Subj.	Init.	Sample time								
1	[redacted]	6:01	7:00	7:10	—	7:20	—	7:30	—	
2		6:01	7:02	7:12	—	7:22	—	7:32	—	
3		6:03	7:04	7:14	—	7:24	—	7:34	—	
4		6:05	7:06	7:16	—	7:26	—	7:36	—	
5		6:09	7:08	7:18	—	7:28	—	7:38	—	
6		6:09	7:10	7:20	—	7:30	—	7:40	—	
7		6:11	7:12	7:22	—	7:32	—	7:42	—	
8		6:21	7:14	7:24	+1	7:34	+1	7:44	—	
9		6:34	7:16	7:26	—	7:36	—	7:46	—	
10		6:05	7:18	7:28	—	7:38	—	7:48	—	
11		6:38	7:20	7:30	—	7:40	—	7:50	—	
12		6:49	7:22	7:32	—	7:42	—	7:52	—	
13		5:59	7:24	7:34	—	7:44	—	7:54	—	
14		6:32	7:26	7:36	—	7:46	—	7:56	—	
15		6:46	7:28	7:38	—	7:48	—	7:58	—	
16		6:24	7:30	7:40	—	7:50	—	8:00	—	
17		6:00	7:32	7:42	—	7:52	—	8:02	—	
18	[redacted]	6:19	7:34	7:44	—	7:54	—	8:04	—	

b(4)

(Technician) [redacted]

(Supervised by) [redacted]

I

(Note)

b(4)

12.08.05 (Date) (Clinical Investigator's Signature)

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

/s/

Amalia Himaya
6/21/2006 05:25:15 PM
CSO
Paper copy signed by Dr. Viswanathan on 6/7/06 and available upon request.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-961

Synthon Pharmaceuticals, Inc.
Attention: Michael H. Hinckle, J.D.
Vice President and General Counsel
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Mr. Hinckle:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

We also refer to your May 30, 2006, correspondence, received May 31, 2006, requesting a meeting to discuss the Agency's May 25, 2006 action letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: July 17, 2006
Time: 12 Noon
Location: White Oak, 10903 New Hampshire Ave, Building 22, Room 1309
Silver Spring, Maryland 20993-0002

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Margaret.Simoneau@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Margaret Simoneau 301-796-1295; the division secretary, 301-796-2290. If you have any questions, please call me.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Margaret Simoneau
6/9/2006 02:59:23 PM

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ORIGINAL

Synthon
Pharmaceuticals, Inc.

CDER/CDR
MAY 31 2006
RECEIVED

May 30, 2006

ORIG AMENDMENT
N-000-MR

VIA FEDERAL EXPRESS

Mary Parks, M.D.
Division Director
Division of Metabolism and Endocrinology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705
Tel: 301.796.2290

RECEIVED
JUN - 1 2006
CDER White Oak DRM

RE: NDA 21-961
Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Synthon Pharmaceuticals, Inc.'s Response to FDA's May 25, 2006 "Not Approvable Letter"

Dear Dr. Parks:

Reference is made to the May 25, 2006 letter from the Division of Metabolism and Endocrinology Drug Products (the "Division") to Synthon Pharmaceuticals, Inc. ("Synthon") concerning the "Not Approvable" status of NDA 21-961 (the "Not Approvable Letter," copy enclosed as Exhibit 1).

In accordance with 21 C.F.R. § 314.120(a)(1), Synthon hereby provides notice to the Division that Synthon intends to amend NDA 21-961 to respond to the deficiency noted in the Not Approvable Letter related to the documentary controls of Synthon's bioequivalence study. Synthon acknowledges that the submission of such an amendment will constitute an agreement between Synthon and the Food and Drug Administration ("FDA") to extend the review period under 21 C.F.R. § 314.60. *See id.*

By this letter, Synthon also requests an "End of Review" meeting with the appropriate representatives of the Division and the Division of Scientific Investigations ("DSI") to discuss the integrity of the data supporting Synthon's NDA. Because of the nature of the issues and the importance of the matter to Synthon, we further request that the meeting be "face-to-face" instead of via teleconference. Synthon intends to have the following people attend the meeting:

b(4)

9000 Development Drive • P.O. Box 110487 • Research Triangle Park, North Carolina 27709
Phone +1 (919) 493-6006 • Fax +1 (919) 493-6104

Wayne Stargel, Pharm.D. – V.P. Medical Affairs, Synthon

b(4)

Michael Hinckle, J.D. – V.P. General Counsel, Regulatory Affairs, Synthon
Gary L. Yingling, J.D. – Kirkpatrick & Lockhart, Nicholson, Graham, LLP

As discussed in greater detail below, there is no reasonable scientific nexus between the inspectional observations, when viewed in their true light, and DSI's recommendation that Synthon's bioequivalence study data are "unacceptable." DSI would have the Division take a "form over function" position whereby any study not conducted using the exact administrative procedures preferred by an individual agency investigator would be suspect and, indeed, unacceptable. Such a narrow interpretation of inspectional findings is not only inconsistent with DSI's mandate, it usurps the Division's authority and responsibility for ultimately determining whether a new drug is safe and effective.

The specific DSI allegations contained in the Not Approvable Letter are restated below (*See* Not Approvable Letter, p.1):

1. "There was no documentation to indicate the actual times of dosing and pharmacokinetic blood sampling, as the information was pre-printed."

