MEMORANDUM

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

DATE: May 18, 2007

FROM: CT. Viswanathan, Ph.D. CTV 5/18/07
Associate Director - Bioequivalence
Division of Scientific Investigations (DSI)

THROUGH: Gary J. Della'Zanna, D.O., M.Sc. GJ Della'Zanna for 5-21-07
Director
Division of Scientific Investigations

SUBJECT: DSI Review of Synthon's Repeat Bioequivalence Study of Amlodipine ODT

TO: Norman L. Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products (DCRP)

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

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence (DBE)

Background

FDA inspections revealed significant deficiencies in documentation and conduct of Synthon's bioequivalence studies conducted at [redacted] at [redacted] The primary concern was the lack of contemporaneous documentation to verify the treatment received by each subject at the time of dosing. Synthon submitted several bioequivalence studies to the Agency. Some of these applications, both generic and NDA 505 b(2), have not been approved by the Agency due to the inspectional findings and some are pending regulatory decisions. b(4)

Synthon met with the Office of Compliance to address the inspectional findings and presented its case. The firm explained [redacted] processes in detail as to how subjects received test articles and why they felt confident that subjects received the correct test articles. In an attempt to resolve inspectional findings and to assist the firm to move forward with both its non-approved and pending applications, the Office of Compliance proposed that Synthon repeat a full bioequivalence study of its Amlodipine ODT 10 mg vs Pfizer's Norvasc 10 mg as a proof of concept that the firm actually performed the studies as they claimed in their verbal statements to b(4)

the Agency and show reproducibility of the data within predefined criteria. Synthon agreed to conduct the proposed study.

DSI Review of Repeat Amlodipine Study

Synthon has recently reported the results of its repeat amlodopine study conducted at [redacted] to NDA 22-026 Amlodipine Orally Disintegrating Tablets, Amendment 004, letter dated March 27, 2007. DSI has made a decision not to inspect the repeat study at the site. However, Dr. Michael Skelly of DSI has reviewed the data submitted with respect to the repeat study and further requested representative copies of the underlying source documentation. Upon evaluation of such records, it was found that the source records were completed satisfactorily. In conclusion, in light of these findings, DSI will now remove the deficiencies of the prior inspectional findings. The subject relief applies to the following studies: b(4)

Studies [redacted]235-05 and [redacted] 236-05 for NDA 22-026 Amlodipine ODT

Study [redacted]226-05 for NDA 21-961 Simvistatin ODT
Studies [redacted]182-03 and [redacted] 183-03 for ANDA 77-080 Amlodipine Tablets

cc:
HFD-45/Della'Zanna/Vaccari
HFD-48/Viswanathan/Himaya/cf
DCRP/Hinton
DMEP/Simoneau
HFD-650/Sanchez
Draft: JAO
Edit: MFS, CTV
O:\BE\EIRCOVER\Synthon March 27 2007.doc

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
5/21/2007 11:12:18 AM
CSO

Appears This Way
On Original

Simoneau, Margaret A

Subject:	Synthon Response NDA 22-026
Location:	telecon
Start:	Thu 5/17/2007 2:30 PM
End:	Thu 5/17/2007 3:30 PM
Recurrence:	(none)
Meeting Status:	Accepted
Required Attendees:	O'Shaughnessy, Jacqueline A; Hinton, Denise; Simoneau, Margaret A; Viswanathan, CT; Skelly, Michael F; Srinivasachar, Kasturi; Haber, Martin T; Noory, Carol A

Patrick

John Hull

reviewed

Teleconference # 888-390-3405
Passcode 57939

1. Simvastatin reproduction 15%
   - review acceptable
   A. DSI Clearing
   #1. Office generic
   #2 review
   #3 MEMO

Appears This Way
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Hill, John

Subject:	Updated: NDA 21-961 Simvastatin ODT April 16th resubmission
Location:	CDER WO 3376 conf rm Bldg22
Start:	Wed 5/16/2007 1:00 PM
End:	Wed 5/16/2007 1:30 PM
Recurrence:	(none)
Meeting Status:	Accepted
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Hill, John; Tran, Suong T; Wei, Xiaoxiong; Chung, Sang
Optional Attendees:	Lau, S. W. Johnny

AGENDA:

What the sponsor needs to submit to the Simva ODT NDA once DSI clears the "proof of concept" bioequivalence study.

1. Clean Copy of CURRENT LABEL

2. Status update on phase IV commitment.

Appears This Way
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Synthon
Pharmaceuticals, Inc.

April 16, 2007

VIA EXPRESS MAIL

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

Save - Dissolution Acceptable? (Phase 4)
Hill - EES Trade name? Proprietary name?
SPL?

RE: NDA # 21-961 / Amendment 014
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
AMENDMENT – REQUEST FOR FINAL APPROVAL

Dear Dr. Parks:

Synthon Pharmaceuticals, Inc. ("Synthon") is amending its New Drug Application ("NDA") for Simvastatin Orally Disingtegrating Tablets 10 mg, 20 mg, 40 mg and 80 mg to request final NDA approval in light of Synthon's completion of a "proof of concept" bioequivalence study that was requested by the Division of Scientific Investigations ("DSI'"). A completed Form FDA-356h is provided as Exhibit 1 to this amendment.

Pursuant to the commitments conveyed to Synthon by the Center for Drug Evaluation and Research's ("CDER's") Office of Compliance ("OC") (see Exhibit 2) and the bioequivalence data submitted to NDA 22-026 (see Exhibit 3 for a summary of the data), we believe that NDA #21-961 is eligible for immediate final approval. Therefore, we hereby request final approval of NDA #21-961.

Please direct any communication or correspondence concerning this matter to my attention at telephone number (919) 493-6006 or via facsimile at (919) 493-6104. Thank you for your attention to this matter.

Sincerely,

Michael H. Hinckle
Vice President & General Counsel

Enclosure(s)

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

K&L|GATES

Kirkpatrick & Lockhart Preston Gates Ellis LLP
1601 K Street NW
Washington, DC 20006-1600

T 202.778.9000 www.klgates.com

Gary L. Yingling
D 202.778.9124
F 202.778.9100
gyingling@klgates.com

April 3, 2007

Via Email

Deborah M. Autor, Esq.
Director, Office of Compliance (HFD-300)
Center for Drug Evaluation and Research
US Food and Drug Administration
Montrose Metro 2 - Room 405
11919 Rockville Pike
Rockville, MD 20852

Re: Request for Approval Based On Submission of Repeat Biostudy To Support Synthon Pharmaceuticals, Inc.'s NDA and ANDA Applications

Dear Ms. Autor:

We submit this letter on behalf of our client, Synthon Pharmaceutical, Inc. ("Synthon"), to inform you that Synthon has reproduced a particular bioequivalence study, as suggested by FDA, and has submitted the study data to the appropriate reviewing Divisions.

As we are sure you remember, you chaired a meeting on September 21, 2006 concerning an inspection of [redacted], a Contract Research Organization ("CRO") that performed several biostudies for Synthon. During that meeting, the major focus was on how [redacted] recorded the information from the studies. Following that meeting, in a conference call on November 30, 2006, the agency proposed to accept the biostudies conducted by [redacted] and submitted by the studies' sponsor, Synthon, provided that one of the studies could be successfully repeated using more detailed data entries and its results reproduced. Synthon initially had concerns about this proposal because in this situation the market required FDA approval to occur shortly after completion of a repeated study for the approval to be of value. After some discussion, Synthon understood that if [redacted] or some other CRO successfully repeated one of the studies, FDA would accept all of the previously submitted biostudies that had been the subject of the meeting and would make every reasonable effort to review the pending applications as expeditiously as possible. b(4)

Synthon agreed and, while it believed that it would be unable to use [redacted] to repeat the study, the [redacted] in fact approved the proposal allowing the study to be repeated. The study has since been conducted and completed collecting the data as discussed during the meeting and the call. We are now notifying the Division of Compliance and all in attendance or having an interest in the meeting on September 21, 2006 that the study has b(4)

been successfully repeated and its results submitted to the agency, and we are asking that FDA make every reasonable effort to review and approve the applications in question as quickly as possible because time is of the essence.

Synthon has notified FDA's Office of Generic Drugs, the Division of Cardiovascular-Renal Drug Products and the Division of Metabolism and Endocrinology Drug Products that it was able to successfully repeat a study at [redacted] to demonstrate that, with the requested documentation and procedures, the results of an earlier study could be reproduced. The product applications that are affected by this successfully-repeated biostudy are as follows: b(4)

ANDA # 77-080, Amlodipine Besylate Tablets, 2.5 mg, 5 mg and 10 mg

b(4)

NDA # 22-026, Amlodipine Orally Disintegrating Tablets, 2.5 mg, 5 mg and 10 mg
NDA # 21-961, Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg

We appreciate FDA's efforts to complete the review of the affected product applications as soon as possible. Please do not hesitate to contact us with any questions.

Sincerely,

Gary L. Yingling

cc: Synthon Pharmaceuticals, Inc.
Gary J. Buehler, FDA OGD
Dale P. Conner, FDA OGD
Mary Parks, FDA DMEP
Eric Colman, FDA DMEP
Margaret Simoneau, FDA DMEP
Joseph Salewski, FDA DSI
Gary Della-Zanna, FDA DSI
San M. Chung, FDA OCP DCP2
Joseph Famulare, FDA OC
James Kewley, FDA NYDO
Jacqueline O'Shaughnessy, FDA DSI
Terri Rumble, FDA OC
Leslie Vaccari, FDA DSI
Jason Woo, FDA OC
Ct. Viswanathan, FDA DSI

[redacted]

Appears This Way
On Original

Simoneau, Margaret A

From: Higgins, Lorraine A. [lorraine.higgins@klgates.com] on behalf of Yingling, Gary L. [gary.yingling@klgates.com]

Sent: Tuesday, April 03, 2007 10:03 AM

To: Autor, Deborah

Cc: Michael H. Hinckle; Buehler, Gary J; Della'Zanna, Gary; Chung, Sang; Colman, Eric C; Conner, Dale P; Famulare, Joseph; Kewley, James M; O Shaughnessy, Jacqueline A; Parks, Mary H; Rumble, Terri F; Salewski, Joseph; Vaccari, Leslie; Viswanathan, CT; Woo, Jason; Simoneau, Margaret A; b(4)

Subject: RE: Synthon Request for Approval

Attachments: DC-#904391-v1-Synthon_Request_for_Approval_(151592-1_04_03_2007_09_50_16_AM).PDF

<<DC-#904391-v1-Synthon_Request_for_Approval_(151592-1_04_03_2007_09_50_16_AM).PDF>>

Dear Ms. Autor,

In the letter sent yesterday, a line of text was not printed at the bottom of the first page. Attached you will find the complete letter. Please accept my deepest apologies for this error and any inconvenience it may have caused.

Gary L. Yingling
K&L Gates
1601 K Street, N.W.
Washington, DC 20006-1600
202.778.9124 (Voice)
202.778.9100 (Fax)
gary.yingling@klgates.com
www.klgates.com

From: Higgins, Lorraine A. **On Behalf Of** Yingling, Gary L.

Sent: Monday, April 02, 2007 11:30 AM

To: 'deborah.autor@fda.hhs.gov'

Cc: Michael H. Hinckle; 'gary.buehler@fda.hhs.gov'; 'gary.dellazanna@fda.hhs.gov'; 'sang.chung@fda.hhs.gov'; 'eric.colman@fda.hhs.gov'; 'dale.conner@fda.hhs.gov'; 'joseph.famulare@fda.hhs.gov'; 'james.kewley@fda.hhs.gov'; 'jacqueline.oshaughnessy@fda.hhs.gov'; 'mary.parks@fda.hhs.gov'; 'terri.rumble@fda.hhs.gov'; 'joseph.salewski@fda.hhs.gov'; 'leslie.vaccari@fda.hhs.gov'; 'ct.viswanathan@fda.hhs.gov'; 'jason.woo@fda.hhs.gov'; 'margaret.simoneau@fda.hhs.gov' b(4)

Subject: Synthon Request for Approval

<< File: DC-#904064-v1-Synthon_Request_for_Approval_(151228-1_04_02_2007_11_10_46_AM).PDF >>

K&L|GATES

Kirkpatrick & Lockhart Preston Gates Ellis LLP
1601 K Street NW
Washington, DC 20006-1600
T 202.778.9000 www.klgates.com

April 2, 2007

Gary L. Yingling
D 202.778.9124
F 202.778.9100
gyingling@klgates.com

Via Email

Deborah M. Autor, Esq.
Director, Office of Compliance (HFD-300)
Center for Drug Evaluation and Research
US Food and Drug Administration
Montrose Metro 2 - Room 405
11919 Rockville Pike
Rockville, MD 20852

Re: Request for Approval Based On Submission of Repeat Biostudy To Support Synthon Pharmaceuticals, Inc.'s NDA and ANDA Applications

Dear Ms. Autor:

We submit this letter on behalf of our client, Synthon Pharmaceutical, Inc. ("Synthon"), to inform you that Synthon has reproduced a particular bioequivalence study, as suggested by FDA, and has submitted the study data to the appropriate reviewing Divisions.

As we are sure you remember, you chaired a meeting on September 21, 2006 concerning an inspection of [redacted] a Contract Research Organization ("CRO") that performed several biostudies for Synthon. During that meeting, the major focus was on how [redacted] recorded the information from the studies. Following that meeting, in a conference call on November 30, 2006, the agency proposed to accept the biostudies conducted by [redacted] and submitted by the studies' sponsor, Synthon, provided that one of the studies could be successfully repeated using more detailed data entries and its results reproduced. Synthon initially had concerns about this proposal because in this situation the market required FDA approval to occur shortly after completion of a repeated study for the approval to be of value. After some discussion, Synthon understood that if [redacted] or some other CRO successfully repeated one of the studies, FDA would accept all of the previously submitted biostudies that had been the subject of the meeting and would make every reasonable effort to review the pending applications as expeditiously as possible. b(4)

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been successfully repeated and its results submitted to the agency, and we are asking that FDA make every reasonable effort to review and approve the applications in question as quickly as possible because time is of the essence.

