Synthon
Pharmaceuticals, Inc.

May 18, 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 009
Simvastatin Orally Disintegrating Tablets (SVT-ODT)
10 mg, 20 mg, 40 mg and 80 mg
Postmarketing Commitment for Dissolution Testing

Dear Dr. Parks:

Synthon Pharmaceuticals, Inc. ("Synthon") hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets (ODTs). This amendment provides a postmarketing commitment to perform additional dissolution testing on Synthon's SVT-ODT drug product. The commitment is provided below. A completed Form FDA-356h is also enclosed.

Synthon hereby commits to concurrently validating the more discriminating dissolution method QC.WO.SVT.odt.020.C/12.02 (submitted as amendment 008 dated 5/16/06) 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 C [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. Appropriate 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.

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

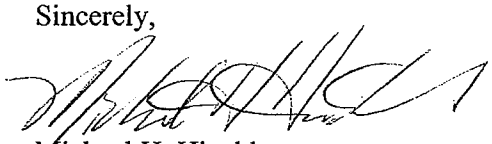
This amendment is to be submitted within [redacted] of approval of NDA 21-961. b(4)

As per 21 CFR 314.60(c), Synthon hereby submits two copies of this **Amendment 009** and certifies that a **true and exact copy** of this amendment has been forwarded as a Field Copy to the FDA District Office at the address below:

Mary H. Woleske, District Director
Atlanta District Office
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA, 30309

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

Sincerely,



Michael H. Hinckle
VP and General Counsel

Enclosures

Appears This Way
On Original

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

FACSIMILE TRANSMITTAL SHEET

DATE: 5/17/06

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

Subject: FORM 483 & SPONSOR LETTER FOR NOVEMBER 3-4, 2005 INSPECTION

Total no. of pages including cover: EIGHT

Comments:

AS DISCUSSED IN THE TELECON, ATTACHED ARE FORM 483 AND THE SPONSOR'S RESPONSE FOR THE NOVEMBER 2005 INSPECTION DONE AT ——— FOR A OGD APPLICATION. b(4)

Jay Buehler
240-276-9310

Document to be mailed: __YES __NO

b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
International and Technical Operations Branch (HFC-134) 5600 Fishers Lane, Rockville, Maryland 20857 phone (301) 827-3777	3-4 November 2005 FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
TO: [redacted]	b(4)
FIRM NAME [redacted]	STREET ADDRESS [redacted]
CITY, STATE AND ZIP CODE [redacted]	TYPE OF ESTABLISHMENT INSPECTED CRO

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

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.

Audit of unblinded studies entitled:

- Randomized, Two Period, Crossover Bioequivalence Study on Amlodipine 10 mg Tablets (Synthon Pharmaceuticals, Ltd., USA) versus NORVASC 10 mg Tablets (Pfizer, USA) in Healthy Volunteers under Fasting Conditions (study 075/182/03);

AND

- Randomized, Two Period, Crossover Bioequivalence Study on Amlodipine 10 mg Tablets (Synthon Pharmaceuticals, Ltd., USA) versus NORVASC 10 mg Tablets (Pfizer, USA) in Healthy Volunteers under Fed Conditions (study 075/183/03);

revealed the following:

1. For both studies, failure to include the 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 (NORVASC 10 mg tablets), or the test article (Amlodipine 10 mg tablets), were labeled "amlodipine 10 mg tbl".

2. For both studies, failure to visually confirm the identity of the medication at the time of administration, and to document the results of the confirmation. Although the test article tablets and reference material tablets are distinctively different in shape, size and scoring, there is no record of the investigator confirming the identity of the tablets after removing them from the dispensing envelope, prior to administering the dose.

3. For both studies covered, failure to include the batch number of the medication on the dispensed envelopes;

4. For both studies covered, the "Drug Administration Record" in the CRF fails to include signatures or initials to document individual dosing and dosing verification for study subjects. In addition, dosing time deviations are documented only with a hand-written line in the "Time Deviation" column, reportedly to indicate no deviation occurred from the intended time for dosing.

5. For both studies covered, failure to maintain adequate and accurate records of receipt and handling of test article and reference materials, as follows:

- Records covering the 5 September 2003 receipt and handling of test articles and reference materials from the study sponsor, through [redacted] fail to document the method of transportation and delivery, the condition of the products upon reciept, or an adequate description of the products received; records do not indicate whether the bottles received were previously unopened, whether safety seals existed or had been broken, or whether the contents of any of the bottles had been examined or counted.

b(4)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	[signature]	James M. Kewley - Compliance Officer/Inv	4 Nov 2005

FORM FDA 483 (8/00) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 OF 2 PAGES

Created by PSG Media-ARM (301) 443-2458 EF

b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
International and Technical Operations Branch (HFC-134) 5600 Fishers Lane, Rockville, Maryland 20857 phone (301) 827-3777	3-4 November 2005 FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

b(4)

FIRM NAME	STREET ADDRESS
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
	CRO

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

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.

6. Failure to confirm that meals received at [redacted] for administration to study subjects complied with protocol requirements. Confirmation of the contents of meal orders received for study subjects is not documented.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		James M.Kewley - Compliance Officer/Invglr	4 Nov 2005

CONTAINS PROPRIETARY
INFORMATION NOT TO BE
DISCLOSED TO A THIRD PARTY

Synthon Laboratories, Inc.
7130 Heritage Village Plaza, Suite 201
Gainesville, VA 20155
Phone 703-754-0065
Fax 703-754-0081

CONFIDENTIAL

May 11, 2006

VIA FEDERAL EXPRESS

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: BIOEQUIVALENCY AMENDMENT
ANDA# 77-080/Amendment 011
Amlodipine Besylate Tablets, 2.5 mg, 5 mg and 10 mg

Dear Mr. Buehler:

Synthon Laboratories, Inc. ("Synthon") is amending its Abbreviated New Drug Application ("ANDA") for Amlodipine Besylate 2.5 mg, 5 mg and 10 mg Tablets. Reference is made to the Food and Drug Administration's ("FDA") April 27, 2006 Bioequivalency deficiency fax. A completed Form FDA 356h is provided in Exhibit 1 to this response. Additionally, a copy of FDA's deficiency letter is enclosed as Exhibit 2. For ease of review, FDA's observation/comment is provided below in *italicized* text followed by Synthon's corresponding response in normal text.

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

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

Please submit new bioequivalence studies on your drug product.

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RESPONSE:

Synthon respectfully disagrees with the Division of Bioequivalence's ("DBE's") conclusion that the integrity of the bioequivalence studies submitted in ANDA No. 77-080 were compromised as a result of alleged deficiencies at the clinical site, [redacted]. As discussed in greater detail below, DBE's conclusion appears to have been based on the limited administrative record that was available at that time. In this response, Synthon will fill in this record with essential data and information that will provide a high degree of assurance as to the integrity of the data in the biostudies. We believe that, upon DBE's review of this additional data, the Division will find that the documentation is sufficient to assure the quality of the biostudies and, therefore, will accept the studies as evidence of bioequivalence to the reference listed drug. b(4)

I. Background

In the deficiency letter, DBE acknowledged the corrective actions that [redacted] proposed in response to observations noted during the November 3-4, 2005 inspection of [redacted]'s facility. However, DBE was not made aware of the extensive measures that [redacted] had in place which ensured the integrity of the biostudies supporting Synthon's ANDA. This disconnect was the result of the way in which [redacted] responded to the inspectional observations. Rather than explaining why [redacted]'s current methods and procedures were adequate [redacted] merely "agreed" with the observations and committed to implement corrective action for future studies.[1] More specifically, [redacted] thought that they were simply agreeing to make minor changes in the way that they documented certain study data in order to align itself with the FDA's preferred approach. [redacted] never intended to "agree" that the methods and procedures used for its previous studies were inadequate to ensure the integrity of those studies. On the contrary, as documented in this response, there is a plethora of data to unequivocally support the conclusion that each study subject received the proper drug product and that each drug administration and sampling time was accurately recorded. FDA and the courts have long recognized that sponsors do not have to adopt the agency's preferred method so long as the same assurance of quality and integrity is achieved. In this instance, [redacted]'s approach may have differed from FDA's preferred methods, but the data and documentation leave no doubt as to the integrity of the study. b(4)

[1] While one of the DBE deficiencies goes to the "accuracy" of "drug sampling times," [redacted] response to the inspectional observations did not specifically address this issue because it was not listed on the Form FDA 483. Nevertheless, as explained herein, [redacted] had adequate procedures in place to control drug sampling times and has, since the inspection, implemented procedures for recording sampling times that are consistent with the FDA recommended approach. b(4)

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II. The Drug Dosing Times/Drug Sampling Times Were Accurately Recorded.