2. "[A]ll dispensing envelopes, whether they were intended to contain the reference material (ZOCOR 80 mg tablet) or the test article (Simvastatin 80 mg tablet) were labeled 'Simvastatin 80 mg tablet' and did not contain the batch number of the tablets."

3. "Although the letter "T" (for test tablet) or "R" (for reference tablet) was pre-printed on the dispensing envelope and the tablets were distinctly different, there was no record of the investigator confirming the identity of the tablets after removing them from the dispensing envelope, prior to administering the dose."

4. "There were no adequate and accurate records of the receipt and condition of the study medications."

We will address each of these allegations in order. However, at the outset, we note that allegation number 1, above, concerning drug administration and sampling times is particularly distressing to Synthon because it is blatantly misleading. The language of the allegation would have one believe that the clinical site (, hereafter ' , simply did not record the drug administration and sampling times. Nothing could be farther from the truth. As explained below, recorded the *actual* drug

b(4)

administration times on the dispensing envelopes and recorded the sampling times as a deviation from the scheduled time. As with all of the other DSI objections, there is no allegation that [redacted] did not follow the protocol or that [redacted] cannot accurately tell the Agency when a subject received the study medication or when a blood sample was taken. Yet, the written allegations give the impression that such a violation occurred. b(4)

It is also important to note that Synthon and [redacted] are committed to full cooperation as to implementing DSI's preferred biostudy methods. In fact, [redacted] has committed to changing its procedures in response to the DSI investigator's recommendations and Synthon do not dispute that DSI's preferred approach is "adequate" under FDA's bioequivalence regulations. Rather, [redacted] and Synthon dispute DSI's conclusion that *only* the DSI approach is "adequate" and other appropriate methods cannot provide reliable study results that clearly support NDA approval. If it were critical that sponsors use only the DSI preferred approach, the Agency would be compelled to promulgate regulations, or a very specific Guidance, *requiring* that such an approach be used for bioequivalence studies. Yet, there are no regulations detailing bioequivalence study procedures to this degree. In fact, there are no FDA Guidance Documents identifying settled methods for documenting drug administration and sampling times. Without such regulatory guidance, regulated entities are free to employ any appropriate means of ensuring the integrity of the study data. As the Division will note from the information and data supplied in this response, Synthon and [redacted] more than adequately met this requirement. Accordingly, we ask that the Division reject DSI's recommendation that the observations are sufficient to justify invalidating the study data. b(4)

I. The actual drug dosing times and drug sampling times were accurately recorded.

The *actual* drug administration times and pharmacokinetic sampling times were accurately recorded by [redacted] in each subject's Case Report Form ("CRF"). Accordingly, the allegation that there was "no documentation to indicate the actual times of dosing and pharmacokinetic blood sampling," is incorrect. Furthermore, DSI's reference to "pre-printed" information is misleading in that only the *scheduled* times are "pre-printed" prior to study commencement. In fact, the *actual* drug administration times were recorded by the clinical investigator, and verified by a nurse, at the time of administration. These were raw data that were recorded in the CRF in the form of the completed dispensing envelopes. Likewise, the *actual* blood sampling times were recorded in the CRF as a deviation from the scheduled time for blood draw. A lack of a deviation from the scheduled time was recorded by a straight line through the "Time Deviation" block in accordance with [redacted] s Standard Operating Procedures ("SOP"). As a result. [redacted] has more than adequate documentation demonstrating the actual times of drug administration and pharmacokinetic sampling. b(4)

[redacted] utilizes a drug envelope system to dispense the study drugs and document the time of drug administration for bioequivalence studies (copies of the original dispensing envelopes are provided in Exhibit 2). On the day prior to administration, the drugs (Reference and Test) were dispensed by a physician from the original containers into the drug envelopes that are labeled with the study number, a unique number identifying the enclosed drug as "test" or "reference," principal investigator, subject number, subject initials, period number (1 versus 2 for crossover studies), drug name (generic only), date of drug administration, and a place for the investigator and study nurse to document administration time at the time of dosing. Simply put, the physician administers the drug and immediately documents the actual time of dosing on the envelope. The study nurse also initials the envelope to independently verify the accuracy of the administration time. As stated above, the envelopes are also included in each subject's CRF. b(4)

In addition to the documentation on the dispensing envelope, [redacted] also completes a "Drug Administration Record" designed to capture the time of dosing and any time deviation from the scheduled dosing time (examples enclosed as Exhibit 3). Likewise, deviations in drug sampling times are recorded on a similarly formatted "Sample Time Record" (examples enclosed as Exhibit 4). For these two documents, which are included in the CRF, [redacted] used a straight line through the "Time Deviation" box to indicate when no deviation occurred from the scheduled administration or dosing time. This procedure not only accurately documented the actual relevant time, it was also described in, and controlled by, an SOP that was in place at the time that these studies were performed. *See* [redacted] SOP No. [redacted] PHA 46-01 (enclosed with English translation as Exhibit 5). Study personnel were trained on this SOP and, as a result, were clearly instructed to document time deviations on CRFs as ± minutes in relation to the scheduled time. b(4)

[redacted]'s approach of documenting the drug administration and sampling times actually provides a reduced likelihood of transcription errors. Consequently, [redacted]'s approach provides at least the same degree of accuracy as the DSI preferred approach.[1] As such, Synthon maintains that this is an acceptable method for documenting deviations from the scheduled administration and/or sampling time. Although, [redacted] agreed to change its procedures to comply with DSI's preferred approach of hand writing the actual dosing/sampling times [redacted]'s acquiescence to DSI was by no means an acknowledgement that the procedures used in the simvastatin biostudy were inadequate. On the contrary, the science and evidence leave no doubt that [redacted]'s procedures for b(4)

[1] It should be noted that [redacted] and [redacted] (the principal investigator for all of [redacted]'s studies) have been using this approach for documenting dosing and sampling times for over 10 years in over 180 studies. Numerous other regulatory authorities have reviewed the methodology and agreed that it adequately records the relevant information. b(4)

documenting administration and sampling times are more than adequate under FDA's regulations.