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Sincerely,

Gary L. Yingling

cc: Synthon Pharmaceuticals, Inc.
Gary J. Buehler, FDA OGD
Dale P. Conner, FDA OGD
Mary Parks, FDA DMEP
Eric Colman, FDA DMEP
Margaret Simoneau, FDA DMEP
Joseph Salewski, FDA DSI
Gary Della-Zanna, FDA DSI
San M. Chung, FDA OCP DCP2
Joseph Famulare, FDA OC
James Kewley, FDA NYDO
Jacqueline O'Shaughnessy, FDA DSI
Terri Rumble, FDA OC
Leslie Vaccari, FDA DSI
Jason Woo, FDA OC
Ct. Viswanathan, FDA DSI

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b(4)

MEMORANDUM

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

DATE: December 15, 2006

TO: To the File of NDA 21-961

FROM: Leslie Vaccari
Project Management Officer
Division of Scientific Investigations
Office of Compliance

SUBJECT: **Minutes of Teleconference 11/30/06**
NDA 21-961, Simvastatin 10 mg, 20 mg, 40 mg and 80 mg

See attached Teleconference Minutes 11/30/06.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

TELECONFERENCE MINUTES

TELECONFERENCE DATE and TIME: November 30, 2006 1:30 – 2:05 PM

ASSOCIATED APPLICATION:
NDA 21-961 Simvastatin orally disintegrating tablets (ODT), 10 mg, 20 mg, 40 mg, and 80 mg

Applicant: Synthon Pharmaceuticals, Inc.
900 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

TELECONFERENCE REQUESTOR: FDA
Draft FDA proposal for discussion during the teleconference faxed to Synthon at 1:00 pm. See attachment.

TELECONFERENCE CHAIR: Deborah Autor, Director, Office of Compliance

TELECONFERENCE RECORDER: Leslie Vaccari, Project Management Officer, DSI

FDA ATTENDEES:
Deborah M. Autor, Esq., Director, Office of Compliance, CDER
Joseph Famulare, Deputy Director, Office of Compliance (OC)
Gary Della'Zanna, D.O., M.Sc., Director, Division of Scientific Investigations (DSI), OC
CT Viswanathan, Ph.D., Associate Director Bioequivalence, DSI
Leslie Vaccari, Project Management Officer, DSI

EXTERNAL CONSTITUENT ATTENDEES:
Michael Hinckle, Esq., V.P. and General Counsel, Synthon
Wayne Stargel, PharmD, V.P. Medical Affairs, Synthon
Gary L. Yingling, Esq., Kirkpatrick and Lockhart, Nicholson, Graham, LLP

TELECONFERENCE OBJECTIVE:
The Office of Compliance is responding to the Synthon request for consideration of the DSI recommendation concerning the validity of the ——— studies inspected by DSI so that the scientific review of Synthon's ANDAs and NDA 21-961 may proceed. At the September 21, 2006 meeting between Synthon and the Office of Compliance, it was agreed that FDA would respond with comments and a decision to Synthon request for consideration at a later date. Refer to Background section following Action Item section for complete background information.

b(4)

SUMMARY OF DISCUSSION:

Following introductions, Ms. Autor opened the discussion by highlighting the FDA's continued concern regarding the data and outlined the FDA's development of a proof-of-concept bioequivalence study which may resolve DSI's concerns and at the same time minimize the burden to the Sponsor by not requiring them to repeat multiple studies.

Mr. Famulare continued by providing a general overview of the background and then a more detailed summary of the proposal that would ensure that the proper test article was given to the appropriate study subjects and that other procedural concerns noted previously are addressed. It was explained that the proof-of-concept study should utilize the same procedures in the original protocol, but include the reinforcing steps in the corrected SOPs, so there is a definitive issuance and recordation of the actual articles to the subjects to eliminate doubt.

This one proof-of-concept study would serve as a model to address FDA concerns that the proper test article was given to the appropriate study subjects in the studies audited by FDA. In summary, the proposal involves a repeat of the amlodipine NORVASC study. Criteria for acceptance were identified as outlined in the fax (attached). If successful, the proposed proof-of-concept study could lead to a reclassification of DSI's inspection results for the previous applications in which approval has not been received based on DSI's review regarding the inability to confirm that proper dosing of subjects.

Ms. Autor offered the remaining time for Dr. Viswanathan to respond to Synthon's questions. Ms. Autor added that the proposal was developed with agreement from the Office of Generic Drugs and the Division of Metabolism and Endocrine Products.

Synthon stated they did not have any questions about the FDA proposal and said the proposal was clear. Synthon stated that their concern was the time required to get approval from the [redacted] and foreign ethics committee to conduct the study, and complete the analytic component and the study report. This additional time would result in their company missing critical time lines, when the innovator patents expire and when launch is needed to capture the market. Synthon added that from a business perspective, if repeating this study is required then they will be better off dropping this product or going back to the review division to see if they will make another recommendation. b(4)

Synthon explained that they have to launch Amlodipine in September in order to make it a viable business decision. This timeline requires preparations begin by the first of the year (2007). Synthon stated they were unable to set aside the API and have validation batches made without knowing if the proof of concept study was going to work.

Mr. Famulare asked for clarification, since they have expressed confidence in the original studies. Synthon responded that they have a high degree of confidence in the study outcome; however, they are concerned that when they submit the study to OGD, there is no guarantee of a timely review to meet the September 2007 amlodipine launch deadline.

On further discussion, Synthon confirmed that their amlodipine product is not the first generic product to market. Synthon noted that simvastatin needed to be launched in December 2006, so that window of opportunity had already been lost. Synthon stated that they are not willing to take the business risk of conducting the proof-of-concept study in addition to the validation, manufacturing and launch requirements since it does not allow them a guarantee for the amlodipine launch by September 2007. Mr. Famulare said the FDA can't control for Synthon's business processes.

Synthon stated that it will take significant time to get the study approved by the [redacted] and this also adds to their concern for meeting the timeline for launch. b(4)

In response to Synthon's concerns about timeline, the FDA proposed that Synthon conduct the proof-of concept study in the United States to save time. FDA noted that, although not optimal, this may be a reasonable alternative under the circumstances. The study would provide the FDA with the reassurance of the data using the same protocol. Synthon responded that this may make things a little easier but does not provide enough time for Synthon to be assured that they would meet the September 2007 amlodipine launch.

CONCLUSION:
Following further general discussion, Ms. Autor noted that it appeared to the FDA that Synthon was not confident that the repeated proof-of-concept study will have acceptable results. In conclusion, Ms. Autor requested that Synthon get back to us by Friday December 1, with their decision about the proposed study. Ms. Autor commented that if Synthon does not want to consider the proof-of-concept study that they may return to the Office of Generic Drugs and the Office of New Drugs review divisions to pursue interaction regarding the specific applications.

ACTION ITEM:
FDA: No action items identified.

Synthon: Synthon will contact FDA by Friday December 1, 2006 with their decision of whether or not to conduct the proposed study. (See ADDENDUM below.)

Leslie Vaccari 12-14-06
Leslie Vaccari
Project Management Officer

Concurrence Chair:
Deborah Autor, Esq.
Director, Office of Compliance

ADDENDUM:
On December 1, 2006 at 9:00 a.m., Michael Hinkle of Synthon called Leslie Vaccari. He stated that Synthon had discussed the FDA proposal further internally and with [redacted] Synthon is

going to proceed forward to do the study as FDA proposed. Their Plan A is to conduct the study in the [redacted] at [redacted] if they can get the government approval before the batch expiration date in February 2007. Their Plan B is to conduct the study in the USA if Plan A can not be done. Mr. Hinkle will contact the FDA with a definite Plan A or Plan B scenario as soon as possible.

ADDITIONAL BACKGROUND INFORMATION:

Background on NDA 21-961, Simvastatin:

- May 15 to 18, 2006. At the request of DMEP, CT Viswanathan, DSI, conducted an audit of th[redacted] facility for the bioequivalence (BE) study that supports NDA 21-961. Deficiencies were documented on FDA Form 483. The BE study for NDA 21-961 was conducted using the same procedures for documentation as the BE study for ANDA 77-080 described in background below.
- May 25, 2006: Division of Metabolism and Endocrinology Products (DMEP) issued a non-approval letter for NDA 21-961 to Synthon Pharmaceuticals. Comments contained in the letter follow.

  "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."
- May 30, 2006: Synthon requested post-action meeting with DMEP.
- June 9, 2006: DMEP scheduled Division/Synthon meeting for July 17, 2006.
- July 11, 2006: DMEP issued letter to Synthon containing review comments on May 30, 2006 meeting request/package.
- July 13, 2006: Synthon received email from Michael Hinkle to Margaret Simoneau /DMEP canceling July 17, 2006 meeting because FDA Form 483 issues will not be discussed.

August 1, 2006: Synthon responded to DMEP July 11, 2006 letter. Synthon advised DMEP that this is a stalemate and that if an approval action did not occur in 10 days, they would file an appeal for dispute resolution.

August 10, 2006: Kirkpatrick& Lockkhart Nicholson Graham submitted all required information to request a formal meeting to the Office of Compliance. The communication stated that this meeting was not a formal dispute resolution request.

August 16, 2006: Synthon notified that the meeting was scheduled for September 21, 2006 from 3 to 4 pm.

- Meeting September 21, 2006. Meeting minutes attached.

Background for ANDA 77-080 Amlodipine Besylate Tablets referred to by Synthon in meeting preparation package:

November 3-4, 2005: James M. Kewley, Compliance Officer New York District Office, conducted an audit of ——— facility for bioequivalence study for ANDA 77-080. Deficiencies were documented on FDA Form 483. b(4)

- November 10, 2005 ——— responded to FDA Form 483 agreeing to adopt and implement recommended changes.
- April 26, 2006: Office of Generic Drugs issued a Bioequivalency Amendment to Synthon identifying deficiencies of ANDA 70-080 necessitating the conduct of new BE studies.

Attachment: FDA Facsimile to Synthon dated 11/30/06
September 21, 2006 Meeting Minutes

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Division of Scientific Investigations

FACSIMILE TRANSMITTAL SHEET

DATE: November 30, 2006

To: Michael Hinkle Vice President and General Counsel Synthon Pharmaceutical, Inc. cc: Gary Yingling	**From: Leslie Vaccari**
Company: Synthon Pharmaceutical, Inc.	Project Management Officer Division of Scientific Investigations
Fax number: 1-919-493-6104 (Hinkle) 1-202-778-9100 (Yingling)	**Fax number:** 301-594-1204
Phone number: 1-919-536-1304 1-202-778-9100	**Phone number:** 301-594-5235
Subject: Telecon	
Total no. of pages including cover: 3	

Comments:

We refer to the scheduled teleconference today at 1:30 pm.

The FDA participants are:

Deborah M. Autor Esq., Director, Office of Compliance, CDER
Joseph Famulare, Deputy Director, Office of Compliance (OC)
Gary Della'Zana, DO, Division Director, Division of Scientific Investigations (DSI), OC
CT Viswanathan, PhD, Associate Director Bioequivalence, DSI, OC
Leslie Vaccari, Project Management Officer DSI, OC

The Synthon participants are:

Michael Hinckle, Esq., V.P. and General Counsel, Synthon
Wayne Stargel, PharmD, V.P. Medical Affairs, Synthon
Gary L. Yingling, Esq., Kirkpatrick and Lockhart, Nicholson, Graham, LLP

The agenda for this teleconference is discussion of the Office of Compliance's attached proposal. This proposal is in response to the information presented during the meeting between Synthon and the Office Of Compliance. We are providing the proposal to facilitate discussion for the teleconference today. Following our teleconference today, we will send you a letter discussing fully our response and proposal.

Draft Response:

Background:

FDA inspections revealed significant deficiencies in the documentation and procedural aspects of bioequivalence studies conducted a ——— The primary concern was a lack of documentation to verify at the time of dosing the treatment received by each subject. Certain studies, both generic and NDA 505 b(2), have not been approved by the Review Division due to DSI's inspectional findings and some Applications have pending regulatory decisions. b(4)

During the September 21, 2006 meeting with the Office of Compliance, you were given the opportunity to address the inspectional findings. After consideration of your responses, FDA has looked for a path forward to alleviate remaining concerns that the procedural processes used brought into question that subjects received the correct test article.

In order to resolve the above issues the following proposal is made by the Office of Compliance. The basis of this proposal is two-fold.

1) Since the study procedures have raised concerns whether subjects received the correct test article, a limited repeat of these procedures with proper documentation is necessary, as a proof of concept.

2) Since several applications are affected by these procedural deficiencies, the Agency will review these applications in light of the confirmatory data from the proof of concept study.

Proposal:

We recommend that Synthon (you) repeat a study at ——— to demonstrate that, with proper documentation and procedures, the results of an earlier study can be reproduced. It is suggested that you conduct/repeat the bioequivalence study of Amlodipine ODT 10 mg vs Pfizer's Norvasc 10 mg. The acceptance criteria of this study are outlined below. If it is determined that the new proof of concept study meets the predefined criteria outlined below, DSI will reclassify the inspectional findings regarding this issue from both the pending (Amlodipine ODT and generic risperidone) and nonapproved applications (simvastatin and generic Amlodipine)[1] b(4)

DSI believes that this proposal will be the most efficient path to provide the Agency with the assurance that the data from the affected bioequivalence studies conducted at ——— are valid. b(4)

Criteria for Acceptance of Synthon's Repeat Amlodipine Study

The repeat amlodipine study [comparing Synthon's 10 mg amlodipine orally disintegrating tablets (ODT) versus Pfizer's NORVASC® 10 mg tablets] to be conducted at ——— should satisfy the following criteria:

- The repeat study must have adequate documentation of the drug products that addresses the FDA audit findings for shipment, receipt, storage, dispensing, and administration of drugs, and blood collection to assure that subjects received the intended product on each occasion.
- The number and gender distribution of subjects should be similar to that of the original study (i.e., 13 males and 13 females), and the age distribution should be similar (18-55 years).
- The repeat study outcome should have a similar bioequivalence outcome (i.e., 90% confidence intervals for AUC_{0-t}, AUC_{0-inf} and Cmax within 80-125%) as the original study.
- The point estimates for AUC_{0-t}, AUC_{0-inf} and Cmax for the two studies should be within 15%* of each other.
- Any pharmacokinetic (PK) repeats (reassays) are subject to the same PK repeat (aka anomalous values) criteria established for the original study's SOP. If there was no SOP with such criteria for the original study, then PK repeats can not be performed for the repeat study.
- The study records, both clinical and analytical, may be subject to FDA inspection. Reserve samples of the drug products, selected at ——— from the products supplied to them, must be available for collection by FDA or submission to FDA upon request. b(4)

1. Specifically, the inspection reclassification applies to the following studies.
Studies ——— 235-05 and ——— 236-05 for NDA 22-026 Amlodipine ODT

Study ——— 226-05 for NDA 21 961 Simvastatin ODT
Studies ——— 182-03 and ——— 183-03 for ANDA 77-080 Amlodipine Tablets

End

If you have questions, please feel to contact me at 301-594-5235.