— utilizes a drug envelope system to dispense and document the time of drug administration for bioequivalence studies. On the evening prior to administration, the drugs (Reference and Test) are dispensed from the original containers into the drug envelopes that are labeled with the study number, Principal Investigator, subject number, subject initials, Period number (1 versus 2 for these crossover studies), drug name (generic only), date of drug administration, and a place to document administration time – to be hand-written at the time of dosing – and a place provided on the label for the two study personnel (i.e., nurse and physician investigator) to confirm dosing administration. Importantly, although the study drugs are both identified on the envelope by the generic name "amlodipine 10 mg tbl.", the envelope also contains a unique internal code following the generic name that classifies the drug as the Test or Reference Drug. For example, the label code for the test drug in Synthon's fasting study was —182-03/T while the code for the reference drug was —182-03/R (copies of the original dispensing envelopes are provided in Exhibit 3A (fasting study) and Exhibit 3B (fed study)). The protocol clearly states that the letter at the end of the code identifies which drug is contained in the envelope. Specifically, the protocol states that the letter "T" corresponds to the Test Drug and the letter "R" to the Reference Drug. This coding system is also intuitive in that one would naturally associate the letter "T" with "test" and the letter "R" with "reference." The study personnel are well trained on the meaning of these codes to further avoid confusion. Furthermore, the drug in the dosing envelope is verified by two independent members of —staff at the time of dispensing. The double verification is documented on the Drug Packaging Record (enclosed as Exhibit 4A (fasting study) and 4B (fed study)). This check and recheck of the content of the drug envelope against the original drug container provides a high degree of assurance that the correct drug will be administered to the correct subject during the correct study period.

b(4)

Additionally, the nurse and physician investigator perform a verification of subject, dose (Reference versus Test), dosing period (1 versus 2), and documentation of time of dosing on the envelope at the time of dosing. To insure accuracy, each study subject wears an identification arm band that is checked by the nurse and verified by the physician prior to dosing. Documentation of the "double verification" is provided by the initials of the nurse and physician investigator on the dosing envelope. The envelope is considered raw data and provides the requisite documentation that the correct dose was administered to the correct subject during the correct dosing period.

In addition to the documentation on the dispensing envelope, —, also completes a "Drug Administration Record" designed to capture the time of dosing and any time deviation from the scheduled dosing time (examples enclosed as Exhibit 5A (fasting study) and Exhibit 5B (fed study)). Likewise, deviations in drug sampling times are

b(4)

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recorded on a similarly formatted "Sample Time Record" (examples enclosed as Exhibit 6A (fasting study) and Exhibit 6B (fed study)). For these two documents, which are included in the case report forms ("CRF") ——— has historically used a straight line through the "Time Deviation" box to indicate when no deviation occurred from the scheduled administration or dosing time. This procedure is described in, and controlled by, a Standard Operating Procedure ("SOP") that was in place at the time that these studies were performed (copy and English translation enclosed as Exhibit 7). Study personnel are trained on this SOP and, as a result, are clearly instructed to document time deviations on CRFs as ± minutes instead of listing the actual dosing or sampling time, which would require subtracting the actual time from the scheduled time. b(4)

Although the FDA investigator took issue with ——— s approach of documenting the drug administration and sampling times ——— continues to believe that this system reduces transcription errors and results in a CRF containing verification of the dose administration by the nurse and investigator for all subjects on the day of dosing.[2] As such, ——— maintains that this is an acceptable method for documenting deviations from the scheduled administration and/or sampling time. Nevertheless, ——— agreed to change its procedures to comply with FDA's preferred approach of writing the actual dosing/sampling time and then calculating the deviation by means of subtraction from the scheduled time. ——— s acquiescence to FDA, however, was by no means an acknowledgement that the procedures used in the amlodipine biostudies were inadequate. In fact, ——— and Synthon question whether FDA's requested changes will provide any additional assurance of study integrity. b(4)

III. Conclusion

The dispensing envelopes, the "Drug Administration Record," and "Sample Time Record" all constitute raw data that provide verifiable and accurate documentation of the drug administration and sampling times. ——— acknowledges that its method of documentation was not consistent with methods typically used by U.S. clinical sites. Consequently, ——— has agreed to change its methods to conform with FDA's desired approach. However, in this instance, there is no scientific justification to reject the results of Synthon's biostudies in light of the fact (which is supported by data) that the studies were carefully performed and documented by clinical personnel committed to good research methods. In fact, Synthon believes that repeating the studies would unnecessarily expose patients to study medications given that ——— has 100% confidence that the current bioequivalence studies were performed with systems that assured that the correct dose was administered to the correct subject at the correct times. b(4)

[2] It should be noted that ——— has been using this approach for documenting dosing and sampling times for over 10 years in over 180 studies. Numerous other regulatory authorities have reviewed the methodology and agreed that it adequately records the relevant information.

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IV. Meeting Request

Synthon hereby requests a meeting with the appropriate representatives of DBE and DSI to discuss this matter. Synthon plans on having the following persons present at the meeting:

[redacted]

Wayne Stargel, Pharm.D. – V.P. of Medical Affairs, Synthon Pharmaceuticals, Inc.
Joe Marchetti – President, Synthon Laboratories, Inc.

b(4)

[redacted]

Please contact us at your earliest convenience to schedule a meeting time. If DBE determines that this response is sufficient to accept the biostudies, the aforementioned meeting request should be considered withdrawn.

Please direct any communication or correspondence concerning this matter to my attention at telephone number (703) 754-0065 or via facsimile at (703) 754-0081.

Thank you for your attention to this matter.

Sincerely,

Joseph Marchetti
President
Synthon Laboratories, Inc.

Enclosure(s)

Appears This Way
On Original

Simoneau, Margaret A

ɔm:	Simoneau, Margaret A
ıt:	Wednesday, May 17, 2006 12:16 PM
.o:	'ralmond@synthon.com'
Cc:	Hill, John; Chung, Sang; Colman, Eric C; Galliers, Enid M
Subject:	NDA 21-961 Simvastatin ODT

Mr. Almond,

In follow-up to the tcon today, the following are the labeling comments and the postmarketing commitment as discussed.

To the **CLINICAL PHARMACOLOGY**, *Phamacokinetics* subsection, please add the following new second paragraph:

[redacted] b(4)

The following is the postmarketing commitment discussed:

The Agency requests that Synthon commit to concurrently validating the more discriminating dissolution method QC.WO.SVT.odt.020.C/12.02 (submitted as amendment XXX, 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 [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. Appropriate 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.

Thank you.

Margaret Simoneau, M.S., R.Ph.
FDA/CDER/DMEP
301-796-1295

Please note new email address
Margaret.Simoneau@fda.hhs.gov

N-000 EC

ORIG AMENDMENT

CDER/CDR

MAY 17 2006

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MAY 18 2006

CDER White Oak DR 1

Synthon
Pharmaceuticals, Inc.

May 16, 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 008
Simvastatin Orally Disintegrating Tablets (SVT-ODT)
10 mg, 20 mg, 40 mg and 80 mg
Additional Dissolution Data and Revised Dissolution Method

Dear Dr. Parks:

Synthon Pharmaceuticals, Inc. ("Synthon") hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets (ODTs). This amendment provides additional dissolution data along with a revised dissolution method. A completed Form FDA-356h is provided in Exhibit 1 to this response.

Reference is made to the following teleconferences and emails:

- May 3, 2006 teleconference between Richard Almond, Christine Walker and Dr. Po Lui of Synthon and Margaret Simoneau, Dr. Sang Chung (FDA/OCPB/DCPB2) and Dr. Hae Young Ahn (FDA/OCPB/DCPB2) requesting that Synthon supply additional dissolution data or separate lots of each strength (10 mg, 20 mg, 40 mg and 80 mg) of Synthon's SVT-ODT using the parameters of 75 rpm paddle speed, 0.1% and 0.15% SDS buffer at pH of 6.8. b(4)

- May 15, 2006 email from Richard Almond of Synthon to Margaret Simoneau, Dr. Sang Chung and Dr. Hae Young Ang supplying the additional dissolution data requested on May 3, 2006 and proposed/revised dissolution method. This email communication is provided in Exhibit 2.

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

Additional dissolution data is provided for —— NDA registration batch of each strength of SVT-ODT 10 mg, 20 mg, 40 mg and 80 mg. The additional dissolution data and updated dissolution method is provided in Exhibits 3 - 4 respectively. For ease of review, a List of Exhibits is attached and delineates the information presented in each exhibit. b(4)

Please note that Dr. Kamali Chance is no longer the contact person at Synthon. The following people may be contacted at with questions regarding this application.