II. The drug identification on the labeling of the dispensing envelopes was in accordance with applicable law and more than adequate to assure the accuracy and integrity of the biostudy.

The observations concerning the lack of the proprietary name (i.e., "ZOCOR") and batch numbers on the dispensing envelopes are factually accurate, but totally irrelevant to the issue of the reliability of the study data. Furthermore, there is no legal requirement or practical need for this information to appear on the clinical study dispensing envelope. As discussed in greater detail below, the envelopes were clearly marked as containing either "test" product or "reference" product. Including the proprietary name and batch numbers on the envelopes would not have provided any meaningful additional assurance of accuracy. In fact, including the proprietary name on the envelope would have potentially biased the reporting of adverse experiences, in that a subject may have known whether he or she received a "brand" drug or a "generic" drug.

Thus, once it is established that the "T" and "R" on label is sufficient to inform the investigator as to whether the envelope contains a "test" or "reference" product, the repackaging of the drugs into the dispensing envelopes becomes the most critical step in assuring that the correct drug is administered to the correct patient at the correct time. In this regard, ——— has a very high degree of assurance that its drug labeling and packaging processes are more than adequate to assure the validity of the study. b(4)

As noted by DSI, both the test and reference drugs are identified on the envelope by the generic name "simvastatin 80 mg tbl." However, the envelope also contains a unique internal code following the generic name that classifies the drug as the test or reference drug. For example, the label code for the "test" drug in this instance was 099/226/05/**T** while the code for the "reference" drug was 099/226/05/**R** (copies of the original dispensing envelopes are provided in Exhibit 2). The protocol clearly states that the letter at the end of the code identifies which drug is contained in the envelope. *See* Study Protocol, at pp. 4 and 16, enclosed as Exhibit 6. Specifically, the protocol states that the letter "**T**" corresponds to the Test Drug and the letter "**R**" to the Reference Drug. *See id.* This coding system is also intuitive in that one would naturally associate the letter "T" with "test" and the letter "R" with "reference." The study personnel are well trained on the meaning of these codes to avoid confusion. Furthermore, the drug in the dosing envelope is verified by two independent members of ——— s staff at the time of dispensing, one of whom is the dispensing physician. The double verification is documented on the Drug Packaging Record (enclosed as Exhibit 7). This check and recheck of the content of the drug envelope against the original drug container provides a b(4)

high degree of assurance that the correct drug will be administered to the correct subject during the correct study period.

Importantly, in the ——— where this study was competed, *only* a physician can package and dispense drugs for clinical studies. Therefore, a physician packaged the drugs the day before dosing, and a different physician was responsible for dosing the subjects the following morning. Each of these physician-performed operations (i.e., packaging and dosing) was verified by a nurse/technician. The physicians involved with these studies were trained and required to know the difference in appearance between the test and reference product. The visual description of the drug products is stated in the prescribing information and the certificates of analysis. Additionally, in this case the two drug products were different dosage forms (orally disintegrating tablets versus solid oral dose tablets) with very different appearance (a red capsule-shaped tablet marked "543" on one side and "80" on the other side, versus a white round tablet marked "S80" on one side and "ODT" on the other side). Importantly, the entire clinical packaging operation is controlled by a ——— SOP that ensures that the correct drug is placed into the correct envelope. *See* ——— SOP No. ——— PHA 20 (enclosed with English translation as Exhibit 8). The key aspects of this SOP are as follows: b(4)

1. A physician investigator is responsible for packaging the drug.
2. A second medical practitioner double checks all packaging steps.
3. The physician investigator verifies the count of the clinical supplies prior to the packaging step. The drug count is matched with the information on the "Drug Accountability Form" (enclosed as Exhibit 9). This is an additional verification of drug received and drug dispensed.
4. The packaging occurs in two separate operations. First, all of the "test" envelopes are filled. Only after this first operation is completed, does the physician move to the second step where all of the "reference" envelopes are filled. Thus, at no time are both test and reference products being placed into envelopes at the same time.

This comprehensive SOP has been reviewed by numerous regulatory authorities and has repeatedly been found acceptable. Once again, ——— has agreed to label its dispensing envelopes with the proprietary name and batch numbers for future FDA regulated studies. However, the labels used in the simvastatin study: (1) clearly identified which drug was enclosed; (2) prevented a potential bias in adverse experiences; and (3) met all applicable regulatory requirements. Furthermore ———'s procedures for filling the envelopes ensured that the enclosed drug matched the envelope label. Therefore, there is no evidence or reason to suspect that the alleged deficiency concerning the labels used for the simvastatin study reduced the accuracy of the study data. b(4)

With regard to the DSI allegation concerning the lack of drug batch numbers on the drug dispensing envelopes, it is important to note that only one batch of each drug product (i.e., test and reference) was used for this study and those batches were clearly identified in the protocol and the Drug Packaging Record (*see* Exhibit 7). The identification of the drug product on the dispensing envelope as either "test" or "reference" made any reference to the batch number superfluous. While [redacted] has agreed to add batch numbers to the envelopes of all future FDA regulated studies, there is simply no basis to conclude that the lack of a batch number on the envelopes used for the simvastatin study reduced the accuracy of the study data. b(4)

III. The signatures on the dispensing envelopes serve as adequate documentation that the investigator and study nurse visually confirmed the identity of the tablets prior to administration.