Leslie Vaccari

Project Management Officer
Office of Compliance/Division of Scientific Investigations
HFD-45 MPN1 Rm 1442
Phone: 301-594-5235

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Division of Scientific Investigations

FACSIMILE TRANSMITTAL SHEET

DATE: November 30, 2006

To: Michael Hinkle Vice President and General Counsel Synthon Pharmaceutical, Inc. cc: Gary Yingling	**From: Leslie Vaccari**
Company: Synthon Pharmaceutical, Inc.	Project Management Officer Division of Scientific Investigations
Fax number: 1-919-493-6104 (Hinkle) 1-202-778-9100 (Yingling)	**Fax number:** 301-594-1204
Phone number: 1-919-536-1304 1-202-778-9100	**Phone number:** 301-594-5235

Subject:
Telecon

Total no. of pages including cover: 3

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Comments:

We refer to the scheduled teleconference today at 1:30 pm.

The FDA participants are:

Deborah M. Autor Esq., Director, Office of Compliance, CDER
Joseph Famulare, Deputy Director, Office of Compliance (OC)
Gary Della'Zana, DO, Division Director, Division of Scientific Investigations (DSI), OC
CT Viswanathan, PhD, Associate Director Bioequivalence, DSI, OC
Leslie Vaccari, Project Management Officer DSI, OC

The Synthon participants are:

Michael Hinckle, Esq., V.P. and General Counsel, Synthon
Wayne Stargel, PharmD, V.P. Medical Affairs, Synthon
Gary L. Yingling, Esq., Kirkpatrick and Lockhart, Nicholson, Graham, LLP

The agenda for this teleconference is discussion of the Office of Compliance's attached proposal. This proposal is in response to the information presented during the meeting between Synthon and the Office Of Compliance. We are providing the proposal to facilitate discussion for the teleconference today. Following our teleconference today, we will send you a letter discussing fully our response and proposal.

Draft Response:

Background:

FDA inspections revealed significant deficiencies in the documentation and procedural aspects of bioequivalence studies conducted at ——— The primary concern was a lack of documentation to verify at the time of dosing the treatment received by each subject. Certain studies, both generic and NDA 505 b(2), have not been approved by the Review Division due to DSI's inspectional findings and some Applications have pending regulatory decisions. b(4)

During the September 21, 2006 meeting with the Office of Compliance, you were given the opportunity to address the inspectional findings. After consideration of your responses, FDA has looked for a path forward to alleviate remaining concerns that the procedural processes used brought into question that subjects received the correct test article.

In order to resolve the above issues the following proposal is made by the Office of Compliance. The basis of this proposal is two-fold.

1) Since the study procedures have raised concerns whether subjects received the correct test article, a limited repeat of these procedures with proper documentation is necessary, as a proof of concept.

2) Since several applications are affected by these procedural deficiencies, the Agency will review these applications in light of the confirmatory data from the proof of concept study.

Proposal:

We recommend that Synthon (you) repeat a study at ——— to demonstrate that, with proper documentation and procedures, the results of an earlier study can be reproduced. It is suggested that you conduct/repeat the bioequivalence study of Amlodipine ODT 10 mg vs Pfizer's Norvasc 10 mg. The acceptance criteria of this study are outlined below. If it is determined that the new proof of concept study meets the predefined criteria outlined below, DSI will reclassify the inspectional findings regarding this issue from both the pending (Amlodipine ODT and generic risperidone) and nonapproved applications (simvastatin and generic Amlodipine)[1] b(4)

DSI believes that this proposal will be the most efficient path to provide the Agency with the assurance that the data from the affected bioequivalence studies conducted at [redacted] are valid.

b(4)

Criteria for Acceptance of Synthon's Repeat Amlodipine Study

The repeat amlodipine study [comparing Synthon's 10 mg amlodipine orally disintegrating tablets (ODT) versus Pfizer's NORVASC® 10 mg tablets] to be conducted at [redacted] should satisfy the following criteria:

- The repeat study must have adequate documentation of the drug products that addresses the FDA audit findings for shipment, receipt, storage, dispensing, and administration of drugs, and blood collection to assure that subjects received the intended product on each occasion.
- The number and gender distribution of subjects should be similar to that of the original study (i.e., 13 males and 13 females), and the age distribution should be similar (18-55 years).
- The repeat study outcome should have a similar bioequivalence outcome (i.e., 90% confidence intervals for AUC_{0-t}, AUC_{0-inf} and Cmax within 80-125%) as the original study.
- The point estimates for AUC_{0-t}, AUC_{0-inf} and Cmax for the two studies should be within 15%* of each other.
- Any pharmacokinetic (PK) repeats (reassays) are subject to the same PK repeat (aka anomalous values) criteria established for the original study's SOP. If there was no SOP with such criteria for the original study, then PK repeats can not be performed for the repeat study.
- The study records, both clinical and analytical, may be subject to FDA inspection. Reserve samples of the drug products, selected at [redacted] from the products supplied to them, must be available for collection by FDA or submission to FDA upon request.

1. Specifically, the inspection reclassification applies to the following studies.
Studies [redacted]235-05 and [redacted]236-05 for NDA 22-026 Amlodipine ODT

b(4)

Study [redacted]226-05 for NDA 21-961 Simvastatin ODT
Studies [redacted]182-03 and [redacted]83-03 for ANDA 77-080 Amlodipine Tablets

End

If you have questions, please feel to contact me at 301-594-5235.

Leslie Vaccari

Project Management Officer
Office of Compliance/Division of Scientific Investigations
HFD-45 MPN1 Rm 1442
Phone: 301-594-5235

Synthon's Repeat Amlodipine Study Meets FDA's Acceptance Criteria

1. The repeat study must have adequate documentation of the drug products that addresses the FDA audit findings for shipment, receipt, storage, dispensing, and administration of drugs, and blood collection to assure that subjects received the intended product on each occasions.
   - [redacted] maintains adequate documentation for shipment, receipt, storage, dispensing, and administration of the drug products, as well as for blood collection in the study files of the CRO. b(4)
2. It is recommended that the number and gender distribution of subjects be similar to that of the original study (i.e., 13 males and 13 females).
   - Yes; demographics were the same for both studies.
3. The repeat study outcome should meet similar bioequivalence criteria (i.e., 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} with 80-125%) as the original study.
   - Yes, the required bioequivalence criteria were met for the second study (see summary tables immediately below).
4. The point estimates for AUC_{0-t}, AUC_{0-inf}, and C_{max} for the two studies should be within 15%.
   - Yes, the point estimates for AUC_{0-t}, AUC_{0-inf}, and C_{max} for the two studies were within 15%. (see summary tables immediately below).

Summary Table for Comparative Bioequivalence Data (Study #1)

Parameter	Geometric Least Squares Means		T/R Ratio (%)	90% Confidence Limits (%)	
	Test (T)	Reference (R)		Lower	Upper
$AUC_{(0-t)}$ (ng h/mL)	246.58	247.50	99.63	95.44	104.00
$AUC_{(0-inf)}$ (ng h/mL)	262.08	263.11	99.61	95.47	103.93
C_{max} (ng/mL)	4.311	4.700	91.73	87.63	96.03

Summary Table for Comparative Bioequivalence Data (Study #2)

Parameter	Geometric Least Squares Means		T/R Ratio (%)	90% Confidence Limits (%)	
	Test (T)	Reference (R)		Lower	Upper
$AUC_{(0-t)}$ (ng h/mL)	258.05	245.81	104.98	101.38	108.70
$AUC_{(0-inf)}$ (ng h/mL)	274.27	260.86	105.14	101.63	108.77
C_{max} (ng/mL)	4.62	4.71	98.08	94.01	102.32

5. Any pharmacokinetic (PK) repeats are subject to the same PK repeat criteria established for the original study's SOP. If there was no SOP with such criteria for the original study, then no PK repeats can be performed for the new study.
   - The original study's SOPs were used for the repeat bioequivalence study. However, no plasma samples were re-analyzed for pharmacokinetic reasons.

6. The study records, both clinical and analytical, may be subject to FDA inspection. Reserve samples of the drug products, selected at [redacted] from the products supplied to them, must be available for collection by FDA or for submission to FDA upon request. b(4)
   - Reserve samples of the drug products are available at [redacted] for collection and submission to FDA.

MEMORANDUM

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

DATE: October 27, 2006

TO: To the File of NDA 21-961

FROM: Leslie Vaccari
Project Management Officer
Division of Scientific Investigations
Office of Compliance

SUBJECT: **Minutes of Meeting 9/21/06**
NDA 21-961, Simvastatin 10 mg, 20 mg, 40 mg and 80 mg

See attached Minutes of Meeting 9/21/06.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

MEETING MINUTES

MEETING DATE and TIME: September 21, 2006 3:00 – 4:15 PM

MEETING LOCATION: Office of Compliance
Center for Drug Evaluation and Research
11919 Rockville Pike
Montrose Metro 2
Rockville, MD 20852
4FL-B Conference Room

MEETING TYPE: Type B

MEETING CATEGORY: Post NDA 21-961 Action Consultation with Office of Compliance

APPLICATION NUMBER: NDA 21-961 [505(b)(2) application]
Meeting Request Submission Date: August 10, 2006
FDA Response Date: August 17, 2006
Briefing Document Submission Date: August 10, 2006

DRUG: Simvastatin orally disintegrating tablets (ODT), 10 mg, 20 mg, 40 mg, and 80 mg

MEETING REQUESTOR and APPLICANT:
Synthon Pharmaceuticals, Inc.
900 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

MEETING CHAIR: Deborah Autor, Director, Office of Compliance

MEETING RECORDER: Leslie Vaccari, Project Management Officer, DSI

FDA ATTENDEES:
Deborah M. Autor, Esq., Director, Office of Compliance, CDER
Joseph Famulare, Acting Deputy Director, Office of Compliance (OC)
Jason Woo, MD, Associate Director for Scientific and Medical Affairs, OC
Joseph Salewski, Acting Division Director, Division of Scientific Investigations (DSI), OC
CT Viswanathan, PhD, Associate Director Bioequivalence, DSI
Jackie O' Shaughnessy, PhD, Pharmacologist, DSI
Dale P. Conner, PharmD, Director, Division of Bioequivalence, Office of Generic Drugs, CDER
Terri Rumble, Associate Director for Operations, OC

Leslie Vaccari, Project Management Officer, DSI
Mary H. Parks, MD, Director, Division of Metabolism and Endocrinology Products (DMEP), Office of New Drugs (OND), CDER
Eric Colman, MD, Acting Deputy Director, DMEP, OND, CDER
Margaret Simoneau, Regulatory Project Manager, DMEP, OND, CDER
Sang M. Chung, Reviewer, Division of Clinical Pharmacology 2, Office of Clinical Pharmacology, Office of Translational Sciences, CDER
James M. Kewley, Compliance Officer, HFR-NE340 New York Compliance Branch (by phone)

EXTERNAL CONSTITUENT ATTENDEES:
Michael Hinckle, Esq., V.P. and General Counsel, Synthon
Wayne Stargel, PharmD, V.P. Medical Affairs, Synthon

b(4)

Gary L. Yingling, Esq., Kirkpatrick and Lockhart, Nicholson, Graham, LLP

MEETING OBJECTIVE: Synthon requested FDA's consideration of DSI's recommendation concerning the validity of the studies so that the scientific review of Synthon's ANDAs and NDA 21-961 may proceed.

On September 19, 2006, DSI faxed the following requests and comments to Synthon.
Synthon's presentation for the meeting needs to include:

- Background information on Synthon Pharmaceuticals, Inc. and and b(4)
- Synthon's succinct description of s actual procedures and documentary controls for the Study No 226-04 evaluating Zocor Tablets (Merck) and Synthon's simvastatin orally disintegrating tablets, especially those procedures ensuring that the data accurately reflected whether, at the time of dosing, the test or reference product had been administered.

The FDA will take this opportunity to clarify and further query the issues as presented by Synthon in their presentation but will not provide conclusions during the meeting.

BACKGROUND:
Background on NDA 21-961, Simvastatin:

- May 15 to 18, 2006. At the request of DMEP, CT Viswanathan, DSI, conducted an audit of the facility for the bioequivalence (BE) study that supports NDA 21-961. Deficiencies were documented on FDA Form 483. The BE study for NDA 21-961 was conducted using the same procedures for documentation as the BE study for ANDA 77-080 b(4) described in background below.

  May 25, 2006: Division of Metabolism and Endocrinology Products (DMEP) issued a non-approval letter for NDA 21-961 to Synthon Pharmaceuticals. Comments contained in the letter follow.

  "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."

- May 30, 2006: Synthon requested post-action meeting with DMEP.
- June 9, 2006: DMEP scheduled Division/Synthon Meeting for July 17, 2006.
- July 11, 2006: DMEP issued letter to Synthon containing review comments on May 30, 2006 meeting request/package.
- July 13, 2006: Synthon received email from Michael Hinkle to Margaret Simoneau /DMEP canceling July 17, 2006 meeting because FDA Form 483 issues will not be discussed.
- August 1, 2006: Synthon responded to DMEP July 11, 2006 letter. Synthon advised DMEP that this is a stalemate and that if an approval action did not occur in 10 days, they would file an appeal for dispute resolution.
- August 10, 2006: Kirkpatrick& Lockkhart Nicholson Graham submitted all required information to request a formal meeting to the Office of Compliance. The communication stated that this meeting was not a formal dispute resolution request.
- August 16, 2006: Synthon notified that the meeting was scheduled for September 21, 2006 from 3 to 4 pm.