Michael Hinckle
VP and General Counsel
(919) 493-6006

Richard Almond
Manager, Regulatory Affairs
(919) 536-1325

As per 21 CFR 314.60(c), Synthon hereby submits two copies of this **Amendment 008** and certifies that a **true and exact copy** of this amendment has been forwarded as a Field Copy to the FDA District Office at the address below:

Mary H. Woleske, District Director
Atlanta District Office
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA, 30309

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

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

Appears This Way
On Original

List of Exhibits
Exhibit 1
Exhibit 2
Exhibit 3
Exhibit 4

Simoneau, Margaret A

From: Richard Almond [ralmond@synthon.com]
Sent: Monday, May 15, 2006 9:03 AM
To: Simoneau, Margaret A; Ahn, Hae Young; Chung, Sang
Cc: Mike Hinckle; Kim Bartakovits
Subject: RE: NDA #21-961 (Simvastatin Orally Disintegrating Tablets)
Attachments: SVT ODT dissolution method pH6.8.pdf; AR-U-SVT-003-06.01.pdf

Good Morning,

Please find attached the dissolution analysis report of Simvastatin Orally Disintegration Tablets (NDA #21-961) from Synthon Pharmaceutical, Inc.'s (Synthon). As requested, Synthon has performed dissolution profiles using 0.1 and 0.15% SDS with a pH of 6.8 on [redacted] batches of each strength (10 mg, 20 mg, 40 mg and 80 mg) of Simvastatin Orally Disintegrating Tablets. Also attached is a proposed dissolution method using the 0.15% SDS/pH 6.8 conditions. Please call me, or email if you have any questions. b(4)

Best Regards,
Rich Almond
Synthon Pharmaceuticals, Inc.
(919) 536-1325

-----Original Message-----
From: Ahn, Hae Young [mailto:haeyoung.ahn@fda.hhs.gov]
Sent: Friday, May 05, 2006 8:01 AM
To: Chung, Sang; Richard Almond
Cc: Simoneau, Margaret A; Mike Hinckle
Subject: RE: NDA #21-961 (Simvastatin Orally Disintegrating Tablets)

During the t-con, the following was also agreed upon:
Because of time constraint, if the sponsor prefers to use [redacted] batches of each strength for 0.1 and 0.15% SDS in stead of 2 step approach (i.e. [redacted] it is acceptable as well. b(4)

Hae-Young Ahn

From: Chung, Sang
Sent: Friday, May 05, 2006 7:27 AM
To: 'Richard Almond'
Cc: Simoneau, Margaret A; 'Mike Hinckle'; Ahn, Hae Young
Subject: RE: NDA #21-961 (Simvastatin Orally Disintegrating Tablets)

Dear Mr. Almond,

Thanks for your kind summary of the telecon. I would like to clarify a few points as follows:

For 0.1% SDS concentration, you can provide results of dissolution study (cf. one of you indicated that you already had this), or you don't have to do a dissolution study for 0.1% SDS concentration if you prove it is not a sink condition.

For dissolution method justification (i.e. 0.1% vs 0.15% SDS), you need to provide dissolution study results using [redacted] batch of each strength. b(4)

Simoneau, Margaret A

bject:	NDA 21-961 Simvastatin ODT INDUSTRY LABELING T-CON
:ation:	; CDER WO 3270 conf rm Bldg22
Start:	Thu 5/11/2006 1:00 PM
End:	Thu 5/11/2006 2:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Lubas, William (CDER); Ahn, Hae Young; Chung, Sang; Hill, John
Optional Attendees:	Davis Bruno, Karen L
Resources:	CDER 520 Calendar; CDER WO 3270 conf rm Bldg22

Appears This Way
On Original

Simoneau, Margaret A

From: Richard Almond [ralmond@synthon.com]
Sent: Wednesday, May 10, 2006 3:02 PM
To: Simoneau, Margaret A
Cc: Mike Hinckle; Kim Bartakovits
Subject: Simvastatin Orally Disintegrating Tablets (NDA 21-961)
Attachments: SVT-ODT SideBySide Package Insert (revised 5.10.06) - FINAL.doc; SVT-ODT Package Insert (revised 5.10.06) - FINAL.doc

Hi Margaret,

In response to our telecon on May 8, 2006 regarding labeling of our pending NDA 21-961 for Simvastatin Orally Disintegrating Tablets (SVT-ODT), I have attached 2 word documents with Synthon Pharmaceuticals, Inc. (Synthon) revised, proposed Physicians Insert for SVT-ODT. One word document is our revised, proposed Physicians Insert, the other word document is a side by side annotated comparison of the innovator's latest Physicians Insert and our revised, proposed Physicians Insert. Please feel free to contact me if you have any questions.

Best Regards,
Rich Almond

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

Simoneau, Margaret A

From: Hill, John
Sent: Monday, May 08, 2006 11:19 AM
To: Colman, Eric C; Simoneau, Margaret A
Cc: Fraser, Blair; Hill, John
Subject: Relevant e-mail concerning the [redacted] manufacturing facility

b(4)

Attachments: [redacted] manufacturing issue part 1 NDA 21961.msg [redacted] manufacturing issue part 2 NDA 21961.msg

To all:

Attached are the two e-mails from the office of compliance which summarize the current state of affairs. I left a voice mail with Shawnte on Friday asking for a status update. I have not received any response yet.

[redacted] [redacted]
ıufacturing issue pa ıufacturing issue pa

As of today the inspectional status for the manufacturing facilities associated with this NDA are as follows:

1. [redacted] (Drug Product manufacturer): Inspection performed 06-APR-2006, there were 483 items noted in this inspection.

2. The [redacted] facilities are now accepted based on profile.

b(4)

summary: All manufacturing facilities EXCEPT for the [redacted] facility have been accepted by the Office of Compliance.

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

Simoneau, Margaret A

bject:	NDA 21-961 Simvastatin ODT INTERNAL LABELING/STATUS MEETING
;ation:	CDER WO 3302 conf rm Bldg22
Start:	Mon 5/8/2006 10:00 AM
End:	Mon 5/8/2006 11:00 AM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	~~Simoneau,~~ Margaret A; ~~Colman,~~ Eric C; ~~Lubas,~~ William (CDER); Hill, John; ~~Chung, Sang; Davis Bruno, Karen~~ L; ~~Ahn, Hae Young~~ Leave
Resources:	CDER WO 3302 conf rm Bldg22 Total 5

Status Mtg
1. AE Action
2. Reviews in by 19th

DETTLEBACK WED May 10th
301-827-1149

1. Send TA back
2. update label on Copyright label (3a) ODT -5mg name
3. Teva / Ranbaxy

301-594-1051

Simoneau, Margaret A

From: Subramaniam, Sriram
Sent: Friday, May 05, 2006 10:35 AM
To: Simoneau, Margaret A
Subject: NDA 21-961 Simva ODT Biopharm Inspection

Margaret,
This is a follow-up to our telecon we had this morning. You can e-mail the information to me. Thank you.

Sriram

Sriram Subramaniam, Ph.D.
DSI, HFD-48
301 594-1051

17th DSI

NFT

Simoneau, Margaret A

From: Ahn, Hae Young
Sent: Friday, May 05, 2006 8:01 AM
To: Chung, Sang; 'Richard Almond'
Cc: Simoneau, Margaret A; 'Mike Hinckle'
Subject: RE: NDA #21-961 (Simvastatin Orally Disintegrating Tablets)

During the t-con, the following was also agreed upon:
Because of time constraint, if the sponsor prefers to use [redacted]atches of each strength for 0.1 and 0.15% SDS in stead of 2 step approach [redacted]it is acceptable as well. b(4)

Hae-Young Ahn

From: Chung, Sang
Sent: Friday, May 05, 2006 7:27 AM
To: 'Richard Almond'
Cc: Simoneau, Margaret A; 'Mike Hinckle'; Ahn, Hae Young
Subject: RE: NDA #21-961 (Simvastatin Orally Disintegrating Tablets)

Dear Mr. Almond,

Thanks for your kind summary of the telecon. I would like to clarify a few points as follows:

For 0.1% SDS concentration, you can provide results of dissolution study (cf. one of you indicated that you already had this), or you don't have to do a dissolution study for 0.1% SDS concentration if you prove it is not a sink condition.

For dissolution method justification (i.e. 0.1% vs 0.15% SDS), you need to provide dissolution study results using [redacted]batch of each strength. b(4)

For your final dissolution method and determination of specification, you need to provide dissolution study results using [redacted]batches of each strength.

Please, let me know if you have any questions.