Contrary to DSI's allegation, the physician investigator's initials on the dispensing envelope constitutes evidence that the physician confirmed the identity of the study drug prior to administration. Physicians are trained to verify the dose prior to drug administration, and in these studies, the physician could easily distinguish the reference and test drugs. The visual confirmation occurred when the physician removed the drug from the envelope and dosed the subject. This process is confirmed by the physician's initials and verified by the nurse's initials on the drug envelope.

In this case, the test and reference products were different dosage forms with very different appearance (i.e., size, shape, and color). Additionally, the two products were administered differently. The test product was given with water after one minute, while the reference product was taken concurrently with water. Thus, the investigator could not appropriately instruct a subject as to drug administration unless he first confirmed that the proper dosage form was included in the envelope. The study nurse also independently verified the identity of the study drug prior to dosing.

Moreover, it is important to note that the visual verification of the study drug at the time of dosing is confirmation that the packaging operation was properly performed. As noted in Section II, above [redacted], packaging operation is carefully controlled to ensure a high degree of assurance that the envelopes contain the proper study drug product. Thus, the identity of the drug was confirmed by a physician and verified by a nurse (or technician) both at the time of packaging and at the time of administration. b(4)

IV. [redacted] has adequate and accurate records of the receipt, inventory, and condition of the study drugs.

The clinical investigator personally received the study drugs, performed an inventory, and documented receipt of the drug products. The study drugs were hand delivered from

the study analytical site, which received the drugs from Synthon. Upon receipt, the investigator signed an "Acknowledgement Form" which serves as documentation of the date of receipt (enclosed as Exhibit 10). Additionally, after performing an inventory of the study drugs, the investigator completed a "Drug Accountability Form," which serves as documentation of the quantity and condition of the drugs (enclosed as Exhibit 9). *See also* ——— SOP No —— PHA 21-01 (enclosed with English translation as Exhibit 11). b(4)

In accordance with the protocol, the clinical investigator was required to be familiar with the appearance and characteristics of all study drug products. With regard to the simvastatin products, the test and reference drugs were dramatically different in appearance. Any discrepancies with respect to product appearance, characteristics, or quality would have been noted during the inventory and documented in the "Comments" section of the "Drug Accountability Form." Furthermore, ——— s SOP requires that the sponsor be immediately notified of any such deficiency. *See* Exhibit 11, section 2.1.). b(4)

In response to DSI's request ——— has implemented procedures for future studies that will provide more detailed documentation for FDA regulated studies. Nevertheless, the documentation of receipt, inventory and condition of the study drugs that was performed for the simvastatin study was more than adequate to ensure the integrity of the study data.

* * * *

In conclusion, the DSI observations, questioning ——— s documentary controls for the biostudy, do not suggest any fraud in the study, nor do they suggest that any of the study data are inaccurate. Therefore, the observations do not rise to the level of justifying the rejection of the biostudy data. The drug administration and sampling times were accurately recorded, albeit using a method that was different from, but equivalent to, the method preferred by the DSI investigator. The labeling of the dispensing envelopes contained sufficient information to ensure drug administration accuracy, and the physician investigator adequately documented the identity of the study drugs at the time of dosing. Furthermore, the receipt and condition of the study medications were properly recorded. Thus, there is no reasonable basis for requiring that the biostudy be repeated. In fact, doing so would unnecessarily expose subjects to study medication. b(4)

Accordingly, we request that the Division reject DSI's recommendation concerning the simvastatin biostudy and proceed with the review of NDA 21-961.

Thank you for your attention to this matter. We look forward to hearing from the Division concerning our request for a face-to-face "End of Review" meeting.

Should you have any questions concerning this matter, please direct them to my attention at telephone number (919) 493-6006 or via facsimile at (919) 493-6104.

Sincerely,

Michael H. Hinckle
Vice President & General Counsel
Synthon Pharmaceuticals, Inc.

Enclosure(s)

cc: Dr. Robert Temple, Director
Office of Medical Policy
Dr. Joanne Rhoads, Director
Division of Scientific Investigations
Ms. Margaret Simoneau,
Division of Metabolism and Endocrinology Drug Products

By May 14th Report of Compliance Joe Famulare

(A) Deb Autor (attorney Office of Compliance)
(B) Viswanathan
(C) Joe Salewski (acting Director)

Mortsure Office of Compliance

C/ Viswanathan
MPN 1 RM 116
HFD-48
7520 Standish Place
Rockville
301-594-0163

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-961

Synthon Pharmaceuticals, Inc.
Attention: Michael H. Hinckle
Vice President and General Counsel
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Mr. Hinckle:

Please refer to your new drug application (NDA) dated July 28, 2005, received July 29, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

We acknowledge receipt of your submissions dated August 12, September 16, and October 13, 1995, and February 3, 9, and 23, March 6, 14, 17, and 27, and May 16, and 18, 2006.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

The Division of Scientific Investigations' audit revealed deficiencies in the accuracy of drug treatment administration, dosing times, and pharmacokinetic blood sampling times. Specifically, all dispensing envelopes, whether they were intended to contain the reference material (ZOCOR 80 mg tablet) or the test article (Simvastatin 80 mg tablet) were labeled "Simvastatin 80 mg tablet" and did not contain the batch number of the tablets. Although the letter "T" (for test tablet) or "R" (for reference tablet) was pre-printed on the dispensing envelope and the tablets were distinctly different, there was no record of the investigator confirming the identity of the tablets after removing them from the dispensing envelope, prior to administering the dose. There were no adequate and accurate records of the receipt and condition of the study medications. Furthermore, there was no documentation to indicate the actual times of dosing and pharmacokinetic blood sampling, as the information was pre-printed.