Background for ANDA 77-080 Amlodipine Besylate Tablets referred to by Synthon in meeting preparation package:

- November 3-4, 2005: James M. Kewley, Compliance Officer New York District Office, conducted an audit of ——— facility for bioequivalence (BE) study for ANDA 77-080. Deficiencies were documented on FDA Form 483. b(4)
- November 10, 2005: ——— responded to FDA Form 483 agreeing to adopt and implement recommended changes.
- April 26, 2006: Office of Generic Drugs issued a Bioequivalency Amendment to Synthon identifying deficiencies of ANDA 70-080 necessitating the conduct of new BE studies.

SUMMARY OF MEETING DISCUSSION:

Following introductions of all attendees, Ms. Autor welcomed Synthon. It was noted that the focus of this meeting was to have Synthon review the study procedures and documentary controls. FDA will pose questions during the presentation. The sponsor questions submitted

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with the meeting request will not be discussed.

Synthon proceeded with their presentation (copy attached). Synthon emphasized that the purpose of today's meeting was to provide information that would confirm that ——— methods were more than adequate to support the accuracy and validity of the data derived from bioequivalence studies and that new bioequivalence studies are not needed. Synthon noted that their presentation will focus on NDA 21-961. However, Synthon emphasized that the acceptability of the inspections for the NDA 21-961 and for the ANDA 70-080 for Amlodipine are critical and have significant impact for Synthon because of ten other BE studies conducted in the same manner which are associated with other applications. b(4)

Synthon highlighted that ——— documentation during the BE study ——— 226-04) pivots on the following four documents that were used at the time of dosing: 1) Subject Identification Tag, 2) Drug Administration Record, 3) Drug Dispensing Envelope, and 4) Fluid Intake Registration Form. Synthon emphasized that these four records in combination and individually document the time of dosing, drug administered, and fluid intake for each study subject.

The following four slides, referred to as exhibits by Synthon, were the focus of the FDA questions for the remainder of the meeting. Please note that the discussion at times jumped between these four exhibits but for the purpose of clarity of content of the minutes, all FDA questions and Synthon responses will be associated with the corresponding exhibits.

Subject Identification Tag b(4)

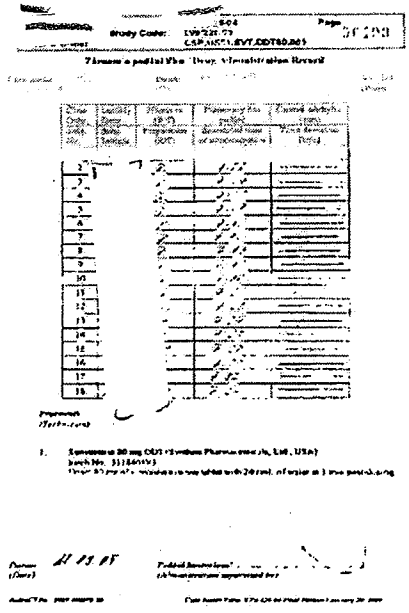
Exhibit 1

Synthon reviewed the procedure for each subject receiving their subject identification tag as seen in Exhibit 1. This step in their procedure was referred to during the discussion and FDA questions for Exhibits 2, 3, and 4.

Synthon provided a detailed overview of the use of the Drug Administration Record, Exhibit 2

(below), described as a pre-printed document present at the time of dosing. FDA queried and received confirmation that the only entry at the time of dosing is in the Time Deviation column. Synthon noted the forms were filled out the day before subject dosing. FDA asked if the meaning of time was described in the SOP for the study. Synthon responded that the SOP only refers to time and does not provide an explicit definition. FDA noted that there is no documentation of the actual time of administration of T (simvastatin 80 mg ODT [Synthon Pharmaceuticals batch No. 3118403V3]) or R (Zocor 80 mg tablets [Merck batch No. N5746] on the Drug Administration Record but only the intended scheduled time of administration. Synthon agreed. [redacted] reviewed that [redacted] did not write down the actual time of dosing on the Drug Administration Record. He added that they interpret that the doctor signing the form is the proper documentation of the actual and scheduled dosing time of T or R. b(4)

Drug Administration Record



b(4)

Exhibit 2

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Synthon provided a detailed overview of the use of the Drug Dispensing Envelope, Exhibit 3 (below), described as the pre-printed source document present at the time of dosing. All envelopes are preprinted with: 1 simvastatin 80 mg tablet: 099/226/05/ T or R. The procedure of filling the envelopes is completed by the doctor and nurse the day before the study. All R envelopes are filled at same time and all T envelopes are filled at the same time. The envelope filling procedure is not documented with initialing on the envelope. Synthon clarified that the Admin Time, Technician initials and Supervisor initials were not preprinted on the envelope and were entered at the time of administration of the dose. FDA asked if the SOP addressed the

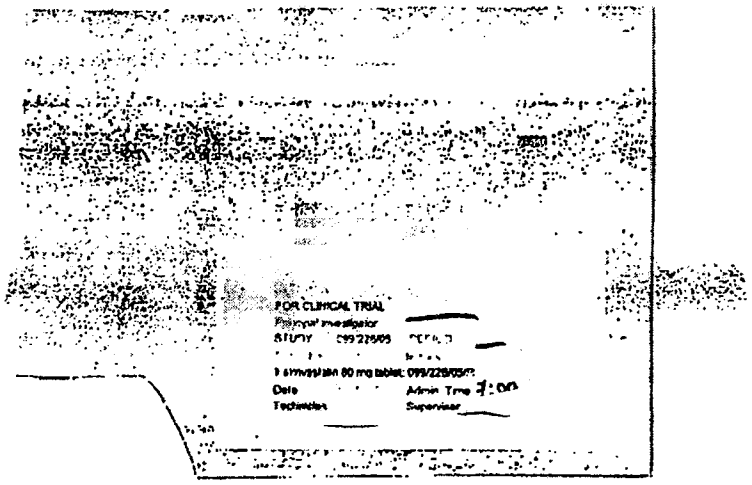
Drug Dispensing Envelope

[redacted] 226-04 Page 00161

[redacted]udy Code: 099/226/05

Sponsor's Code: CSP.US01.SVT.ODT80.001

Drug Label



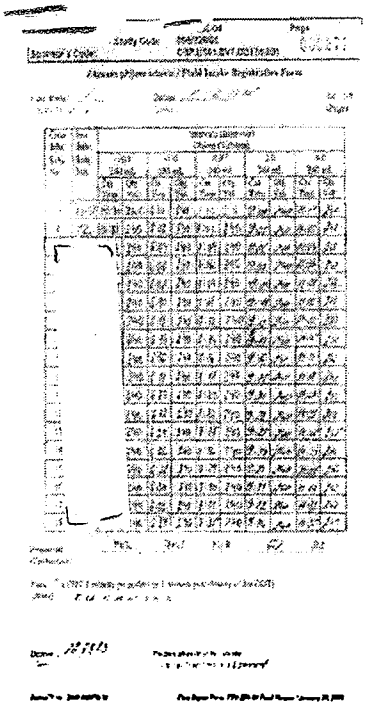
b(4)

Exhibit 3

documentation of the drug identification and the three entries on the envelope at the time of dosing. Synthon responded that the SOP (attachments) does not address the documentation of the drug identification but speaks to the time given by the tech and doctor. Synthon noted that the package SOP for filling the envelopes covers this and ensures the confidence of the T and R authenticity.

Synthon provided a detailed overview of the use of the Fluid Intake Registration Form, Exhibit 4 (below), described as the pre-printed Fluid Intake Registration Form also present at the time of dosing. The columns labeled Subject Number and Subject Initials was preprinted. Synthon confirmed that the purpose of this form is to document the time that all subjects received 240 mL of water. All subjects should have received either 240 mL water with the ODT test drug at one minute post-dose or with Zocor at dose time. The time of dosing and the identification of T or R are not included on this form. [redacted] noted that when the dose is given to the subject, he recognizes the tablet and also checks the subject's mouth at one minute to visually confirm disintegration of the ODT. Upon FDA questioning, he added that no documentation is made of this step and the protocol does not describe such documentation. FDA asked if there is a record of the disintegration time for the ODT. [redacted] responded no. b(4)

Fluid Intake Registration Form



b(4)

Exhibit 4

The FDA did not have any further questions on the remaining slides in the presentation.

FDA requested that Synthon comment on the Drug Inventory and Dispensing Form which was not included in the presentation. FDA stated that although the form contained information to supplement the identity of the dosage forms (it identified the treatments by name (e.g., Zocor for the reference product) and lot number), it lacked a relevant date (the form was not signed by [redacted] and the clinical monitor until after the study was completed). FDA noted that the instructions for use of the form indicate that "As dispensing of these supplies occurs, it is to be recorded on this form." Dr. Stargel agreed with FDA's comments and stated that this form is intended as an inventory form only. The clinical monitor was not present at the time of dosing and, therefore, this form is not intended as a documentation of dosing. b(4)

[redacted], offered his personal assurance that all study procedures and documentation were done consistently.

CONCLUSION:
Ms. Autor thanked Synthon for the presentation and their responses to all FDA questions. b(4)

ACTION ITEM:
Office of Compliance will respond to Synthon with comments and decision.

Leslie Vaccari 10/25/06
Leslie Vaccari
Project Management Officer

Concurrence Chair:
Deborah Autor, Esq.
Director, Office of Compliance

Attachments:
Synthon Power Point Slide Presentation (20 pages)
FDA Form 483 May 15-18, 2006 [redacted] Inspection for NDA 21-961
[redacted] SOP for Drug Administration – discussed by Synthon
[redacted] SOP for Packaging and Labeling – discussed by Synthon b(4)

20 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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	STREET ADDRESS
[redacted]	[redacted]
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
[redacted]	CRO

THIS DOCUMENT LISTS CONDITIONS NOTICED 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 BY THE UNITED STATES

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 o.1

   - Simvastatin 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
   -

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"

b(4)

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

FORM FDA 483 (7/93) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS Page 1 of 2 Pages

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	STREET ADDRESS
[redacted]	
CITY, STATE AND ZIP CODE	TYPE ESTABLISHMENT INSPECTED
[redacted]	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.

b(4)

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.

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

Purpose: To ensure the right procedure of administration of tested drugs in the pharmacokinetics studies

Scope: Administration of tested drugs for the volunteers

Responsibility: All pharmacokinetics studies carry out by [redacted] Company

b(4)

1.Introductory

The clinical investigator is responsible for the assurance of individual dosages of evaluated drugs, preparing according to S.O.P. [redacted] PHA 20 in the locked mobile safety box stored until the administration in the secure place with the controlled temperature.

2.Procedure:

The administration of the drugs is carrying out with the other responsible personal. Before the actual administration, the clinical investigator unlocks the safe box in the appointed place for the drugs administration and prepares the envelops with the drugs for the administration.

With the administration of the drugs the clinical investigator checks the name of the volunteer on his or hers name tag and on the envelope with the code of the product and in the record of "Drugs Administration Record". After the worker opens the envelope by cutting one of the corners of the envelope, the tablet has to stay in the cut part and checked, if the amount of the drug is the same as it is written on the envelope.

At the scheduled time the responsible personal administers drug the to the volunteer, together with specified amount of the liquid. It is necessary to check if the volunteer drinks all the required amount of liquid.

After that, the clinical investigator checks the volunteer's mouth with a flashlight (under the tong and inside of the mouth), if the drug was swallowed. This procedure must be written in the information for the volunteers. Volunteers must know this procedure before the study.

The exact time of the administration is recorded on the envelope of the preparation and the clinical investigator signs the envelope of the preparation with the other responsible person.. Envelopes are archived together with the documentation.

The responsible personal, records the real time of the drug administration also in to the "Drug administration Record" and the amount of the given fluid in to the "Fluid Intake Record Form".

All the amounts of preparation, which were not administrate (e.g. drop out of the volunteer) are locked back in to the safe and the clinical investigator is assuring their handover in to the box with controlled temperature for the long term storage.

Note: In the case of using different form than the oral form of the administrating drug the procedure of the application is described in the protocol of the study.

5 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Leslie Vaccari
12/18/2006 10:08:47 AM
CSO

Appears This Way
On Original

Simoneau, Margaret A

Subject:	NDA 21-961 Simvastatin ODT INTERNAL T-con DMEP and Compliance/ f/up to Synthon's September 21, 2006 meeting
cation:	Phone # TBD
Start:	Thu 10/12/2006 11:00 AM
End:	Thu 10/12/2006 11:30 AM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Autor, Deborah; Famulare, Joseph; Parks, Mary H; Colman, Eric C

Simoneau, Margaret A

From: Parks, Mary H
nt: Wednesday, September 27, 2006 6:48 AM
Simoneau, Margaret A
ubject: FW: simvastatin ODT

Hi Peggy

Can you set up a tcon for us? You're more than welcome to sit in on this just to be informed of the discussion but I know you're busy so I leave that up to you. Definitely not asking you to join for taking minutes.

Thanks,
Mary

-----Original Message-----
From: Autor, Deborah
Sent: Friday, September 22, 2006 5:13 PM
To: Parks, Mary H
Cc: Colman, Eric C; Famulare, Joseph; Hukle, Linda C
Subject: Re: simvastatin ODT

Sounds good. Please invite Joe Famulare. Thanks.
-- Deb

----- Original Message -----
From: Parks, Mary H
To: Autor, Deborah
Cc: Colman, Eric C
nt: Fri Sep 22 17:05:26 2006
bject: simvastatin ODT

Deborah

Eric Colman and I would like an opportunity to speak with you regarding your thoughts on yesterday's meeting. The company's presentation on the conduct of the study and the investigator's response to our inquiries were helpful and we will gladly discuss our proposals for a path forward specific to this application. I can ask Margaret Simoneau, our project manager, to place something on our calendars if this works for you.