Regards,

Sang M. Chung, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics

From: Richard Almond [mailto:ralmond@synthon.com]
Sent: Thursday, May 04, 2006 2:55 PM
To: Simoneau, Margaret A
Cc: Mike Hinckle; Chung, Sang
Subject: NDA #21-961 (Simvastatin Orally Disintegrating Tablets)

Hi Margaret,

Please reference the May 3, 2006 telecon between Synthon Pharmaceuticals, Inc. (Synthon) and FDA regarding the dissolution parameters of Synthon's Simvastatin Orally Disintegrating Tablets, NDA #21-961. During the telecom, FDA requested that Synthon perform additional dissolution studies using the

following parameters:

1. buffer pH of 6.8
2. paddle rotation speed of 75 rpm
3. SDS buffer concentrations of BOTH 0.1% and 0.15%
4. batches of each strength of drug product (10 mg, 20 mg, 40 mg and 80 mg) b(4)

Studies are currently being scheduled and the data will be available to FDA (electronically) no later than May 15, 2006. Please contact me if you have any questions.

Thanks for your help.

Best Regards,
Rich Almond

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

Simoneau, Margaret A

From: Himaya, Amalia
Sent: Thursday, May 04, 2006 11:37 AM
To: Yau, Martin K; Simoneau, Margaret A
Subject: RE: Inspection status - NDA 21-961

301-82 7732

Hi Margaret,

This inspection is scheduled to start May 15, 2006.

FYI
Amalia

From: Yau, Martin K
Sent: Thursday, May 04, 2006 9:54 AM
To: Simoneau, Margaret A
Cc: Himaya, Amalia
Subject: Inspection status - NDA 21-961

Hi Margaret:

I was out of my office this week and just returned this morning. I have received your voice mail concerning the inspection status for NDA 21-961 (Simvastatin Orally Disintegration Tablets sponsored by Sinton Pharmaceuticals, Ltd.). Our project manager, Ms. Amelia Hamada will check on the status of the inspections in [redacted] and will get back to you soon. b(4)

Thanks.
Martin

Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations
GLP and Bioequivalence Investigations Branch

Appears This Way
On Original

Biopharm data to arrive 5/15/06

Simoneau, Margaret A

From: Adams, Shawnte L
Sent: Thursday, May 04, 2006 8:05 AM
To: Hill, John
Cc: Simoneau, Margaret A; Fraser, Blair
Subject: RE: NDA 21961

b(4)

We should have our evaluation completed before then. We received the inspection report for [redacted] yesterday and once we get the information on [redacted] we can make sure that's taken care of as well.

Thanks,

Shawnte L. Adams
Program Analyst
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-8909 (Fax)

From: Hill, John
Sent: Thursday, May 04, 2006 7:10 AM
To: Adams, Shawnte L
Cc: Simoneau, Margaret A; Fraser, Blair
Subject: RE: NDA 21961

Shawnte:

Thank you for the status update.

Not to be a worry wart, but I do want to remind you that the medical division (510) wants to take an action on this NDA by May 26. Time flies when a PDUF goal data draws near. Let me know if you need any help.

I do have a question, since I canceled the inspection request in EES do I now need to re-enter it? I did note that the scheduling of the inspection occurred after I canceled the request. Hopefully there is an administrative means of correction this inspection request.

Again, thanks for the update and happy Thursday!

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

From: Adams, Shawnte L
Sent: Wednesday, May 03, 2006 4:58 PM
To: Hill, John
Subject: NDA 21961

John,

Apparently there is some manufacturing at the [redacted] site as well as it being the administrative address. We received conflicting information from the US Agent's office intially. DFI found this out and went ahead and sent an inspection team. I've requested the results because that information has not been passed on to our office yet. I'm interested in the recommendation so that I can find out exactly what they are manufacturing at the [redacted] site. b(4)

Thank you,

Shawnte L. Adams
Program Analyst
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-8909 (Fax)

Appears This Way
On Original

Simoneau, Margaret A

ubject:	NDA 21-961 Simvastatin ODT/T-con with Synthon (Biopharm)
cation:	CDER WO 3376 conf rm Bldg22
Start:	Wed 5/3/2006 2:30 PM
End:	Wed 5/3/2006 3:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Ahn, Hae Young; Chung, Sang
Optional Attendees:	Colman, Eric C
Resources:	CDER WO 3376 conf rm Bldg22

1. C. Walker
2. Poe houie (analytical - dissolve)

C - Batch info

— Batch / per Strength
+

b(4)

1. email - not data looking for!
#1 — lots per Strength
all based on same lot #
does not meet Standard
all based on single lot per Strength

#3 Not enough data
Recommend additional Study
AHN a 75 RPM Ph 6.8 fixed condition
2 different .1% .15%

note: data .1 → 5.0% They have at 7.0 ph

METHOD DEVEL Report is available

Problem
1. METHOD
2. specs

SDS

Sodium Dodecial Sulfate

USP Monograph Said ph 7

Want
Propose 4 Strength
need — batch data
— lots per Strength for the dissolution condition

b(4)

Simoneau, Margaret A

From: Richard Almond [ralmond@synthon.com]
Sent: Monday, April 24, 2006 2:04 PM
To: Chung, Sang
Cc: Simoneau, Margaret A; Kim Bartakovits
Subject: NDA # 21-961 (Simvastatin Orally Disintegrating Tablets)
Importance: High

Dr. Chung,

Please reference Synthon Pharmaceuticals Inc.'s:

NDA #21-961 for Simvastatin Orally Disintegrating Tablets (SVT-ODT) submitted to the FDA on July 27, 2005.
FDA's acceptance to file fax dated October 4, 2005.
NDA #21-961 Amendment 006 presenting a revised, more discriminating dissolution method for SVT-ODT submitted to the FDA on March 14, 2006.

As a follow up to our teleconference on April 21, 2006 with Margaret Simoneau, I would like to highlight the points of our discussion and present where in the dissolution validation document (VR-U-SVT-001-06.01) that was submitted in amendment 006 to NDA #21-961 the information is located.

1. FDA recommends at leas[redacted]lots of the drug product be used in the validation of the dissolution method.

   Up t[redacted]ts of SVT-ODT were used in the validation of the dissolution method. Refer to pages 5 and 6 of 63. Batch (lot) numbers 3117702V2 (10 mg), 3117902V (20 mg), 3118202V2 (40 mg) and 3118402V2 (80 mg) were used.

   a. Deaeration of dissolution mediu[redacted]lot (80 mg), page 28/63, 6 vessels – individual dissolution data is presented. b(4)
   b. Precision/Repeatability [redacted]lots (10 mg, 20 mg, 40 mg and 80 mg), pp 31/63 and 32/63, 6 vessels – individual dissolution data presented.
   c. Intermediate Precision [redacted]lots (10 mg, 20 mg, 40 mg and 80 mg), pp 33/63, 34/63, 35/63 and 36/63, 3 vessels – individual dissolution data presented.
   d. Accuracy [redacted]lots (10 mg, 20 mg, 40 mg and 80 mg), pp 37/63, 38/63, 39/63, 40/63, 41/63 and 42/63, 3 vessels – individual dissolution data presented.
   e. Adsorption test [redacted]lots (10 mg, and 80 mg), pp 43/63, 6 vessels – individual dissolution data presented.
   f. Robustness [redacted]lot (80 mg) for 8 different conditions (pH, stirring speed and medium molarity), pp 49/63, 50/63, 51/63, 52/63, and 53/63) 1 vessel – individual dissolution data presented (note that section 16.1 on page 49/63 incorrectly states that 6 dissolution vessels were used).

2. FDA would like to see individual dissolution data as a means to help justify the dissolution specifications.

   As indicated in item #1 above, all individual dissolution data is presented in validation report VR-U-SVT-001-06.01. The dissolution specification of [redacted] (Q) dissolved in 30 minutes was met using the revised dissolution method. b(4)

3. FDA would like justification for using a buffer pH of 7.0 instead of 6.8.

   The pH of 7.0 used in the dissolution buffer for SVT-ODT is recommended by the current USP under the Simvastatin immediate release monograph and Synthon used this as a starting point for developing the

dissolution method. In addition, Synthon received recommendations from the FDA on a revised dissolution method in the acceptance to file letter received on October 11, 2005. In the letter, FDA recommended that Synthon revise their current dissolution method to "use a lower paddle speed with lower ——— concentration". Synthon used the FDA's recommendations and specifically looked at lower paddle speed and ——— concentration only. b(4)

Please feel free to contact me via email (richard.almond@synthon.com) or phone (919) 536-1325 if you have additional questions.