This Division considers the inspection results to be significant enough to compromise the integrity of the bioequivalence study and finds the data from the study unacceptable.

Before this application is approved you will need to conduct a new bioequivalence study.

In addition, we encourage you to develop a dissolution method and specification to assure the characteristics of Simvastatin Orally Disintegrating Tablets.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Eric Colman
5/25/2006 10:06:35 AM
Acting Deputy Division Director

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Synthon
Pharmaceuticals, Inc.

May 24, 2006

VIA FEDERAL EXPRESS

Mary Parks, M.D.
Division Director
Division of Metabolic and Endocrine Drug Products
US Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705
Tel: 301.796.2290

RE: NDA # 21-961 / Amendment 010
Simvastatin Orally Disintegrating Tablets
Labeling revision

Dear Dr. Parks:

Reference is made to the May 17, 2006 telecon between Synthon Pharmaceuticals, Inc. ("Synthon") and FDA. Referenced is also made to the email sent to Synthon May 17, 2006 from FDA in which FDA requested Synthon to add a second paragraph to the **CLINCAL PHARMACOLOGY**, *Pharmacokinetics* subsection of the package insert of Simvastatin Orally Disintegrating Tablets ("SVT-ODT").

Synthon hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets (ODTs) to add the second paragraph to the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* subsection. The second paragraph of this section states:

[ ] b(4)

A completed Form FDA-356h is provided in Exhibit 1 to this response. The May 17, 2006 email from FDA is provided in Exhibit 2. The proposed package insert including the additional paragraph for Synthon's Simvastatin Orally Disintegrating Tablets is provided in Exhibits 3 to this amendment. For ease of review, a List of Exhibits is attached and delineates the information presented in each exhibit. The labeling information submitted in this amendment is being provided in both paper and electronic format.

9000 Development Drive • P.O. Box 110487 • Research Triangle Park, North Carolina 27709
Phone +1 (919) 493-6006 • Fax +1 (919) 493-6104

Should you have any questions or comments concerning this NDA, please do not hesitate to contact me at (919) 493-6006.

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

Simoneau, Margaret A

From: O Shaughnessy, Jacqueline A
Sent: Tuesday, May 23, 2006 11:19 AM
To: Simoneau, Margaret A; Colman, Eric C
Cc: Viswanathan, CT; Subramaniam, Sriram
Subject: DSI Inspection RE: 21-961

Attachments: 21961 letter summary.doc; 21512.pdf

Hi Margaret and Eric,

As per your conversation with Vish and Sriram, attached please find DSI draft text for the agency letter. Please note that the format we used is similar to another 505b2 NDA letter with DSI inspection findings (attached for your reference).

Please let us know if you have any questions.
Jackie

21961 letter ummary.doc (31 K..

1512.pdf (2 MB)

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The Agency has determined that Synthon Protocol CSP.US01.SVT.ODT80.001 entitled "Randomized, Two-Period, Crossover Bioequivalence Study on Simvastatin 80 mg ODT (Synthon Pharmaceuticals, Ltd, USA) versus ZOCOR® 80 mg Tablets (Merck & Co., Inc., USA) in Healthy Volunteers under Fasting Conditions" is not valid in establishing bioequivalence of the test simvastatin tablets and the reference listed drug product. The Division of Scientific Investigations audit revealed deficiencies in the accuracy of drug treatment administration, dosing times, and pharmacokinetic blood sampling times. Specifically, all dispensing envelopes, whether they were intended to contain the reference material (ZOCOR 80 mg tablet) or the test article (Simvastatin 80 mg tablet) were labeled "Simvastatin 80 mg tablet" and did not contain the batch number of the tablets. Although the letter "T" (for test tablet) or "R" (for reference tablet) was pre-printed on the dispensing envelope and the tablets were distinctly different, there was no record of the investigator confirming the identity of the tablets after removing them from the dispensing envelope, prior to administering the dose. There were no adequate and accurate records of the receipt and condition of the study medications. Furthermore, there was no documentation to indicate the actual times of dosing and pharmacokinetic blood sampling as the information was pre-printed.

Simoneau, Margaret A

From: Sigler, Aaron
Sent: Tuesday, May 23, 2006 8:17 AM
To: Simoneau, Margaret A
Cc: Conner, Dale P
Subject: 77-080 Synthon

Attachments: 77080OTH1105.doc

Hi Margaret,
Here is the review with our letter addressing the DSI inspection.
Aaron

77080OTH1105.doc
(141 KB)

Aaron W. Sigler, Pharm.D.
LCDR, USPHS
Project Manager, Branch I
Division of Bioequivalence
Office of Generic Drugs
FDA

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-080
Drug Product Name	Amlodipine Besylate Tablets
Strength	Eq. to 2.5 mg, 5 mg and 10 mg of Amlodipine
Applicant Name	Synthon Laboratories, Inc.
Address	17 Loudoun St., SE, Leesburg, VA 20175
Submission Date(s)	November 10, 2005
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	No
File Location	V:\firmsNZ\Synthon\ltrs&rev\77080OTH1105.doc

Executive Summary

This is a review of a DSI inspection report. The original ANDA was submitted (03/12/05) containing fasting and fed BE studies on the 10 mg tablets with biowaiver request for the lower strengths (2.5 mg and 5 mg) was found acceptable. At the request of the DBE, the Division of Scientific Investigations (DSI) conducted (11/3/05) an audit of the clinical portions of the BE studies.