Regards,
Mary

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
Note change in email address: mary.parks@fda.hhs.gov

MEMORANDUM

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

DATE: 24-SEP-2006

TO: NDA 21-961 Review File

FROM: John Hill, Ph.D., Chemistry Reviewer, Branch II/DPA-I/ONDQA

Through: Ali Al-Hakim, Ph.D., Chief, Branch II/DPA-I/OMDQA

SUBJECT: **NDA 21-965: Final Review**

SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BL Amendment	24-MAY-2007
BL Amendment	4-SEP-2007

Synthon has provided updated copies of both the Package Insert (PI) and carton/container labeling for their Simvastatin drug product. The carton labeling has been revised, incorporating comments and corrections recommended by DMETS. The CMC related sections of the PI remain unchanged and acceptable from the initial PI reviewed in December, 2005.

The company has indicated that they will not apply for a trade name at this time.

There will still be one Post-Marketing Commitment included in the approval letter for this NDA. This commitment is notes as follows:

> The Agency requests that Synthon commit to concurrently validating the more discriminating dissolution method QC.WO.SVT.odt.020.C/12.02 (submitted as a BC amendment 16-MAY-2006, e-mail dated 15-MAY-2006) to NDA 21-961 while performing Simvastatin lot release testing using dissolution method QC.US01.SVT.020.C/6. The new dissolution test method (QC.WO.SVT.odt.020.C/12.02) will be validated to support a lot release specification of Q[redacted] at 15 minutes. b(4)
>
> The new dissolution test method (QC.WO.SVT.odt.020.C/12.02) will also be included in the stability protocol. Appropiate real-time and accelerated stability data will be required to support the use of the new dissolution test method instead of the current dissolution test method. These stability data can

be updated in the annual report to support the proposed dating period. Upon validation.

Synthon will amend NDA 21-961 to replace lot release dissolution testing method QC.US01.SVT.020.C/6 with the fully validated dissolution method QC.WO.SVT.odt.020.C/12.02.

This amendment is to be submitted within six (6) months of approval of NDA 21-961.

This commitment has been discussed with the Sponsor and they have agreed to it.

From a CMC viewpoint this NDA can be approved (AP). All outstanding CMC issues have been resolved. The pre-approval inspections have been completed and the Office of Compliance recommendation is acceptable.

Based on the provided real-time and accelerated stability data, the proposed expiry period of 18 months is granted.

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

/s/

John C. Hill
9/24/2007 10:38:40 AM
CHEMIST

Ali Al-Hakim
9/24/2007 01:46:32 PM
CHEMIST

Simoneau, Margaret A

Subject:	Updated: Industry Meeting N21961 Synthon/Kirkpatrick
Location:	CDER Montrose Metro Conf Room 4FL-B
Start:	Thu 9/21/2006 3:00 PM
End:	Thu 9/21/2006 4:00 PM
Recurrence:	(none)
Meeting Status:	Accepted
Required Attendees:	Vaccari, Leslie; Autor, Deborah; Rumble, Terri F; Parks, Mary H; Purucker, Mary E; Salewski, Joseph; Viswanathan, CT; Colman, Eric C
Optional Attendees:	King, Crystal A; Famulare, Joseph; Subramaniam, Sriram; Simoneau, Margaret A; Vaccari, Leslie

Rescheduled to 9/21 to accomodate required attendees schedules.

Industry Meeting 9/21 3-4 pm See preMtg calendar for attachments
[Pre-Meeting 9/15 10-11:30]

NDA 21-961 Simvastatin orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg, 80 mg
505(b)(2) application

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

MEETING MINUTES

MEETING DATE and TIME: September 21, 2006 3:00 – 4:15 PM

MEETING LOCATION: Office of Compliance
Center for Drug Evaluation and Research
11919 Rockville Pike
Montrose Metro 2
Rockville, MD 20852
4FL-B Conference Room

MEETING TYPE: Type B

MEETING CATEGORY: Post NDA 21-961 Action Consultation with Office of Compliance

APPLICATION NUMBER: NDA 21-961 [505(b)(2) application]
Meeting Request Submission Date: August 10, 2006
FDA Response Date: August 17, 2006
Briefing Document Submission Date: August 10, 2006

DRUG: Simvastatin orally disintegrating tablets (ODT), 10 mg, 20 mg, 40 mg, and 80 mg

MEETING REQUESTOR and APPLICANT:
Synthon Pharmaceuticals, Inc.
900 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

MEETING CHAIR: Deborah Autor, Director, Office of Compliance

MEETING RECORDER: Leslie Vaccari, Project Management Officer, DSI

FDA ATTENDEES:
Deborah M. Autor, Esq., Director, Office of Compliance, CDER
Joseph Famulare, Acting Deputy Director, Office of Compliance (OC)
Jason Woo, MD, Associate Director for Scientific and Medical Affairs, OC
Joseph Salewski, Acting Division Director, Division of Scientific Investigations (DSI), OC
CT Viswanathan, PhD, Associate Director Bioequivalence, DSI
Jackie O' Shaughnessy, PhD, Pharmacologist, DSI
Dale P. Conner, PharmD, Director, Division of Bioequivalence, Office of Generic Drugs, CDER
Terri Rumble, Associate Director for Operations, OC

Leslie Vaccari, Project Management Officer, DSI
Mary H. Parks, MD, Director, Division of Metabolism and Endocrinology Products (DMEP), Office of New Drugs (OND), CDER
Eric Colman, MD, Acting Deputy Director, DMEP, OND, CDER
Margaret Simoneau, Regulatory Project Manager, DMEP, OND, CDER
Sang M. Chung, Reviewer, Division of Clinical Pharmacology 2, Office of Clinical Pharmacology, Office of Translational Sciences, CDER
James M. Kewley, Compliance Officer, HFR-NE340 New York Compliance Branch (by phone)

EXTERNAL CONSTITUENT ATTENDEES:
Michael Hinckle, Esq., V.P. and General Counsel, Synthon
Wayne Stargel, PharmD, V.P. Medical Affairs, Synthon

b(4)

Gary L. Yingling, Esq., Kirkpatrick and Lockhart, Nicholson, Graham, LLP

MEETING OBJECTIVE: Synthon requested FDA's consideration of DSI's recommendation concerning the validity of the ——— studies so that the scientific review of Synthon's ANDAs and NDA 21-961 may proceed.

On September 19, 2006, DSI faxed the following requests and comments to Synthon.
Synthon's presentation for the meeting needs to include:

- Background information on Synthon Pharmaceuticals, Inc. and ———, and
- Synthon's succinct description of ———'s actual procedures and documentary controls for the ——— Study No ——— 226-04 evaluating Zocor Tablets (Merck) and Synthon's simvastatin orally disintegrating tablets, especially those procedures ensuring that the data accurately reflected whether, at the time of dosing, the test or reference product had been administered. b(4)

The FDA will take this opportunity to clarify and further query the issues as presented by Synthon in their presentation but will not provide conclusions during the meeting.

BACKGROUND:
Background on NDA 21-961, Simvastatin:

- May 15 to 18, 2006. At the request of DMEP, CT Viswanathan, DSI, conducted an audit of the ——— facility for the bioequivalence (BE) study that supports NDA 21-961. Deficiencies were documented on FDA Form 483. The BE study for NDA 21-961 was conducted using the same procedures for documentation as the BE study for ANDA 77-080 described in background below. b(4)

  May 25, 2006: Division of Metabolism and Endocrinology Products (DMEP) issued a non-approval letter for NDA 21-961 to Synthon Pharmaceuticals. Comments contained in the letter follow.

  "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."

- May 30, 2006: Synthon requested post-action meeting with DMEP.
- June 9, 2006: DMEP scheduled Division/Synthon Meeting for July 17, 2006.
- July 11, 2006: DMEP issued letter to Synthon containing review comments on May 30, 2006 meeting request/package.
- July 13, 2006: Synthon received email from Michael Hinkle to Margaret Simoneau /DMEP canceling July 17, 2006 meeting because FDA Form 483 issues will not be discussed.
- August 1, 2006: Synthon responded to DMEP July 11, 2006 letter. Synthon advised DMEP that this is a stalemate and that if an approval action did not occur in 10 days, they would file an appeal for dispute resolution.
- August 10, 2006: Kirkpatrick& Lockkhart Nicholson Graham submitted all required information to request a formal meeting to the Office of Compliance. The communication stated that this meeting was not a formal dispute resolution request.
- August 16, 2006: Synthon notified that the meeting was scheduled for September 21, 2006 from 3 to 4 pm.

Background for ANDA 77-080 Amlodipine Besylate Tablets referred to by Synthon in meeting preparation package:

- November 3-4, 2005: James M. Kewley, Compliance Officer New York District Office, conducted an audit of [redacted] facility for bioequivalence (BE) study for ANDA 77-080. Deficiencies were documented on FDA Form 483. b(4)
- November 10, 2005: [redacted] responded to FDA Form 483 agreeing to adopt and implement recommended changes.
- April 26, 2006: Office of Generic Drugs issued a Bioequivalency Amendment to Synthon identifying deficiencies of ANDA 70-080 necessitating the conduct of new BE studies.

SUMMARY OF MEETING DISCUSSION:

Following introductions of all attendees, Ms. Autor welcomed Synthon. It was noted that the focus of this meeting was to have Synthon review the study procedures and documentary controls. FDA will pose questions during the presentation. The sponsor questions submitted

with the meeting request will not be discussed.

Synthon proceeded with their presentation (copy attached). Synthon emphasized that the purpose of today's meeting was to provide information that would confirm that ——s methods were more than adequate to support the accuracy and validity of the data derived from bioequivalence studies and that new bioequivalence studies are not needed. Synthon noted that their presentation will focus on NDA 21-961. However, Synthon emphasized that the acceptability of the inspections for the NDA 21-961 and for the ANDA 70-080 for Amlodipine are critical and have significant impact for Synthon because of ten other BE studies conducted in the same manner which are associated with other applications. b(4)

Synthon highlighted that —— documentation during the BE study —226-04) pivots on the following four documents that were used at the time of dosing: 1) Subject Identification Tag, 2) Drug Administration Record, 3) Drug Dispensing Envelope, and 4) Fluid Intake Registration Form. Synthon emphasized that these four records in combination and individually document the time of dosing, drug administered, and fluid intake for each study subject. b(4)

The following four slides, referred to as exhibits by Synthon, were the focus of the FDA questions for the remainder of the meeting. Please note that the discussion at times jumped between these four exhibits but for the purpose of clarity of content of the minutes, all FDA questions and Synthon responses will be associated with the corresponding exhibits.

Subject Identification Tag

Subject 1 Study 099/226/05	Name ——

b(4)

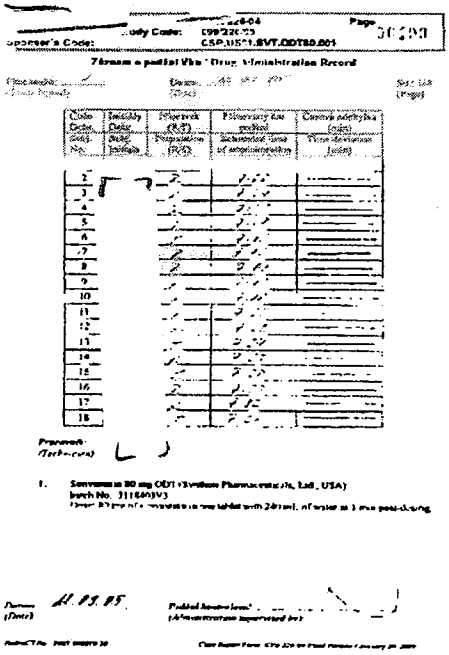
Exhibit 1

Synthon reviewed the procedure for each subject receiving their subject identification tag as seen in Exhibit 1. This step in their procedure was referred to during the discussion and FDA questions for Exhibits 2, 3, and 4.

Synthon provided a detailed overview of the use of the Drug Administration Record, Exhibit 2

(below), described as a pre-printed document present at the time of dosing. FDA queried and received confirmation that the only entry at the time of dosing is in the Time Deviation column. Synthon noted the forms were filled out the day before subject dosing. FDA asked if the meaning of time was described in the SOP for the study. Synthon responded that the SOP only refers to time and does not provide an explicit definition. FDA noted that there is no documentation of the actual time of administration of T (simvastatin 80 mg ODT [Synthon Pharmaceuticals batch No. 3118403V3]) or R (Zocor 80 mg tablets [Merck batch No. N5746] on the Drug Administration Record but only the intended scheduled time of administration. Synthon agreed. [redacted] reviewed that [redacted] did not write down the actual time of dosing on the Drug Administration Record. He added that they interpret that the doctor signing the form is the proper documentation of the actual and scheduled dosing time of T or R. b(4)

Drug Administration Record



b(4)

Exhibit 2

Synthon provided a detailed overview of the use of the Drug Dispensing Envelope, Exhibit 3 (below), described as the pre-printed source document present at the time of dosing. All envelopes are preprinted with: 1 simvastatin 80 mg tablet: 099/226/05/ T or R. The procedure of filling the envelopes is completed by the doctor and nurse the day before the study. All R envelopes are filled at same time and all T envelopes are filled at the same time. The envelope filling procedure is not documented with initialing on the envelope. Synthon clarified that the Admin Time, Technician initials and Supervisor initials were not preprinted on the envelope and were entered at the time of administration of the dose. FDA asked if the SOP addressed the

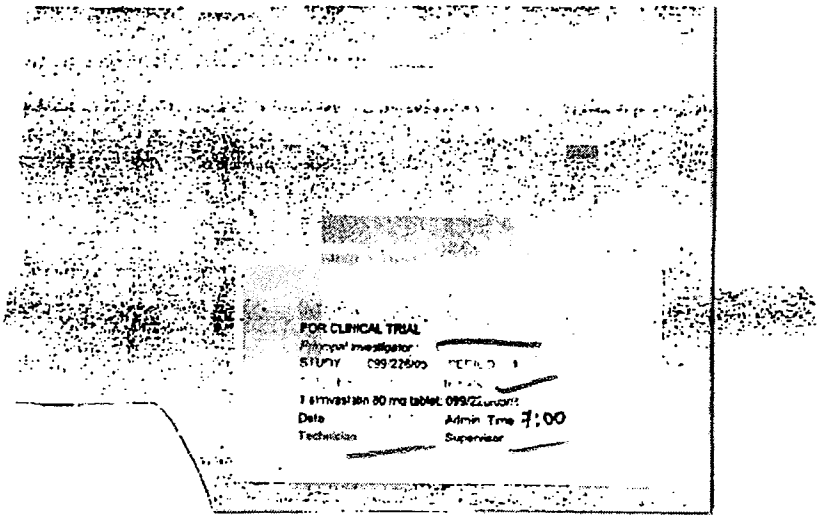
Drug Dispensing Envelope

[redacted]-226-04 Page 00161

Study Code: 099/226/05

Sponsor's Code: CSP.US01.SVT.ODT80.001

Drug Label



b(4)

Exhibit 3

documentation of the drug identification and the three entries on the envelope at the time of dosing. Synthon responded that the SOP (attachments) does not address the documentation of the drug identification but speaks to the time given by the tech and doctor. Synthon noted that the package SOP for filling the envelopes covers this and ensures the confidence of the T and R authenticity.