Best Regards,
Rich Almond

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

Simoneau, Margaret A

bject:	NDA 21-961 Simvastatin ODT/T-con with Synthon re: F/up Biopharm issues
cation:	Bld 22 Rm 3372 (Peggy's office)
Start:	Fri 4/21/2006 1:30 PM
End:	Fri 4/21/2006 2:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Chung, Sang

moneau, Margaret A

)m: Ahn, Hae Young
nt: Friday, April 21, 2006 2:59 PM
: Chung, Sang; Simoneau, Margaret A
: Galliers, Enid M
bject: RE: Update: Dissolution study and NDA21-961 for simvastatin ODT

ıg and Peggy
ıat the sponsor will submit early next week may not be sufficient. The sponsor should be informed on what they need to ıerate:
ısolution data using 75rpm, 0.15%, 0.3% and 0.5% SDS, pH 6.8
atches per strength

e-Young

---

n: Chung, Sang
t: Friday, April 21, 2006 2:52 PM
Simoneau, Margaret A
Galliers, Enid M; Ahn, Hae Young
ject: Update: Dissolution study and NDA21-961 for simvastatin ODT

ıgy,

ıt had a discussion with Hae-Young regarding T-CON with the sponsor we had yesterday and today. In conclusion, she gested we could call it as a major amendment if the sponsor needs to conduct additional study to generate new data if we can not make the final decision without the new data.

ı sponsor will send to me any available data in early next week, and I will update you whether the sponsor need to do itional study or not.

ıards,

g

Appears This Way
On Original

Simoneau, Margaret A

Subject: NDA 21-961 Simva ODT T-con with Synthon; Additional biopharm data requirement
Location: Bldg 22 Rm 3372/ Time: whenever you get here!

Start: Wed 4/19/2006 2:30 PM
End: Wed 4/19/2006 3:00 PM

Recurrence: (none)

Meeting Status: Meeting organizer

Required Attendees: Simoneau, Margaret A; Chung, Sang

Minutes

T- Con discussion:

Referrence March 14, 2006 submission, requests:

1. Individual dissolution data for 16.1, .2 &.3
2 Agency recommend ph dissolution media of 6.8 (this is the ph of the small intestine); if you want a ph of 7.0 then justification is required
3. In 16.12, the ph is 6.8, therefore, no new studies are needed.
4. Information request response will be sent to to the NDA, with a copy to Dr. Chung

#2
4/18/06

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-961 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name:
Established Name: Simvastatin Orally Disintegrating Tablets
Strengths: 10, 20, 40 and 80 mg

Applicant: Synthon Pharmaceuticals, Inc
Agent for Applicant: Kamali Chance

Date of Application: July 28, 2005
Date of Receipt: July 29, 2005
Date clock started after UN: N/A
Date of Filing Meeting: September 19, 2005
Filing Date: September 27, 2005
Action Goal Date (optional): User Fee Goal Date: May 29, 2006

Indication(s) requested: Reductions in Risk of CHD Mortality and CV Events; Pts with Hypercholesterolemia Req. modifications of Lipid Profiles; Adolescent Pts with HeFH

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☒ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification (1,2,3 etc.):
Other (orphan, OTC, etc.):

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: Zocor/ April 18, 2006 (ped)

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒

  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Is the submission complete as required under 21 CFR 314.50? YES ☒ NO ☐

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.

  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Was the patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Was exclusivity requested? YES, _____ Years NO ☒

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO ☒

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☒

- Were financial disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- Are the PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Are the trade, established, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
  Is the established name correct in COMIS IND(s) file(s): YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- List referenced IND numbers: PIND 70,964

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) Advice lt and t-con with User Fee NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☐ NO ☒

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☒
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☒
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☒
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/19/05

NDA #: 21-961

DRUG NAMES: Simvastatin ODT

APPLICANT: Synthon Pharmaceuticals, Inc.

BACKGROUND: Synthon's Simvastatin ODT is a new dosage form of the lipid-lowering drug product Zocor tablets, NDA 19-766, by Merck & Co., Inc.

(Provide a brief background of the drug, e.g., the molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: M. Parks, W. Lubas, H. Ahn, S. Chung, J. Hill and M. Simoneau

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline	**Reviewer**
Medical:	W. Lubas
Secondary Medical:	M. Parks
Statistical:	nn
Pharmacology:	Davis-Bruno
Statistical Pharmacology:	nn
Chemistry:	J. Hill
Environmental Assessment (if needed):	nn
Biopharmaceutical:	S. Chung
Microbiology, sterility:	nn
Microbiology, clinical (for antimicrobial products only):	nn
DSI:	nn
Regulatory Project Management:	M. Simoneau
Other Consults:	Biopharm Consult

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Zocor, NDA 19-766

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). Merck is tablet formulation; Synthon is orally disintegrating tablets

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference? YES ☒ NO ☐
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES ☒ NO ☐
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A ☐ YES ☒ NO ☐
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
N/A ☐ YES ☒ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES ☐ NO ☒

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted? YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application? YES ☒ NO ☐

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

/s/

Margaret Simoneau
4/18/2006 02:09:11 PM
CSO

Appears This Way
On Original

Simoneau, Margaret A

From: Hill, John
Sent: Tuesday, March 28, 2006 10:10 AM
To: Simoneau, Margaret A
Subject: Notification of amendment to DMF

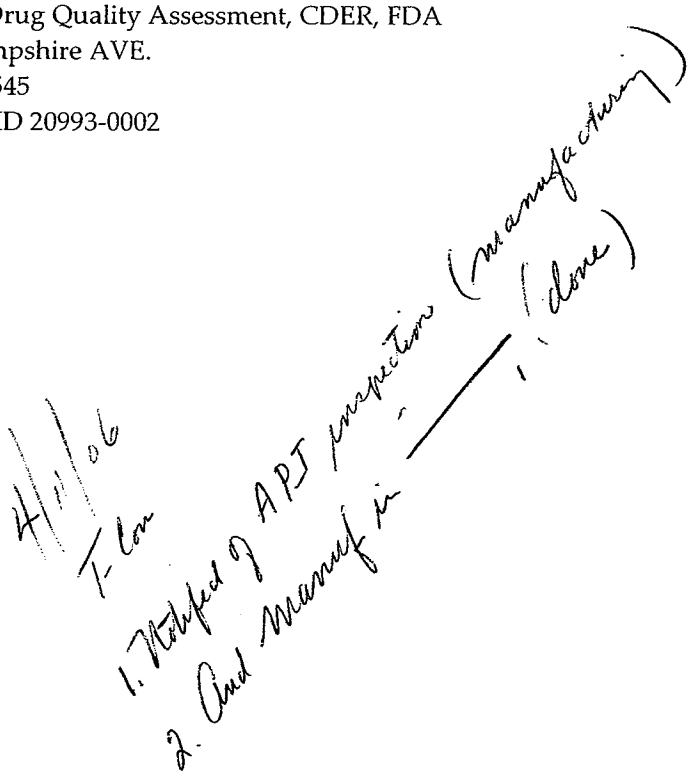
Peggy:

I checked with Art Shaw (the DMF guru) about this letter that Synthon BV sent me indicating that they have filed and amendment to DMF 18384 in response to our IR comments. The holder of the NDA (Synthon Pharmaceuticals, Inc.) needs to officially amend the NDA (NDA 21-961) indicating that the holder of DMF 18384 (Synthon BV) has notified them that they have submitted an amendment to DMF 18384. This amendment to the NDA is required so that I can officially review the amendment to the DMF.

Isn't Government work fun???

Please call me if this is at all confusing to you; together we can work this out.

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



b(4)

ORIGINAL

Synthon
Pharmaceuticals, Inc.

March 27, 2006

N-000(C)
NEW CORRESP

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
Simvastatin Orally Disintegrating Tablets
Notification of Amendment to DMF #18384

Dear Dr. Parks,

Reference is made to New Drug Application (NDA) #21-961 for Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg and 80 mg, as amended, originally submitted by Synthon Pharmaceuticals, Inc. on July 28, 2005. This NDA references the Type II Drug Master File (DMF) #18384 for Simvastatin drug substance, held by Synthon BV, Nijmegen, The Netherlands.

Synthon Pharmaceuticals, Inc. hereby provides notification to the FDA that Synthon BV has submitted Amendment 001 to DMF #18384 to the FDA on March 23, 2006. The purpose of this amendment was to address deficiencies to the DMF that were provided to Synthon BV on February 23, 2006 in a letter from the FDA.

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

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

Simoneau, Margaret A

Subject:	NDA 21-961 Simva ODT/ March 14, 2006 submission
Location:	CDER WO 3376 conf rm Bldg22
Start:	Thu 3/23/2006 11:00 AM
End:	Thu 3/23/2006 11:30 AM
Recurrence:	(none)
Meeting Status:	Meeting organizer Total 6
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Galliers, Enid M; Chung, Sang; Hill, John; Ahn, Hae Young
Optional Attendees:	Fraser, Blair
Resources:	CDER WO 3376 conf rm Bldg22

Agenda:
1. Extend the review clock with the March 14, 2006 submission?
2. Possibility of "overdue" status with DSI inspection

C/I
TA
1. DSI Dir Dead May 4th + EER
2. AE - + Inspect Mon 22
3. Labeling Tues

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

Patent Data

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

Exclusivity Data

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

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

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

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through February, 2006
Patent and Generic Drug Product Data Last Updated: March 20, 2006

ORIGINAL

Synthon
Pharmaceuticals, Inc.