The DSI report contains DSI's evaluation of [redacted] Response to Form 483 Findings. The study amendment contains the firm's responses to the deficiency comments. The firm accepted all DSI recommendations and proposed to implement them in future studies. b(4)

Since the DSI deficiencies concerning the accuracy of study drug administration, dosing times and drug sampling times are enough to compromise the integrity of the bioequivalence studies, the DBE has decided NOT to accept the two bioequivalence studies and to withdraw the DBE acceptance letter to the firm (dated 10/13/2005).

I. Division of Scientific Inspection (DSI) Report
(Submitted January 6, 2006)

Bioequivalence Studies

075/182/03: Randomized, Two-period, Crossover Bioequivalence Study on Amlodipine 10 mg Tablets (Synthon Pharmaceuticals, Ltd) versus Norvasc® 10 mg Tablets (Pfizer) in Healthy Volunteers under Fasting Conditions.

075/183/03: Randomized, Two-period, Crossover Bioequivalence Study on Amlodipine 10 mg Tablets (Synthon Pharmaceuticals, Ltd) versus Norvasc® 10 mg Tablets (Pfizer) in Healthy Volunteers under Fed Conditions.

The clinical portion of the BE studies (075/182/03 and 075/183/03) were conducted at [redacted]. The analytical part of the studies was conducted at [redacted] b(4)

The DSI inspection was conducted only at clinical facility [redacted] (November 3-4, 2005) and a Form 483 was issued at the end of the inspection. The following is the DSI's evaluation of [redacted] response to Form 483 Findings.

DSI's Evaluation of [redacted] Response to Form 483 Findings

1. Failure to include the name of the dosage form (e.g. Generic or Innovator) on the unit dose labels prior to dosing.

DSI Summary: Although the labels on the unit dose envelopes indicated the treatment codes as "T" or "R", the labels did not distinguish the treatment codes (drug name and lot number), rather both treatments were referred as "1 amlodipine 10 mg tbl." The treatments listed in the Drug Administration were also preprinted prior to dosing. There was no documentation that unit doses were administered to the study subjects even though the firm's packaging records indicated unit dose packaging. Therefore, due to the lack of documentation of the treatments administered to the subjects at the time of dosing, the accuracy of dosing cannot be verified.

[redacted] **Response:** The firm agreed with the observation and will include the full names (trade names, as appropriate) of the dispensed medication on the label of the dispensing envelopes in all future studies. Furthermore, they will ensure that the appropriate sections of all protocols for future studies will include provisions for such labeling. b(4)

DBE Comment:
The DBE agrees with DSI that the accuracy of dosing could not be verified without proper documentation of treatment administered at dosing time. This is a major deficiency since lack of proper documentation by the firm makes it impossible verify that the appropriate study treatment is administered to the right subject during the right dosing period.

2. Failure to visually confirm the identity of the medication at the time of administration.

DSI Summary: none

Response: The firm agreed with the observation and will implement the procedure of visual confirmation of the identity of the medication at the time of administration including the appropriate documentation of the results in studies conducted in the future. b(4)

DBE Comment:
The DBE concurs with the DSI that confirmation of the identity of the study drug prior to administration is necessary to verify that the appropriate study treatment is administered to a subject during a dosing period. Lack of documentation of such practice casts doubts on accuracy of treatment administration.

3. Failure to include the batch numbers of the study medications on the unit dose labels.

DSI Summary: the clinic failed to record the physical identity of the study drugs at the *time of dosing* although the test and reference medications were physically distinctive. In addition, the unit dose labels did not include the lot numbers of the unit doses (see item 1). This information would have been useful to distinguish the test and reference treatments (see item 1). It should be noted that the descriptions of the test and reference drug products in the drug administration records were preprinted.

Response: the firm agreed with DSI observation and will include the batch numbers of the study drugs on the labels for future studies. b(4)

DBE Comment:
The DBE agrees with DSI that batch numbers, as appeared on the original drug bottles, should have been included in unit dose labels of study drug. In the absence of appropriate batch numbers, accuracy of treatment administration becomes even more doubtful.

4. The Drug Administration record in the CRF fails to include signatures or initials to document individual dosing and dosing verification for study subjects.

DSI Summary: the Drug Administration records only noted the person responsible for dosing the study drugs and did not include subject dosing dates and initials of the technician. Moreover, the records included only the scheduled times and not the actual times the drug were administered. This is contrary to the firm's SOP that required that the "real time" be reported in the Drug Administration records. Similarly, only deviations from the preprinted schedule times were recorded for pharmacokinetic blood sampling in the Sampling Time records. Therefore, the accuracy of the dosing and sampling times cannot be assured due to the absence of records of the actual times and the technicians' initials and dates to confirm the times.

Although the actual administration times were recorded in the unit dose envelopes, the date of administration cannot be verified since the technicians failed to date and initial. The administration dates on the dosing envelopes were preprinted.