Synthon provided a detailed overview of the use of the Fluid Intake Registration Form, Exhibit 4 (below), described as the pre-printed Fluid Intake Registration Form also present at the time of dosing. The columns labeled Subject Number and Subject Initials was preprinted. Synthon confirmed that the purpose of this form is to document the time that all subjects received 240 mL of water. All subjects should have received either 240 mL water with the ODT test drug at one minute post-dose or with Zocor at dose time. The time of dosing and the identification of T or R are not included on this form. [redacted] noted that when the dose is given to the subject, he recognizes the tablet and also checks the subject's mouth at one minute to visually confirm disintegration of the ODT. Upon FDA questioning, he added that no documentation is made of this step and the protocol does not describe such documentation. FDA asked if there is a record of the disintegration time for the ODT. [redacted] responded no.

b(4)

Fluid Intake Registration Form

b(4)

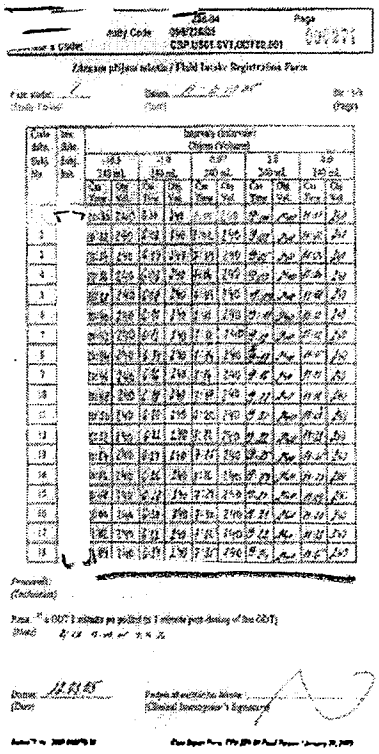


Exhibit 4

The FDA did not have any further questions on the remaining slides in the presentation.

FDA requested that Synthon comment on the Drug Inventory and Dispensing Form which was not included in the presentation. FDA stated that although the form contained information to supplement the identity of the dosage forms (it identified the treatments by name (e.g., Zocor for the reference product) and lot number), it lacked a relevant date (the form was not signed by [redacted] and the clinical monitor until after the study was completed). FDA noted that the instructions for use of the form indicate that "As dispensing of these supplies occurs, it is to be recorded on this form." Dr. Stargel agreed with FDA's comments and stated that this form is intended as an inventory form only. The clinical monitor was not present at the time of dosing and, therefore, this form is not intended as a documentation of dosing. b(4)

[redacted] offered his personal assurance that all study procedures and documentation were done consistently. b(4)

CONCLUSION:
Ms. Autor thanked Synthon for the presentation and their responses to all FDA questions.

ACTION ITEM:
Office of Compliance will respond to Synthon with comments and decision.

Leslie Vaccari 10/25/06
Leslie Vaccari
Project Management Officer

Concurrence Chair:
Deborah Autor, Esq.
Director, Office of Compliance

Attachments:
Synthon Power Point Slide Presentation (20 pages)
FDA Form 483 May 15-18, 2006 [redacted] Inspection for NDA 21-961
[redacted] SOP for Drug Administration – discussed by Synthon
[redacted] SOP for Packaging and Labeling – discussed by Synthon
b(4)

19 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRAT ON

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)

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~~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 —— study 226-05
   Amlodipine 10 mg ODT tablet (Synthon)vs NORVASC 10 mg (Pfizer) in healthy volunteers under fed and fasting conditions —— 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]

b(4)

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 CT V. Swamathan	EMPLOYEE(S) NAME AND TITLE (Print or Type) CT. Viswanathan, Ph.D., Associate Director, Div. Scientific Investigations	DATE ISSUED May 18, 2006

FORM FDA 483 (1/03) PREVIOUS EDITION OBSOLETE [illegible] INSPECTIONAL OBSERVATIONS

Purpose: To ensure the right procedure of administration of tested drugs in the pharmacokinetics studies

Scope: Administration of tested drugs for the volunteers

Responsibility: All pharmacokinetics studies carry out by [redacted] Company

b(4)

1.Introductory

The clinical investigator is responsible for the assurance of individual dosages of evaluated drugs, preparing according to S.O.P [redacted] in the locked mobile safety box stored until the administration in the secure place with the controlled temperature.

2.Procedure:

The administration of the drugs is carrying out with the other responsible personal. Before the actual administration, the clinical investigator unlocks the safe box in the appointed place for the drugs administration and prepares the envelops with the drugs for the administration.

With the administration of the drugs the clinical investigator checks the name of the volunteer on his or hers name tag and on the envelope with the code of the product and in the record of "Drugs Administration Record". After the worker opens the envelope by cutting one of the corners of the envelope, the tablet has to stay in the cut part and checked, if the amount of the drug is the same as it is written on the envelope.

At the scheduled time the responsible personal administers drug the to the volunteer, together with specified amount of the liquid. It is necessary to check if the volunteer drinks all the required amount of liquid.

After that, the clinical investigator checks the volunteer's mouth with a flashlight (under the tong and inside of the mouth), if the drug was swallowed. This procedure must be written in the information for the volunteers. Volunteers must know this procedure before the study.

The exact time of the administration is recorded on the envelope of the preparation and the clinical investigator signs the envelope of the preparation with the other responsible person.. Envelopes are archived together with the documentation.

The responsible personal, records the real time of the drug administration also in to the "Drug administration Record" and the amount of the given fluid in to the "Fluid Intake Record Form".

All the amounts of preparation, which were not administrate (e.g. drop out of the volunteer) are locked back in to the safe and the clinical investigator is assuring their handover in to the box with controlled temperature for the long term storage.

Note: In the case of using different form than the oral form of the administrating drug the procedure of the application is described in the protocol of the study.

5 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Division of Scientific Investigations

FACSIMILE TRANSMITTAL SHEET

DATE: September 19, 2006

To: Michael Hinkle Vice President and General Counsel Synthon Pharmaceutical, Inc. cc: Gary L. Yingling 202-778-9100	**From: Leslie Vaccari** Project Management Officer
Company: Synthon Pharmaceutical, Inc.	Division of Scientific Investigations Office of Compliance, CDER
Fax number: 1-919-493-6104	**Fax number:** 301-594-1204
Phone number: 1-919-536-1304	**Phone number:** 301-594-5235

Subject: Meeting September 21, 2006 at 3-4 pm

Total no. of pages including cover: 2

Comments Follow.

Michael Hinckle, J.D.

Please refer to the meeting regarding NDA 21-961 scheduled between Synthon and the Office of Compliance on September 21, 2006 at 3:00 to 4:00 PM.

Synthon's presentation for the meeting needs to include :

- Background information on Synthon Pharmaceuticals, Inc. and [redacted]
- Synthon's succinct description of [redacted]'s actual procedures and documentary controls for the [redacted] Study No. [redacted] 226-04 evaluating Zocor Tablets (Merck) and Synthon's simvastatin orally disintegrating tablets, especially those procedures that ensured that the data accurately reflected whether, at the time of dosing, the test or reference product had been administered. b(4)

The FDA will take this opportunity to clarify and further query the issues as presented by Synthon in your presentation but will not provide conclusions during the meeting.

Please have all attendees bring photo identification and allow 15to 30 minutes to complete security clearance. Upon arrival our FDA building, give the guards either of the following numbers to request an escort to the conference room: Marlene Sue Ling at 301-827-9071 or Linda Hukle at 301-827-9070. I will then come to escort you to the conference room. I would like to bring you to the conference room by 2:50 pm so that you can set up. The proxima will be set up for your arrival.

If you have questions, please feel to contact me at 301-594-5235.

Leslie Vaccari

Project Management Officer
Office of Compliance/Division of Scientific Investigations
HFD-45 MPN1 Rm 1442
Phone: 301-594-5235

Simoneau, Margaret A

From: Simoneau, Margaret A
Sent: Thursday, August 31, 2006 8:43 AM
To: Colangelo, Kim M; Simoneau, Margaret A
Subject: SIMONEAUM has sent you a scanned document

Attachments: ScanDoc.pdf

ScanDoc.pdf (152 KB)

Hi Kim,\nI assume this submission is just an amendment to the NDA at this time with no action required. The sponsor received an NA action letter in May 2006 due to the DSI inspection results. Please let me know if there is anything else required with this submission.\n\nThanks,\nMargaret

Simoneau, Margaret A

From: Colangelo, Kim M
Sent: Thursday, August 31, 2006 9:42 AM
To: Simoneau, Margaret A
bject: RE: SIMONEAUM has sent you a scanned document

Margaret,

Nothing needed at this time!

Thanks!
Kim

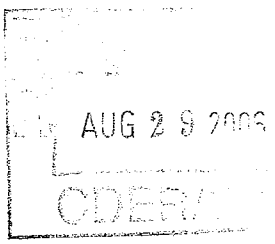
PS: I mentioned this to Curt again, but please make sure that Mary is at the meeting with Synthon and Compliance in case they want to pursue formal dispute resolution.

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs, CDER, FDA
>301-796-0700 (OND IO main)
>301-796-0140 (direct)
>301-796-9856 (facsimile)
>Kim.Colangelo@fda.hhs.gov
>
>

-----Original Message-----
From: SIMONEAUM [mailto:margaret.simoneau@fda.hhs.gov]
Sent: Thursday, August 31, 2006 8:43 AM
: Colangelo, Kim M; Simoneau, Margaret A
bject: SIMONEAUM has sent you a scanned document

Hi Kim,\nI assume this submission is just an amendment to the NDA at this time with no action required. The sponsor received an NA action letter in May 2006 due to the DSI inspection results. Please let me know if there is anything else required with this submission.\n\nThanks,\nMargaret

DUPLICATE



August 28, 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 013
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
Notification of expiry of 45-day period provided for in 21 C.F.R. § 314.52 (f)

Dear Dr. Parks:

We have enclosed one original and two copies of Amendment 013 to Synthon Pharmaceuticals, Inc.'s ("Synthon's") new drug application ("NDA") for Simvastatin Orally Disintegrating Tablets (NDA # 21-961).

Reference is made to amendment 011 to NDA #21-961, filed June 30, 2006. This amendment provided a "Paragraph IV" patent certification for U.S. Patent Nos. RE36481 and RE36520; these patents were "re-listed" in FDA's "Orange Book" ***after*** Synthon submitted its NDA for Simvastatin Orally Disintegrating Tablets. Reference is also made to amendment 012 to NDA # 21-961, filed July 6, 2006. This amendment provided documentation of the receipt, by the appropriate NDA holder and patent owner of Synthon's notice of patent invalidity or noninfringement.

This amendment is being submitted as notification that the patent holder, Merck, has ***not*** filed a lawsuit within the prescribed 45-day period and, therefore, cannot delay approval of Synthon's NDA for Simvastatin Orally Disintegrating Tablets. The NDA holder received notice of patent invalidity or noninfringement for the aforementioned patents on July 5, 2006. The last day of the 45-day period, provided for in 21 C.F.R. § 314.52 (f), was August 20, 2006.

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 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)

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-961

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

Dear Mr. Hinkle:

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 August 3 and 10, 2006 correspondence, received August 10, 2006, addressed to Deborah M. Autor, Esq., Director, Office of Compliance, Center for Drug Evaluation and Research. You requested a meeting to discuss the issues described in 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:	September 21, 2006
Time:	3:00 to 4:00 PM
Location:	Office of Compliance 11919 Rockville Pike Montrose Metro 2 Rockville, MD 20852
CDER participants:	Deborah M. Autor , Joseph Famulare, Mary E. Purucker, CT Viswanathan, Joseph Salewski, Sriram Subramaniam, Terri Rumble, Leslie Vaccari, Mary H. Parks, Eric C. Colman, Margaret Simoneau

Please have all attendees bring photo identification and allow 15to 30 minutes to complete security clearance. If there are additional attendees that were not identified in your August 10, 2006 meeting request, email that information to Marlene Sue Ling **marlene.sueling@fda.hhs.gov**. Upon arrival our FDA building, give the guards either of the following numbers to request an escort to the conference room: Marlene Sue Ling at 301-827-9071 or Linda Hukle at 301-827-9070.

If you have any questions, call Leslie Vaccari, Project Management Officer, at 301-594-5235.

Sincerely,

{See appended electronic signature page}

Leslie A. Vaccari
Project Management Officer
Office of Compliance, HFD-300
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/

Leslie Vaccari
8/17/2006 01:56:04 PM

Appears This Way
On Original

Simoneau, Margaret A

From: Hill, John
Sent: Tuesday, May 16, 2006 4:44 PM
To: Fraser, Blair; Ysern, Xavier J
Cc: Simoneau, Margaret A
Subject: Establishment inspections for NDA 21-961, Synthon Simvastatin

Attachments: EES report.txt

OC has completed the pre-approval inspections. The recommendation is acceptable; there are no outstanding facility issues.