March 17, 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 007
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
Submission of Additional Adverse Event Information

ORIGINAL AMENDMENT
N 000 BM

Dear Dr. Parks:

Reference is made to New Drug Application (NDA) #21-961 for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg, submitted by Synthon Pharmaceuticals, Inc. (Synthon) on July 28, 2005. Synthon hereby amends the aforementioned NDA to include additional information on adverse events observed during a bioequivalence study that was performed on Simvastatin 80 mg Orally Disintegrating Tablets; Form FDA 356h is provided in Exhibit 1 to this amendment. This study was sponsored by Synthon BV, an affiliate of Synthon based in Nijmegen, Netherlands for the purpose of seeking registration in the European Union. The clinical protocol for this study was similar to the clinical protocol that is presented in the Module 5 of the original NDA submission. However, please note that the reference product for this study is Zocor® Forte XL 80 mg Tablets [redacted], which is authorized for marketing in Europe. The bioequivalence studies that were conducted in support of Synthon's proposed product used the US reference product, Zocor® 80 mg Tablets (Merck & Co., Inc.).

Information on the adverse events observed during this clinical study is summarized in the final clinical study report, which is provided in Exhibit 2 to this amendment. The severity of the adverse events was mild (2 cases) or moderate (3 cases). Of these events, the clinical investigators judged three adverse events as "probably related" (two cases of abdominal pain and one case of headache). No serious adverse event, unexpected adverse drug reaction or other significant adverse event occurred during the study. The adverse events noted in this study are summarized in Table 1.

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

Table 1: Adverse Events Summarized by the Test (T) and Reference (R) Products

Symptom	Incidence after T	Incidence after R	Total Incidence
Abdominal pain	2	1	3
Headache	0	1	1
Common Cold	1	0	1
Total	3	2	5

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

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

Appears This Way
On Original

ORIGINAL

Synthon
Pharmaceuticals, Inc.

March 14, 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 006
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
Revision of Dissolution Method

Dear Dr. Parks:

Reference is made to FDA's Acceptance to File Letter for the New Drug Application (NDA) #21-961 for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg, dated October 4, 2006. Synthon Pharmaceuticals, Inc. (Synthon) acknowledges that the Orally Disintegration Tablet (ODT) is a substantially different formulation compared to that of the innovator product, Merck's Zocor® (simvastatin) tablets, and that the dissolution method submitted with the original application (and updated in Amendment 004 to the NDA submitted on February 9, 2006), is not sufficiently discriminative for the ODT formulation. As requested by the FDA, Synthon has therefore developed and validated a new dissolution method that is more discriminative for the ODT; specifically, the new method utilizes a lower ——— concentration. The new analytical method will be used to perform the dissolution test for future drug product release and stability testing. b(4)

Synthon hereby amends the aforementioned NDA to provide the new dissolution analytical method and the corresponding analytical method validation report. As part of the analytical method validation, the dissolution test was performed for ——— NDA registration batch of each strength of Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg and 80 mg. The individual dissolution profiles are presented in a separate exhibit to this amendment and demonstrate that the dissolution method is more discriminating. Updates to the materials specifications and the master certificates of analysis for the drug product are also provided, as these documents reference the currently approved analytical methods.

Form FDA 356h is provided in Exhibit 1 to this amendment. The information presented in this amendment is provided in the subsequent exhibits as delineated in the attached "List of Exhibits."

As per 21 CFR 314.60(c), Synthon hereby submits two copies of this **Amendment 006** and certifies that a **true and exact copy** of this amendment has been forwarded as a Field Copy to the FDA District Office at the address below:

Mary H. Woleske, District Director
Atlanta District Office
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA, 30309

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

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

Appears This Way
On Original

Simoneau, Margaret A

Subject:	NDA 21-961 Simvastatin ODT INTERNAL T-CON regarding the DSI Consult for Biopharm Inspections
Location:	CDER WO 3376 conf rm Bldg22
Start:	Thu 3/9/2006 11:30 AM
End:	Thu 3/9/2006 12:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Colman, Eric C; Viswanathan, CT
Optional Attendees:	Chung, Sang
Resources:	CDER WO 3376 conf rm Bldg22

1. 505b2
2. Sang → Alan → Vinod (f/up)

Generic same site
Clinical No good record for dosing

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On Original

#120 1 mo ago
Minrin
mini Rin

Simoneau, Margaret A

om: Viswanathan, CT
Sent: Wednesday, March 08, 2006 3:23 PM
To: Simoneau, Margaret A
Cc: Himaya, Amalia; O Shaughnessy, Jacqueline A
Subject: NDA 21-961

Margaret:
I tried calling you twice today with regard to the subject NDA (Simvastain ODT) and the need for the inspection. Please get back to me asap so we can decide whether an inspection necessary and the available time if so..
Thanks

CT. Viswanathan, Ph.D
Associate Director
Division of Scientific Investigations, HFD-48
Office of Medical Policy, CDER, FDA
Tel: (301) 594 0163
Fax:(301) 480 1728

Issued a 483 + recom Generic disapproval.

Appears This Way
On Original

#120 1 mo age
Minrin
mini Rin

Simoneau, Margaret A

From: Viswanathan, CT
Sent: Wednesday, March 08, 2006 3:23 PM
To: Simoneau, Margaret A
Cc: Himaya, Amalia; O Shaughnessy, Jacqueline A
Subject: NDA 21-961

Margaret:
I tried calling you twice today with regard to the subject NDA (Simvastain ODT) and the need for the inspection. Please get back to me asap so we can decide whether an inspection necessary and the available time if so..
Thanks

CT. Viswanathan, Ph.D
Associate Director
Division of Scientific Investigations, HFD-48
Office of Medical Policy, CDER, FDA
Tel: (301) 594 0163
Fax:(301) 480 1728

Issued a 483 + recom Simva disapproved.

Appears This Way
On Original

1. Left Voice mail on 5/1/06 for update

Simoneau, Margaret A

From: Viswanathan, CT
Sent: Monday, May 01, 2006 3:54 PM
To: Simoneau, Margaret A
Subject: Out of Office AutoReply: NDA 21-961 Simva ODT Biopharm Inspection

Out of the office until May 4, 06. For immediate assistance please contact Dr.Martin Yau (301) 827 5458

Simoneau, Margaret A

om: Adams, Shawnte L
Sent: Wednesday, March 08, 2006 3:03 PM
To: Hill, John
Subject: RE: NDA 21961

John,

Thank you for the information. The manufacturing is at [redacted] located at [redacted] not [redacted]. The [redacted] is listed in EES. Please cancel the request for the existing [redacted] located at [redacted] and submit the [redacted] site. That site was recently inspected therefore an inspection will not be necessary. b(4)

Thank you,

Shawnte L. Adams
Program Analyst
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-8909 (Fax)

From: Hill, John
Sent: Wednesday, March 08, 2006 2:31 PM
To: Adams, Shawnte L
Subject: RE: NDA 21961

Shawnte:

Attached is the information that was supplied in the NDA. I am also attaching a copy of my DMF review of the [redacted] that is manufactured at the [redacted] facility. Let me know if you need any other information

<< File: 006_1.3.pdf >> << File: DMF [redacted] FINAL.doc >> b(4)

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

From: Adams, Shawnte L
Sent: Wednesday, March 08, 2006 12:54 PM
To: Hill, John
Subject: NDA 21961

John,

I was just informed that the [redacted] facility listed in this application appears to be an administrative address. Can you check with the sponsor to confirm the address of the manufacturing site. b(4)

Thank you

Shawnte L. Adams
Program Analyst
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-8909 (Fax)

Synthon
Pharmaceuticals, Inc.

March 6, 2006

VIA FEDERAL EXPRESS

N-000-C

Margaret Simoneau, R.Ph.
Project Manager
Division of Metabolic and Endocrine Drug Products
US Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NEW CORRESP

RE: Request for Additional Copies of Amendment 005 to NDA #21-961
Simvastatin Orally Disintegrating Tablets
Use of Established Name in lieu of Trade Name on Product Labeling

Dear Ms. Simoneau

As requested, please find enclosed two (2) copies of Amendment 005 to New Drug Application (NDA) #21-961, which was submitted by Synthon Pharmaceuticals, Inc. (Synthon) on February 23, 2006 to Mary Parks, M.D., Division Director for the Division of Metabolic and Endocrine Drug Products. Electronic copies of the new proposed labeling for Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg and 80 mg are also enclosed.

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

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

ORIGINAL

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-961

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

Dear Mr. Hinckle:

Please refer to your submission dated September 16, 2005, requesting a waiver for pediatric studies for Simvastatin Orally Disintegrating Tablets.