—— **Response:** the firm agreed with the DSI's finding and will modify the "Drug Administration Record" and the corresponding procedure to require initials for individual dosing record to provide dosing verification for every subject. The firm plans to replace the current practice with a revised form and procedure where the administration time will be recorded in the "Drug Administration Record." b(4)

DBE Comment:
The DBE concurs with DSI that the accuracy of the dosing and sampling times cannot be assured without complete documentation of the actual administration times and the technicians' initials and dates to confirm the times. This is a deficiency since the exact times of administration could not be verified with an incomplete drug administration record.

5. Failure to maintain adequate and accurate records of receipt and handling of test articles and reference materials.

DSI Summary: the firm failed to record the mode of delivery and condition of study medication received from the study sponsor on 9/5/2003. In addition, no documentation was made on the description of products received, whether the bottles were sealed, and the number of study tablets received.

—— **Response:** the firm agreed with the DSI's observation and plans to keep detailed records of delivery, receipt, and handling of test articles and reference materials.

DBE Comment:
The DBE agrees with the DSI's finding. However, this is a minor deficiency that would not compromise the integrity of the conducted studies.

b(4)

6. Failure to confirm that the meals received by the subjects at —— for administration to study subjects complied with the protocol requirements.

DSI Summary: the firm did not document the contents of meals given to the study subjects.

—— **Response:** the firm agreed with the DSI's finding and plans to document the composition and quantity of study meals in future studies.

DBE Comment:
The DBE also agrees with the DSI's finding. This is a minor deficiency that would not have significant impact on the studies.

Conclusion:

The Division of Bioequivalence concurs with DSI that there were several problems in the study conduct that cast doubts regarding accuracy of treatment administration. The firm's response is a commitment to avoid the noted errors in future BE studies. Its response does not correct the mistakes made in the studies already submitted. Therefore, the DBE accepts the DSI recommendation of **not to accept** the bioequivalence studies.

Recommendations

1. The DSI deficiencies concerning the accuracy of study drug administration, dosing times and drug sampling times cast doubts regarding accuracy of treatment administration in the BE studies, hence integrity of the BE studies. Therefore, the BE studies previously found acceptable should be regarded as unacceptable.

2. The DBE's acceptance letter to the firm (dated 10/13/2005) is should be withdrawn.

Patrick Nwakama, Pharm.D. Team III Date Signed 4/10/06

Moheb H. Makary, Ph.D. Team I Date Signed 4/10/06

Dale P. Conner, Pharm. D. 4/10/06
Director, Division of Bioequivalence
Office of Generic Drugs

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BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE FIRM

ANDA: 77-080 APPLICANT: Synthon Laboratories

DRUG PRODUCT:Amlodipine Besylate Tablets, 2.5 mg, 5 mg and 10 mg

The Division of Bioequivalence has completed its review of the DSI report of your bioequivalence studies and has the following deficiencies.

The Division of Bioequivalence deems the DSI deficiencies concerning the accuracy of study drug administration dosing times and drug sampling times to be significant enough to compromise the integrity of the bioequivalence studies.

In response to the DSI inspection, your proposal to implement corrective measures for future studies is acknowledged. However, it does not address deficiencies in the conduct of the submitted studies. Therefore, the DBE finds your two bioequivalence studies unacceptable.

Please submit new bioequivalence studies on your drug product.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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CC: ANDA #77-080

ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer P. Nwakama

Endorsements: (Final with Dates)
HFD-658/ P. Nwakama 4/10/06
HFD-658/ M.Makary 4/10/06
HFD-650/ D. Conner BMD 4/10/06

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Printed in final on 4/10/2006

BIOEQUIVALENCE - INCOMPLETE Submission Dates: 11/10/05

1. OTHER (DSI Report) Strengths: 2.5 mg, 5 mg and 10 mg
Outcome: IC

Outcome: Incomplete

Simoneau

MEMORANDUM

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

DATE: April 21, 2006

TO: Associate Director
International Operations Drug Group
Division of Field Investigations (HFC-130)

FROM: C.T. Viswanathan, Ph.D. CTV Apr 21,06
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2006, Data Validation FOR CAUSE Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-961
DRUG: Simvastatin Orally Disintegrating Tablets
SPONSOR: Synthon Pharmaceuticals, Ltd.

Sponsor Monitor: Wesley R. Anderson, Ph.D.
TEL: 919-493-6006
FAX: 919-493-6104

This memo requests that you arrange for an inspection of the clinical and analytical portions of the following bioequivalence studies. **Due to Review Division deadline, these inspections should be completed before May 19, 2006.**

This inspection is a result of a telecon held on March 9, 2006 between the review division and DSI. The review division needs assurance that the dosing was carried out with specific products as intended. This was a problem in a previous study of an application inspected at the same clinical site. That application was recommended for disapproval. Therefore, this inspection needs to verify and document which subject got what treatment in addition to the regular aspects of the inspection.

[redacted] Study No. [redacted]226-04
[redacted] Study No: 099/226/05 b(4)

"Randomized, Two-period, Crossover, Bioequivalence Study on Simvastatin 80 mg ODT (Synthon Pharmaceuticals, Ltd., USA) versus ZOCOR® 80 mg Tablets (Merck & Co., Inc., USA) in Healthy Volunteers under Fasting Conditions."