Happy, happy, joy, joy.....

EES report.txt (16 KB)

John C. Hill, Ph.D., CDR. USPHS
Chemist
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment, CDER, FDA
10903 New Hampshire AVE.
Bldg. 21, RM. 2545
Silver Spring. MD 20993-0002
(301) 796-1679

9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-961

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

Dear Mr. Hinkle:

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If you have any questions, call Leslie Vaccari, Project Management Officer, at 301-594-5235.

Sincerely,

{See appended electronic signature page}

Leslie A. Vaccari
Project Management Officer
Office of Compliance, HFD-300
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/

Leslie Vaccari
8/17/2006 01:56:04 PM

Kirkpatrick & Lockhart Nicholson Graham LLP

1601 K Street, N.W.
Washington, DC 20006-1600
202.778.9000
Fax 202.778.9100
www.klng.com

August 3, 2006

Gary L. Yingling
202.778.9124
Fax: 202.778.9100
gyingling@klng.com

Deborah M. Autor, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration -HFD-300
Montrose Metro 2 - Room 406
11919 Rockville Pike
Rockville, MD 20852

Re: Request for a Meeting to Review the Division of Scientific Investigations' Findings from the Inspection of [redacted] and DSI's Rejection of the Bioequivalence Data

Dear Ms. Autor:

We are writing on behalf of our client Synthon Pharmaceuticals, Inc. ("Synthon") who used [redacted] as the Contract Research Organization ("CRO") for a number of bioequivalence studies that have been or will be submitted to the U.S. Food and Drug Administration ("FDA") in support of the company's pending, or to be filed, new drug applications ("NDAs") and/or abbreviated new drug application ("ANDAs"). Synthon was recently informed that three of its studies were found "unacceptable" on the basis of an inspection of the [redacted] facility by FDA's Division of Scientific Investigations ("DSI"). As a result of these findings, Synthon's NDA 21-961 (simvastatin orally disintegrating tablets) and ANDA 77-080 (amlodipine besylate tablets) were deemed "not approvable" and Synthon has been instructed to conduct new bioequivalence studies to support those applications. Four additional bioequivalence studies were identified in the same DSI inspection reports and therefore are expected to be impacted in a similar way. This will result in the rejection of two more Synthon applications. Furthermore, recent communications from DSI, which are discussed below, lead Synthon to believe that six additional studies (two applications) are also potentially at risk. (*see* Exhibit 1). Synthon believes that DSI incorrectly relied on the arbitrary and capricious recommendation of an individual agency inspector in reaching its decision. We request a meeting with you and your office to address the questions raised, and to find a resolution that will allow the subject study data to be used in support of Synthon's previously submitted and soon to be submitted applications.

b(4)

As discussed in greater detail below, Synthon has requested meetings with two FDA review divisions in an attempt to provide details on the merits of the studies conducted at [redacted]. The meeting requests stemmed from a Bioequivalency Amendment and a deficiency letter issued by the Office of Generic Drugs' ("OGD") Division of Bioequivalency ("DBE") and a "Not Approvable" letter issued by the Division of Metabolic and Endocrine Drug Products ("DMEP"). OGD effectively denied our client's request for a meeting when it reiterated the DBE's position

b(4)

that the issue involved was a "field issue," and refused to discuss the matter. As to the DMEP meeting request, we understood that the basis of the DSI inspection driven "Not Approvable" letter would be discussed at a proposed July 17, 2006 meeting. However, less than a week before that meeting, DMEP notified Synthon that it would not entertain any discussion of the DSI inspection or the collected data at the meeting, and would only discuss the design of new bioequivalence studies. We firmly believe that the data collected by [redacted] is accurate and fully complies with not only the FDA's regulatory requirements and policies but those of the European Union and ICH. We request that a meeting be scheduled for the purpose of reviewing the accuracy and integrity of the data in question. b(4)

I. Background

A. Synthon Pharmaceuticals, Inc. and [redacted]

Founded in 1991, the Synthon corporate group is dedicated to the development, registration, production, marketing and distribution of a wide range of pharmaceutical products. Over the past few years, Synthon, and its affiliates, have filed a number of NDAs and ANDAs including NDA 21-961, a section 505(b)(2) application for the approval of Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg, and 80 mg ("Simvastatin") which is bioequivalent to Merck's Zocor, NDA 19-766; and ANDA 77-080 for the approval of Amlodipine Besylate Tablets, 2.5 mg, 5 mg and 10 mg which is bioequivalent to Pfizer's Norvasc, NDA 19-787. b(4)

[redacted] is a Contract Research Organization ("CRO") based in [redacted]. [redacted]'s facility includes an on-site facility for the housing of study subjects and an in-house bioanalytical lab. The bioequivalence studies conducted by [redacted] are performed in compliance with the European Union's and FDA's laws and regulations applicable to clinical testing. In connection with Synthon's development of several drug products, the company contracted with [redacted] to conduct a series of bioequivalence studies for the collection of data supporting the bioequivalence of several drug products. The bioequivalence studies were conducted under the direct supervision of [redacted] (*see* Exhibit 2) b(4)

Prior to selecting [redacted] as its CRO, Synthon made arrangements for an audit of [redacted]'s facilities. The audit was performed by [redacted]

[redacted] In February 2003, he conducted an audit of the [redacted] facility, the clinical personnel, procedures, and records, for adequacy and compliance with FDA requirements. [redacted] inspection resulted in no major concerns. He concluded that [redacted] clinical practices complied with all applicable FDA requirements and were consistent with industry standards," and that the procedural controls implemented by [redacted] were more

than adequate to ensure the integrity of any data collected at the site. Based on those findings, [redacted] and Synthon moved forward with the clinical tests. (*see* Exhibit 3)

[redacted] returned to th[redacted]s facility at Synthon's request in May 2006 to review records associated with the company's bioequivalence studies in anticipation of a second FDA inspection of the facility [redacted] inspected the facility and once again found that "the records complied with all applicable FDA requirements and were more than adequate to ensure the validity of the study data." [redacted] has since reviewed DSI's findings and recommendations, and disagrees with its conclusions. [redacted] was scheduled to attend and provide comments at the scheduled July 17, 2006 meeting. b(4)

B. Procedural History

James M. Kewley, Compliance Officer, Foreign Inspection Cadre conducted an investigation of the [redacted] facility on November 3-4, 2005. During his investigation, Mr. Kewley cited a number of alleged deficiencies associated with the documentary controls used by [redacted] to administer its studies. The deficiencies noted on the FDA Form 483 (Notice of Inspectional Observations) were: 1) failure to include the proprietary name of the reference (i.e., brand) drug on the dispensing envelope; 2) failure to visually confirm the identity of the drug at the time of administration; 3) failure to include drug product batch numbers on the dispensing envelopes; 4) the "Drug Administration Record" in the Case Report Forms ("CRFs") failed to include signatures and initials to document individual dosing times, and dosing time deviations were documented using a straight line to indicate no deviation; 5) failure to maintain adequate and accurate records of receipt and handling of test and reference drugs; and 6) failure to confirm that meals provided to study subjects complied with the study protocol. A copy of the Form 483 issued to [redacted] on November 4, 2005 is enclosed. (*see* Exhibit 4) The Establishment Inspection Report ("EIR") for this inspection was not provided to [redacted] until May 16, 2006. (*see* Exhibit 5) b(4)

[redacted] responded to the Form 483 on November 10, 2005. In its response, [redacted] notified DSI of its intent to adopt and implement DSI's preferred methods of documentary controls. At the time [redacted] thought that it was merely making minor changes to its procedures in order to align itself with FDA's preferred approach. [redacted] never intended to agree with the position that its methods and procedures were inadequate to insure the integrity of those studies. On the contrary, as documented below, there is more than adequate documentation to support the integrity of these bioequivalence studies. (*see* Exhibit 6) b(4)

Synthon received a Bioequivalency Amendment and a deficiency letter from DBE on April 27, 2006 concerning its ANDA for Amlodipine Besylate Tablets, 2.5 mg, 5 mg and 10 mg (ANDA 77-080). For Synthon, the DBE letter was the first indication that there was a problem with the company's bioequivalence study. Citing DSI's alleged deficiencies, DBE stated that it deemed

the "deficiencies concerning the accuracy of the study drug administration dosing times and drug sampling times to be significant enough to compromise the integrity of the bioequivalence studies." Despite acknowledging Synthon's and [redacted]s proposal to adopt and implement DSI's preferred approach for future studies, DBE still concluded that the proposed corrective measures failed to address the deficiencies in the conduct of the submitted studies, and DBE found the studies "unacceptable." (*see* Exhibit 7) b(4)

In a letter dated May 11, 2006, Synthon responded to that decision, challenging DBE's determination that Synthon's studies were "unacceptable" and asking for a meeting. Synthon noted that although not consistent with DSI's preferred methods, the documentary controls used by [redacted] were more than appropriate to ensure and support the accuracy and integrity of the collected data. (*see* Exhibit 8) The company stated that there was no scientific justification for the rejection of the bioequivalence studies, especially considering that the studies were carefully performed and documented by clinical personnel in accordance with good research practices. Synthon pointed out to OGD that [redacted] had agreed to adopt DSI's preferred methods of recordkeeping for all future studies but in no way was that offer an acknowledgement by either Synthon o[redacted] that the methods previously employed by [redacted] failed to comply with agency requirements. OGD replied to Synthon's letter on June 20, 2006 by rejecting our client's request for a meeting with DBE and DSI stating that it doubted "the usefulness of the meeting..." since the decision was based on an inspection in the field. Reaffirming its earlier position that DSI's alleged deficiencies concerning the accuracy of the study drug administration dosing times and drug sampling times were significant enough to compromise the integrity of the bioequivalence studies, DBE again labeled the studies "unacceptable" and directed Synthon to submit new bioequivalence studies for the drug product. (*see* Exhibit 9). b(4)

Six months after FDA's inspection by Mr. Kewley in November 2005, [redacted] was notified that C.T. Viswanathan, Ph.D. of the Good Laboratory Practice and Bioequivalence Investigations Branch would be conducting a second inspection of the [redacted] facility on May 15-18, 2006. Synthon asked to have [redacted] and Wayne Stargel, Pharma.D, Vice President of Medical Affairs at Synthon present for the inspection. After a four day inspection, a Form 483 was given to [redacted] identifying only one new [redacted] related observation associated with its blood processing procedures, and three Synthon-related observations (*see* Exhibit 10) Despite the absence of any significant new findings and the general clerical nature of the deficiencies, Dr. Viswanathan recommended that Synthon's pending biostudies, including the bioequivalence study intended to support the Simvastatin NDA, be rejected and the related applications be deemed "not approvable". Following the Viswanathan inspection, Synthon received a letter dated May 25, 2006 from DMEP concerning the "Not Approvable" status of NDA 21-961, Simvastatin Orally Disintegrating Tablets. (*see* Exhibit 11). As with the DBE letter of April 27, 2006 concerning Amlodipine Besylate, this letter cited the alleged deficiencies identified during DSI's inspections as the basis for its decision, concluding that the inspectional concerns were b(4)

significant enough to compromise the integrity of the bioequivalence study, and that before the application could be approved, Synthon would need to conduct a new bioequivalence study.

On May 30, 2006, Synthon responded to the Not Approvable letter by requesting a face-to-face "End of Review" meeting with appropriate members of DMEP and DSI to discuss the integrity of the bioequivalence study. (*see* Exhibit 12) In that response, Synthon again provided DMEP with a detailed analysis of the documentary controls and recordkeeping practices used by [redacted], pointing out that [redacted]'s methods were more than adequate to ensure the accuracy and integrity of the collected data, and that there was no scientific justification for the rejection of the bioequivalence study. A meeting was subsequently scheduled for Monday July 17, 2006. b(4)

On July 11, 2006, less than a week before the scheduled meeting, Synthon received a letter via fax from DMEP reaffirming its position that the not approvable action taken on NDA 21-961 was appropriate. (*see* Exhibit 13) The letter contained an Appendix that included newly identified deficiencies that had never before been communicated to either Synthon or [redacted]. The letter also signaled DMEP's refusal to discuss the integrity of the clinical data at the July 17, 2006 scheduled meeting. It did however note, that DMEP "would be happy to discuss the details of another bioequivalence study" with the company at the July 17, 2006 meeting. b(4)

Because of DMEP's unwillingness to entertain a discussion of the accuracy and integrity of the collected data, in an email to Margaret Simoneau, of DMEP on July 13, 2006, Synthon asked that the meeting be cancelled. (*see* Exhibit 14)

Synthon responded to DMEP's July 11, 2006 letter and its new allegations on August 1, 2006. Neither the Form 483 issued to [redacted] nor the Not Approvable Letter sent to Synthon on May 25, 2006 mentioned several of the matters referenced in the Appendix. Furthermore, neither of the FDA investigators who inspected [redacted]'s facility ever mentioned these alleged deficiencies to [redacted]. Given the inclusion of the newly cited deficiencies, Synthon felt obligated to respond to these new allegations before taking the matter on appeal through formal dispute resolution. (see Exhibit 15) b(4)

C. [redacted]'s Documentary Controls, DSI's Cited Deficiencies and Synthon's Response

DMEP's basis for rejecting the data was the clerical procedures used by [redacted] to collect the data. [redacted] used the same methods for all the studies performed. To focus the requested meeting, Synthon proposes using its May 30, 2006 response / submission to FDA's May 25, 2006 Simvastatin O.D.T. Not Approvable Letter to analyze the issues involved. A copy of Synthon's letter and submission is attached. (*see* Exhibit 16) We have also set forth the inspector's observations and our responses below. b(4)

1. Overview of ——'s Procedures

—— used a drug envelope system to dispense drugs and to document the drug dosing times during its bioequivalence studies. This procedure is described in, and controlled by, a Standard Operating Procedure ("SOP") that was in place at the time the studies were performed. The drug envelopes were labeled with the study number, the name of the Principal Investigator, subject number, subject initials, period name (1 versus 2 for crossover studies), drug name (generic name only – however, each envelope contained a unique internal code allowing for the reference drug to be distinguished from the generic), date of drug administration, a space to record the drug administration time (to be handwritten at time of dosing), and a place for two study personnel to confirm dosing administration (a physician and a nurse). (*see* Exhibit 17) The study drugs were packaged into the envelopes the night before the study subjects were to be dosed. This packaging operation was verified by two independent members of —— s staff and documented on the "Drug Packaging Record." Before providing a study participant with the drug, both the physician investigator and a nurse verified the subject's name, dose, dosing period and dosing time information listed on the envelope. At the time of dosing, the physician hand wrote the actual drug administration time on each envelope. Finally, the physician and study nurse initialed the envelopes to provide "double verification" of the accuracy of the dosing procedure. In addition to recording the drug administration time on the actual envelopes, —— also completed a "Drug Administration Record" designed to capture both the time of dosing and any deviation from the scheduled dosing time. (*see* Exhibit 18) Likewise, any deviations from scheduled drug sampling times (i.e., time of blood draws) were recorded on a similarly formatted "Sample Time Record". (*see* Exhibit 19) Both of these documents, the Drug Administration Record and the Sample Time Record were included in the study's CRFs. In accordance with —— 's SOPs in place at the time, a lack of time deviations for drug administration and blood sampling were recorded using a straight line through the "Time Deviation" box on the appropriate form (i.e., Drug Administration Record or Sample Time Record, respectively) to indicate that there was no deviation from the scheduled preprinted drug administration or sampling time. When a deviation occurred, —— procedure called for the deviation to be documented in the form of plus or minus minutes from the scheduled time.

b(4)

2. DSI's Cited Deficiencies and Synthon's Response

a. Dosing and Blood Sampling Times

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

Synthon: "The actual drug dosing times and drug sampling times were accurately recorded."