We have reviewed the submission and agree that a waiver is justified for Simvastatin Orally Disintegrating Tablets for all indications for the entire pediatric population.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

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

Sincerely,

{See appended electronic signature page}

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

Appears This Way
On Original

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

/s/

Kati Johnson
2/23/2006 08:45:38 AM
signing for Mary Parks, MD

Synthon
Pharmaceuticals, Inc.

ORIGINAL

RECEIVED

FEB 28 2006

CDER White Oak DR1

RECEIVED
FEB 24 2006
CDER/CDR

February 23, 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

N-000-BL

RE: NDA # 21-961 / Amendment 005
Simvastatin Orally Disintegrating Tablets
Use of Established Name in lieu of Trade Name on Product Labeling

ORIG AMENDMENT

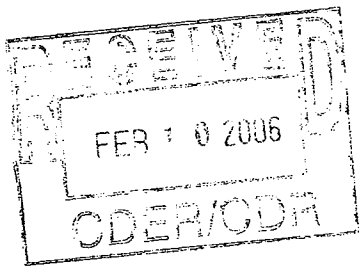
Dear Dr. Parks:

Synthon Pharmaceuticals, Inc. ("Synthon") hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets (ODTs). This amendment provides revised proposed container labels and package insert in which the proposed product trade name has been replaced by the established name and dosage form (i.e. "Simvastatin Orally Disintegrating Tablets"). A completed Form FDA-356h is provided in Exhibit 1 to this response. The proposed container labels for each packaging configuration and the proposed package insert for Synthon's Simvastatin Orally Disintegrating Tablets are provided in Exhibits 2 - 6 to this amendment. The annotated side-by-side labeling comparison of the proposed package insert for Synthon's product to the approved package insert of the innovator product, Merck's Zocor Tablets, is provided in Exhibit 7 to this amendment. For ease of review, a List of Exhibits is attached and delineates the information presented in each exhibit. The labeling information submitted in this amendment is being provided in both paper and electronic format.

Reference is also made to FDA's Acceptance to File Fax for the aforementioned NDA, dated October 6, 2005. Synthon acknowledges that the proposed "patient package insert" that was submitted with the original application is considered a "consumer brief summary", and should be submitted to the Division of Drug Marketing, Advertising, and Communication (DDMAC) for review after final approval of the NDA. Should Synthon choose to distribute a patient package insert, the appropriate information will be submitted to DDMAC for review after the package insert is approved and in compliance with the applicable regulations. Please note that the proposed patient package insert will not be included with the actual drug product.

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

ORIGINAL



RECEIVED

FEB 1 0 2006

CDER White Oak DR1

February 9, 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

ORIG AMENDMENT
N-000-(BC)

RE: NDA # 21-961 / Amendment 004
Simvastatin Orally Disintegrating Tablets
Updates to Analytical Methods, Materials Specifications and Master Certificates of Analysis

Dear Dr. Parks:

Synthon Pharmaceuticals, Inc. ("Synthon") hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets for the purpose of providing updates to the analytical methods that are described in Volume 1, Module 3, Section 2.S.4.2.1 and in Volume 9, Module 3, Section 2.S.5.2.1 of the original application. Updates to the materials specifications and the master certificates of analysis for the drug substance and drug product are also provided, as these documents reference the currently approved analytical methods. Please note that the changes to the analytical methods are primarily administrative and/or for the purpose of harmonization for international use. No additional validation or re-validation was deemed necessary for the updated analytical methods therefore the analytical method validation described in the original application is still applicable.

The specific changes to the analytical methods are described in the enclosed Purpose of Amendment section. The completed Form FDA-356h, the updated analytical methods, a summary comparison of the original to the new analytical methods, updates to the materials specifications for the drug substance and drug product, and updates to the master certificates of analysis for the drug substance and drug product are provided in the attached exhibits. For ease of review, a List of Exhibits is included, and summarizes the information presented with this amendment.

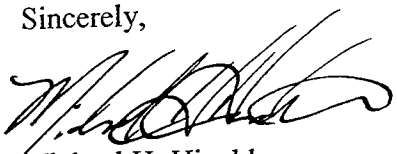
9000 Development Drive • P.O. Box 110487 • Research Triangle Park, North Carolina 27709
Phone +1 (919) 493-6006 • Fax +1 (919) 493-6104

As per 21 CFR 314.60(c), Synthon hereby submits two copies of this **Amendment 004** and certifies that a **true and exact copy** of this amendment has been forwarded as a Field Copy to the FDA District Office at the address below:

Mary H. Woleske, District Director
Atlanta District Office
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA, 30309

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

Sincerely,



Michael H. Hinckle
VP and General Counsel

Enclosures

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N-000 BC

ORIG AMENDMENT

ORIGINAL

RECEIVED
FEB 06 2006
CDR/CDER

Synthon
Pharmaceuticals, Inc.

February 3, 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

RECEIVED
FEB - 7 2006
CDER White Oak DR 1

RE: NDA # 21-961 / Amendment 003
Simvastatin Orally Disintegrating Tablets
Response to CMC Deficiencies

Dear Dr. Parks,

Synthon Pharmaceuticals, Inc. ("Synthon") hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets (ODTs). A completed Form FDA-356h is provided in Exhibit 1 to this response. This amendment provides a complete response to the Food and Drug Administration's ("FDA") January 19, 2006 CMC deficiency fax, which is included in Exhibit 2 to this response. For ease of review, the FDA's observation/comment is followed by Synthon's corresponding response.

FDA Observation/Comment:

1. *Provide a description of the drug substance [redacted] process, a summary of the manufacturing development of the drug substance [redacted] process, in-process controls for the [redacted] operation, and justifications for the final [redacted] drug substance particle size.* b(4)

Synthon's Response:

The DMF Holder Synthon BV has been notified of this deficiency and will provide the requested process and manufacturing information.

The specification for the final [redacted] drug substance particle size is based on manufacturing data obtained during research and development. A [redacted] portion of Simvastatin was [redacted] for R&D purposes; the particle size of the R&D batch is b(4)

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

provided in Table 1. Based on these results, Synthon established a specification for particle size analysis of [redacted] b(4)

Table 1: Particle Size of an R&D Batch of Simvastatin Drug Substance

Particle Size	Result
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

FDA Observation/Comment: b(4)

2. *Provide a table comparing the pre and post [redacted] mean drug substance particle size and size distribution for exhibit lots 71415, 71423 and 71431.*

Synthon's Response:

Please refer to Table 2 for the post [redacted] particle size and size distribution for drug substance lots 71415, 71423 and 71431. The DMF Holder Synthon BV has been notified, and will provide the requested information including the pre [redacted] drug substance particle size and size distribution.

Table 2: Post [redacted] Particle Size Distribution for Drug Substance Lots 71415, 71423 and 71431 b(4)

Size Distribution	Drug Substance Batch #		
	71415	71423	71431
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

FDA Observation/Comment:

3. *In-process specifications of "Record Results for information only" are not acceptable for the [redacted] and final blend for the commercial batches. Specify acceptance criteria for these tests or justify why these in-process control tests are not required, based on formulation and manufacturing developmental data.* b(4)

Synthon's Response:

Synthon acknowledges an error in the original application. Volume 2, Module 3, Section 2.P.3.3, Table 5 (page 15/35) of the original submission was inadvertently a copy of a table on the preceding page that listed the tests and specifications for in-process testing performed for the NDA registration batches. The correct information is provided in Table 3. Additional parameters will also be monitored for the [redacted] and final blends during the manufacture of the first [redacted] commercial batches (validation batches); these additional tests are listed in Table 4. Synthon proposes to exclude the parameters described in Table 4 from routine in-process testing of commercial lots. The justifications for Synthon's proposed in-process testing and specifications for the [redacted] is provided below. b(4)

Table 3: In-Process Controls During the [redacted] and Blending for Commercial Batches of Simvastatin orally disintegrating tablets

In-Process Controls	Specifications, Target/Range	Sample Frequency/ Location
[redacted] Prior to [redacted]		
Water Content (IR) [%]	Less than [redacted] w/w	[redacted] b(4)
Final Blend		
Water Content (IR) [%]	[redacted]	After [redacted]
Bulk density [g/mL]	[redacted]	
Tapped density [g/mL]	[redacted]	
Flowability [cot]	[redacted]	

Table 4: Additional Parameters that will be Monitored During the Manufacturing of the [redacted] Commercial Lots (Validation Batches)

In-Process Controls	Sample Frequency/ Location
[redacted]	
Water Content (IR) [%]	After [redacted]
Water Content (KF) [%]	
Bulk density [g/mL]	
Tapped density [g/mL]	
Flowability [cot]	
[redacted] Analysis	
Final [redacted] Blend	
Blend Uniformity in Mixing Tote (Blends for 10 mg and 80 mg Tablets)	Samples taken at the end of [redacted] Specification: % RSD [redacted], and all individual values are within [redacted] of mean.
[redacted] Analysis	After Final [redacted] Blending

b(4)