Clinical Site:

b(4)

TEL:
FAX:

Clinical Investigator:

Please check the batch numbers of the test drug formulation used in the studies with descriptions in the documents submitted to the Agency. Samples of the test drug formulation should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Analytical Site:

TEL:
FAX:

b(4)

Analytical Investigator:

Instrumentation: LC/MS/MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the

reason for such repetitions, if any, should be examined. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background material will be forwarded directly. **A member of the Division of Scientific Investigations will participate in the inspection.**

Following identification of the investigator, background material will be forwarded directly.

Headquarters Contact Person: Sriram Subramaniam, Ph.D.
301-594-1051

cc:
HFD-45/RF
HFD-48/Subramaniam(2)/Himaya/CF
DMEP/Simoneau (WO22, Rm 3372)
Draft: ACH 3/9/06
DSI:5659; O:\BE\ASSIGN\BIO21961.doc
FACTS# 730511
UIC : 3065366024

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy, DSI
GLP and BIOEQUIVALENCE BRANCH

FACSIMILE TRANSMITTAL SHEET

DATE: 5/22/06

To: MARGARET SIMONEAU	**From:** SRIRAM SUBRAMANIAM
	CDER HFD-48
Fax number: 301-796-9712	**Fax number:** 301-480-1728
Phone number 301-796-1295	**Phone number** 301-594-1051

Subject: FORM 483 FROM THE RECENT INSPECTION OF [redacted] FOR NDA 21-961

Total no. of pages including cover: THREE

Comments:

FYI: FORM 483 ISSUED TO [redacted] FOR NDA 21-961. CALL ME IF YOU HAVE QUESTIONS. b(4)

THANKS

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Document to be mailed: _YES _NO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION MAY 15-18, 2006 FEI NUMBER
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: [redacted]	
FIRM NAME [redacted]	STREET ADDRESS [redacted]
CITY, STATE AND ZIP CODE [redacted]	TYPE OF ESTABLISHMENT INSPECTED CRO

b(4)

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

~~DURING AN INSPECTION OF YOUR FIRM, [WE] OBSERVED:~~

This For-Cause Inspection led to the following observations

1. A review and re-audit of the study data of the Randomized,Two Period,Crossover Bioequivalence Study on Amlodipine 10 mg tablet (Synthon Pharmaceuticals, Ltd. USA) versus Norvasc 10 mg tablets (Pfizer) in healthy volunteers under Fasting (Study 075-182-03) and Fed (Study 075-183-03) conditions confirmed the inspectional findings (November 3-4,2005) of Mr. James M. Kewley, Compliance Officer-Investigator, of U.S. Food and Drug Administration. The deficiencies found by Mr. Kewley are also applicable generally to studies conducted prior to November, 2005 and specifically to
   Randomized,Two Period,Crossover,Bioequivalence study on
   - Simvastain 80 mg ODT (Synthon Pharm)vs.ZOCOR 80 mg tablet(Merck) in healthy volunteers under fasting conditions [redacted] study 226-05
   - Amlodipine 10 mg ODT tablet (Synthon)vs NORVASC 10 mg (Pfizer) in healthy volunteers under fed and fasting conditions [redacted] study 235-05,236-05
   - [redacted]

b(4)

2. Failure to include the correct name of the dispensed medication (dosage form) on the dispensing envelope prior to dosing. All dispensing envelopes, whether they were intended to contain
   - the reference material (ZOCOR,80 mg tablet) or the test article (Simvastatin 80 mg tablet) were labeled "Simvastatin 80 mg tablet".
   - the reference material (NORVASC 10 mg tablet) or the test article (Amlodipine 10 mg ODT) were labeled "Amlodipine 10 mg tablet"
   - [redacted]
3. Failure to include the batch number of the medication on the dispensed envelope.
4. Failure to visually confirm the identity of the medication at the time of drug administration and to document the results of the confirmation. Although the test and reference dosage forms are different, there are no records of the investigator confirming the identity of the dosage forms after removing them from the packaged envelope, prior to administering the dose.
5. Repackaging records of test and reference medications fail to indicate that individual checks were made. Only signature at the bottom of the page and one other checked signature were found to document 13 different repackaging operations.
6. The CRF fails to include signatures or initials to document individual dosing and dosing verification for study subjects.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	C.T. Viswanathan	C.T. Viswanathan, Ph.D., Associate Director, Div. Scientific Investigations	May 18, 2006

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION May - 15 - 18, 2006 FEI NUMBER
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: [redacted]	
FIRM NAME [redacted]	STREET ADDRESS
CITY, STATE AND ZIP CODE [redacted]	TYPE OF ESTABLISHMENT INSPECTED CRO

b(4)

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED,

7. Failure to record the actual time of blood draw from the subjects. Only intended draw times are pre filled.
8. Failure to maintain adequate and accurate records of receipt and to check for the conditions of the test medications such as intact safety seals, unopened bottles, description of the content etc.,
9. Failure to maintain laboratory records to indicate the blood processing procedures and the time elapsed in such process. This is necessary due to the conversion of simvastatin to SVTA.
10. Failure to exclude subject 20 from Simvastatin study since the subject vomited within 6 hrs following the dosing. (for SVTA calculation)
11. The sponsor monitor has signed and approved the drug packaging record, drug administration, sample time record and dispensing envelope templates that were used in the studies. These forms fail to provide for individual check, correct name of the medications and actual blood collection times.
12. Although the simvastatin study was conducted the [redacted] the Drug Inventory and Dispensing Record was signed as verified by the sponsor clinical monitor in North Carolina, U.S on April 21,2006 after the study completion.

b(4)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	CT. Visvanathan	CT. Visvanathan, Ph.D., Associate Director, QSIT	May 18, 2006