Actual dosing times were recorded on the dispensing envelopes while only the scheduled dosing times were pre-printed on the "Drug Administration Record." Referencing the pre-printed times on the "Drug Administration Record" and the "Sample Time Record" forms, Dr. Viswanathan cited a failure "to include signatures or initials to document individual dosing and dosing verification for study subjects" and a "failure to record the actual time of blood draws from the subjects." As noted in Synthon's May 30, 2006 letter, this is blatantly misleading for it implies that ——— failed to record drug administration and sampling times. Reviewing the records from the study, one clearly finds that this is untrue. Drug administration times were recorded on the actual dispensing envelopes while deviations from scheduled dosing times were recorded on the Drug Administration Record. Only scheduled times were preprinted prior to commencement. Actual dosing times were recorded and initialed on the dispensing envelopes by the physician investigator and accompanying nurse. Deviations from the scheduled times were then recorded on the Drug Administration Record. Under ——— 's SOP, deviations from scheduled dosing times were to be reported in the form of +/- minutes. Likewise, the actual blood sampling times were recorded as deviations from the scheduled times on the Sample Time Record. b(4)

b. Drug Identification

DSI: "[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."

Synthon: "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."

——— used its own unique coding system on the dispensing envelopes to distinguish between the listed and reference drugs. Dr. Viswanathan's next deficiency concerned the absence of proprietary names (i.e. Zocor) and batch numbers on the dispensing envelopes. On his Form 483, he noted a "failure to include the correct name of the dispensed medication (dosage form) on the dispensing envelope prior to dosing" and a "[f]ailure to include the batch number of the medication on the dispensed envelope." As Synthon noted in its May 30, 2006 letter, this observation is factually accurate, but totally irrelevant to the integrity of the study data. There is no legal requirement or practical need for this information to appear on the dispensing envelopes. Instead ——— adopted a procedure whereby a unique internal code was placed on each envelope. That code included the name of the generic drug product, an 8-digit code unique to the study, and a "T" or "R" (referring to "test" and "reference" drug respectively). For example, a typical label would read "1 Simvastatin 80 mg tablet: 099/226/05/T" or "1 Simvastatin 80 mg tablet: 099/226/05/R". Study personnel were trained in the meaning of the codes to avoid confusion. ——— felt that including the proprietary name of the drug on the envelope could bias the study by allowing a subject to see whether he or she was receiving the test or reference b(4)

drug. For these reasons, [redacted] maintains its system was more than adequate to ensure the integrity of the study data. b(4)

c. Study Drug Identification and Confirmation

DSI: "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."

Synthon: "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."

Both a physician investigator and a nurse confirmed the identity of the study drug prior to administration. The third deficiency identified by Dr. Viswanathan involved an alleged failure by the investigator to confirm the identity of the tablets after removing them from the dispensing envelope and prior to administration. Specifically, he cited a "[f]ailure to visually confirm the identity of the medication at the time of drug administration and to document the results of the confirmation." Contrary to Dr. Viswanathan's conclusions, the physician investigator's initials on the dispensing envelope constitute evidence that the physician confirmed the identity of the study drug prior to administration. Physicians were trained to confirm the dose prior to drug administration, and in these studies, the physician could easily distinguish the reference and test drugs as they were different in size, shape and color. (*see* Exhibit 20) 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. (*see* Exhibit 21) This confirmation process was evidenced by the physician's initials and verified by the nurse's initials on the drug envelope.

d. Receipt and Condition of the Study Medication

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

Synthon: '[redacted] has adequate and accurate records of the receipt, inventory, and condition of the study drugs." b(4)

Adequate controls were in place to guarantee the accurate receipt and condition of the study medication. Dr. Viswanathan cited [redacted] "failure to maintain adequate and accurate records of receipt and to check for the condition of the test medications ..." Again, this allegation is untrue. The drugs were hand delivered to the principal investigator from the Study Director.

The clinical investigator personally received the study drugs, performed an inventory, and documented receipt of the drug products. Upon receipt, the investigator signed an "Acknowledgement Form" which served as documentation of date of receipt. Additionally, after completing an inventory of the study drugs, the investigator completed a "Drug Accountability Form" which served as documentation of the quantity and condition of the drugs. (*see* Exhibit 22)

II. Reasons for Allowing the Data to Be Used

A. The Division of Scientific Investigation's Recommendation that Synthon's Bioequivalence Studies are Invalid Was Arbitrary and Capricious.

The deficiencies identified by Mr. Kewley and Dr. Viswanathan during the investigations of the ——— facility are wholly clerical in nature, and totally unrelated to the scientific integrity of the study data. Considering the absence of established regulations, published Guidance documents or agency rules mandating the use of specific documentary controls, rejecting a bioequivalence study on the basis of a party's failure to use an individual investigator's preferred approach, where more than adequate controls were in place to ensure the accuracy and integrity of the study data, is not only unreasonable, but arbitrary and capricious. Upholding DSI's integrity recommendation in this case, signals the application of a "form over function" approach to bioequivalence inspections. b(4)

———, a major clinical testing facility, has used the methods described above for documenting dosing and sampling times for over 10 years in over 180 studies. The controls comply with EU, ICH and other foreign regulatory rules, and have been used by numerous other testing facilities. Synthon and ——— dispute DSI's conclusion that only the DSI preferred approach is "adequate" and that other appropriate methods cannot provide reliable study results to support an NDA or ANDA application. In the absence of established regulations or guidelines providing for how information is to be recorded, basing a "not approvable" decision on perceived deficiencies in clerical controls, despite the use of a system that complies with regulations and ensures the accuracy and integrity of the study data, is unreasonable. b(4)

If it were critical that sponsors use only the DSI preferred approach, the Agency clearly would have issued a very specific Guidance at a minimum, requiring that such an approach be used for bioequivalence studies. Yet, no such Guidance detailing bioequivalence study procedure and the agency's preferred methods for document drug administration and sampling times, have been developed. Without such regulatory guidance, a party should be permitted to use any appropriate means of ensuring the accuracy and integrity of the study data, and the rejection of a bioequivalence study for failure to follow DSI's preferred approach should be reversed as arbitrary and capricious.

Additionally, Synthon has been required to defend itself against a series of constantly changing deficiencies. As detailed above, DMEP's July 11, 2006 response included an Appendix setting forth allegations concerning Synthon's bioequivalence that had not been previously communicated to Synthon or [redacted] Neither the Form 483 issued to [redacted] nor the Not Approvable Letter sent to Synthon mentioned several of the matters referenced in the Appendix. Furthermore, neither of the FDA investigators who inspected [redacted]'s facility ever mentioned these alleged deficiencies to [redacted] With new deficiencies still being identified despite more than two months having passed since Dr. Viswanathan's investigation of [redacted], Synthon and [redacted] feel as if they are being forced to chase a perpetually moving target. As noted in [redacted] Declaration attached as Exhibit 2, during the May 2006 inspection [redacted] asked Dr. Viswanathan if any written information describing the required controls besides the regulations themselves exist to help a clinical researcher develop and implement a recordkeeping system that fully complies with FDA requirements. Dr. Viswanathan responded that no such materials exist and that it is only through DSI inspections that a facility can learn what is required. Given the absence of publicly available established rules for the creation and implementation of documentary controls, DSI's continued identification of alleged deficiencies, serves as another example of its arbitrary and capricious practices. b(4)

B. Rejecting Synthon's Bioequivalence Study Has Far Reaching Implications

The decision to reject the Simvastatin study impacts every U.S. study performed by [redacted] and has the potential to impact every other clinical trial currently being conducted inside and outside the United States. Synthon's bioequivalence studies were deemed "unacceptable" based on the fact that [redacted]'s documentary controls differed from DSI's preferred method of record keeping, although [redacted]'s methods were more than adequate to safeguard and ensure the accuracy and integrity of study data. The various preprinted forms used are not significantly different from the forms used inside and outside the U.S. for clinical data collection. If upheld, this decision would in effect, force [redacted] and similar U.S. and foreign clinical testing facilities to adopt and implement DSI's preferred system of documentary controls, even where parties already have adequate systems in place. Applying this rationale, failure to follow DSI's preferred methods of documentary controls would result in a clinical study being deemed "unacceptable" by the Agency and denial of the associated NDA or ANDA. b(4)

C. International Harmonization

Neither Synthon nor [redacted] is suggesting that because a procedure is acceptable in the EU, it should be acceptable to the U.S. FDA. Instead, it is suggested that at a time of widespread international clinical testing and harmonization as fostered by ICH, it is inappropriate and wrong for the FDA to question the data integrity of a study merely because the data collection method is not what the FDA investigator wants to see. b(4)

As described above, ——'s methods satisfy EU rules and are consistent with the current practices of other CROs both inside and outside the U.S. Dr. Viswanathan's recommendation and the "not approvable" decision based on that recommendation puts numerous, otherwise adequately performed, clinical studies currently being conducted both inside and outside the United States in danger. Many of the CROs use preprinted forms similar to those used by ——which DSI has rejected as inadequate. Synthon itself has 8-10 addition biostudies pending in other applications that will be affected by Dr. Viswanathan's decision. From a policy perspective, the DSI's decision will have a profound impact on pharmaceutical development and testing, as clinical testing facilities interested in performing research for pharmaceutical companies, will be forced to change currently established administrative practices to comply with DSI's preferred methods. b(4)

III. Conclusion

Synthon and —— believe that the questioning of the data integrity in this specific situation is wrong. Neither firm objects to amending or changing the way data is collected in the future, but to reject bioequivalence studies where the data was accurately collected and to require retesting is unfair and unjust. Furthermore, requiring additional bioequivalence studies would be contrary to FDA's basic "guiding principle" that "no unnecessary research should be done." 21 C.F.R. § 320.25(a)(1). We are asking for a face to face meeting with you and your office in an attempt to resolve this matter in a way that allows FDA and the companies to move forward. We will be calling your office in a few days to request a meeting date. b(4)

Sincerely,

Gary L. Yingling

Encl.

cc: Synthon Pharmaceutical, Inc. (w/o exhibits)
Gary J. Buehler, FDA OGD (w/o exhibits)
Dale P. Conner, FDA OGD (w/o exhibits)
Mary Parks, FDA DMEP (w/o exhibits)
Eric Colman, FDA DMEP (w/o exhibits)
Margaret Simoneau, FDA DMEP (w/o exhibits)
Joseph Salewski, FDA DSI (w/o exhibits)
Linda Huckle, FDA OC (w/o exhibits)
—— (w/o exhibits)

b(4)

Exhibit List

Exhibits Referenced in Synthon Pharmaceutical Inc.'s August 3, 2006 Letter to Deborah M. Autor, Esq., Director, Office of Compliance Requesting a Meeting

Exhibit 1 – List of Bioequivalence Studies that [redacted] Conducted for Synthon

Exhibit 2 – Declaration of [redacted]

Exhibit 3 – Declaration of [redacted]

Exhibit 4 – James M. Kewley's Form FDA 483 (11/04/05)

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Exhibit 5 – Establishment Inspection Report ("EIR") provided to [redacted] (05/16/06)

Exhibit 6 – [redacted] Response to Kewley's FDA Form 483 (11/10/05)

Exhibit 7 – Bioequivalence Amendment and Deficiency Letter from OGD (04/27/06)

Exhibit 8 –Synthon' Response to OGD's 04/27/06 Letter (05/11/06)

Exhibit 9 – OGD's Letter Denying Synthon's Request for a Meeting (06/20/06)

Exhibit 10 – C.T. Viswanathan's Form FDA 483 (05/18/06)

Exhibit 11 – DMEP's "Not Approvable" Letter for NDA 21-961 (5/25/06)

Exhibit 12 – Synthon's Response to DMEP's "Not Approvable" Letter (5/30/06)

Exhibit 13 – DMEP Letter Reaffirming Position on NDA 21-961(07/11/06)

Exhibit 14 – Synthon's Email to Margaret Simoneau Canceling Meeting (7/13/06)

Exhibit 15 –Synthon's Response to DMEP's "Not Approvable" Letter (08/01/06)

Exhibit 16- Synthon's Response to FDA's 05/25/06 "Not Approvable" letter (5/30/06)

Exhibit 17 –Drug Dispensing Envelope

Exhibit 18 – Drug Administration Record

Exhibit 19 – Sample Time Record

Exhibit 20 – Zocor v. Simvastatin Picture

Exhibit 21 –Fluid Intake Charts

Exhibit 22 – Drug Acknowledgement and Accountability Forms