Proposed Exclusion of Routine In-Process Testing of [redacted]

Information on water content, bulk density, tapped density, and flowability was recorded for the [redacted] during the manufacture of the qualification and NDA registration batches. A summary of the results for water content, bulk density, tapped density and flowability of the various [redacted] batches are provided in Table 5. A comparison of the water content of the [redacted] pre- and post-[redacted] is provided in Table 6.

b(4)

Table 5: Summary of In-Process Control Test Results for the [redacted] for NDA Registration Batches of Simvastatin ODTs

Tests	Specification	[redacted] Batch Numbers			
		Q-Batch 30944G01*	NDA Batch 3117750V1	NDA Batch 3117752V2	NDA Batch 3117752V3
Bulk density [g/mL]	Record Result	[redacted]	[redacted]	[redacted]	[redacted]
Tapped density [g/mL]	Record Result	[redacted]	[redacted]	[redacted]	[redacted]
Flowability [cot]	Record Result	[redacted]	[redacted]	[redacted]	[redacted]
Water content IR [%]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Water content KF [%]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b(4)

Table 6: Comparison of Pre- and Post- Water Content Results for used for Production of the NDA Registration Batches

b(4)

Water Content by LOD (IR) [%]	Specification	Batch Numbers			
		Q-Batch 30944G01 *	NDA Batch 3117750V1	NDA Batch 3117752V2	NDA Batch 3117752V3
Pre [%]	≤				
Post [%]	≤				

* These results are based on the manufacturing of Q-Batch #30944G01, " , 1" (with the (the same parameters used for the manufacture of the NDA registration batches). For additional information and manufacturing process development, please refer to Volume 2, Module 3, Section 2.P.2.3 of the original submission.

The data in Table 5 indicate that the results of this in-process control testing were consistent from batch to batch. Additionally, the information in Table 6 indicates that the step does not significantly affect the water content. Therefore, an additional determination of water content after is unnecessary; the determination of water content prior to is sufficient. Based on these results, b(4)
Synthon proposes to exclude in-process testing of bulk density, tapped density, flowability and water content of the Please note that Synthon will continue to monitor these parameters during manufacturing process validation on the commercial batches as specified in Table 4.

Proposed In-Process Test Specifications for the Final Blend
The proposed specifications for the in-process control testing of water content, bulk density, tapped density and flowability are provided in Table 3. These specifications b(4)
are also listed in the proposed commercial manufacturing batch records that were provided with the original application. These specifications are supported by in-process data collected for the final blends manufactured for the qualification batches and NDA registration batches; these data are provided in Table 7 along with the proposed commercial specifications.

Table 7: Results of In-Process Testing of NDA Registration Batch Final Blends and Proposed Commercial Specifications

Tests	10 mg			20 mg			40 mg			80 mg		
	V1	V2	V3	V1	V2	V3	V1	V2	V3	V1	V2	V3
Water Content (IR) [%]	[redacted]											
	Proposed Specification: [redacted]											
Bulk density [g/mL]	[redacted]											
	Proposed Specification: [redacted]											
Tapped density [g/mL]	[redacted]											
	Proposed Specification: [redacted]											
Flowability [cot]	[redacted]											
	Proposed Specification: [redacted]											

b(4)

nd = not determined

Proposed Exclusion of Blend Uniformity Testing of Final [redacted] Blend

A summary of the blend uniformity of the final blends for the qualification batches and the NDA registration batches of Simvastatin 10 mg and 80 mg ODTs is provided in Table 8. The information presented in this table indicates that the blend uniformity was acceptable for all lots. Because blend uniformity and corresponding content uniformity of tablets was acceptable for several batches produced using the manufacturing process, Synthon proposes that routine testing of blend uniformity during production of commercial lots is unnecessary. Synthon will continue to monitor blend uniformity for the production of the [redacted] commercial lots (validation batches). Synthon also performs routine content uniformity analysis as part of finished tablet lot release testing, and will perform additional content uniformity sampling during the production of the validation batches. Acceptable content uniformity is an indicator of acceptable blend uniformity. The results of content uniformity of tablets sampled at the beginning, middle, and end of the [redacted] process for the qualification batches and NDA registration batches are provided in Table 9; all content uniformity results were acceptable and consistent.

b(4)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Proposed Exclusion of [redacted] Analysis of [redacted] and Final Blend
Synthon proposes to exclude particle size testing of the [redacted] and final blends of the commercial lots based on the following: b(4)

1. An assessment of the manufacturing data for [redacted] and final blends obtained during production of the qualification batch and NDA registration batches indicates that the manufacturing process produces [redacted] and final blends with acceptable and consistent particle size and size distributions b(4)

2. Synthon determined that the addition of excipients to the [redacted] does not significantly affect the particle size of the final blend

Synthon will monitor the particle size and size distribution of the [redacted] and final blends during the manufacturing of the [redacted] commercial (validation) batches.

b(4)

Assessment of Manufacturing Data for [redacted] and Final Blends
The particle size and size distribution information for the qualification batch and NDA registration batches of [redacted] and final blends is provided in Tables 10 and 11 respectively; the particle size distributions represented graphically are provided in Figures 1 and 2 respectively.

Table 10: Particle Size of [redacted] of the Qualification Batch and [redacted] NDA Registration Batches

[redacted] Analysis [% retained or [redacted]				
Particle Size	Q-Batch 30944G01	NDA Batch 3117750V1	NDA Batch 3117752V2	NDA Batch 3117752V3
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Particle Size Distributions				
[redacted] [µm]				
[redacted] [µm]				
[redacted] [µm]				
% < [redacted]				
% > [redacted]				

b(4)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

The information summarized in Tables 10 and 11, as well as in Figures 1 and 2 indicates that the manufacturing process produces [redacted], and final blends with consistent particle size and size distribution from batch to batch. b(4)

Evidence that Excipients do not Significantly Affect the Final Blend Particle Size
Synthon determined that the addition of excipients to the [redacted] does not significantly affect the particle size of the final blend. The major excipient added to the [redacted] in the preparation of the final blend is [redacted]. Because this excipient is no[redacted], the particle size distribution of [redacted] could significantly impact the size distribution of the final blend. The particle size distribution of a typical lot of [redacted] received from [redacted], and used in the NDA batches is provided in Table 12, and a comparison of the particle size distributions of the [redacted] and corresponding [redacted] olends is provided in Table 13. b(4)

Table 12: [redacted] Particle Size Distribution and Typical Results [redacted] batch number D9S4005 [redacted] number 139850)

Particle Size Distribution [redacted]	Specification [redacted]	[redacted] batch D9S4005
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
% > [redacted]	[redacted]	[redacted]
% > [redacted]	Not more thar [redacted]	[redacted]

b(4)

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Table 13: Particle Size Distributions of the [redacted] and Corresponding Final Blends of the NDA Registration Batches

b(4)

[redacted] Batches	3117750V1				3117751V2				3117752V3			
%> [redacted]												
%> [redacted]												
Final Blend Strength & Batches	10 V1	20 V1	40 V1	80 V1	10 V2	20 V2	40 V2	80 V2	10 V3	20 V3	40 V3	80 V3
%< [redacted]	[redacted]											
%< [redacted]												
Average Blends	V1 Blends				V2 Blends				V3 Blends			
%> [redacted]												
%< [redacted]												

Batch Numbers: (10 mg Tablets): V1 = 3117701V1 V2 = 3117702V2 V3 = 3117703V3
(20 mg Tablets): V1 = 3117901V1 V2 = 3117902V2 V3 = 3117903V3
(40 mg Tablets): V1 = 3118201V1 V2 = 3118202V2 V3 = 3118203V3
(80 mg Tablets): V1 = 3118401V1 V2 = 3118402V2 V3 = 3118403V3

The information provided in Tables 12 suggests that the percentage of particles greater than [redacted] in [redacted] is very close to that of the [redacted] Therefore, the addition of [redacted] to the [redacted] should not significantly influence the particle size of the [redacted] blend. This is supported by the information provided in Table 13, which reveals that the percentage of particles greater than [redacted] is unchanged between the [redacted] and the final blend. b(4)

FDA Observation/Comment:

4. *Justify the exclusion of [redacted] in-process testing of commercial lots, based on the formulation and manufacturing development data reported in this NDA.*

Synthon's Response:

Information on water content, bulk density, tapped density, flowability and [redacted] analysis will be recorded for the [redacted] as part of manufacturing process validation. Synthon proposes to exclude testing for these parameters from routine in-process testing of commercial lots based on manufacturing data from the qualification batches and the NDA registration batches. For additional information, please refer to the sub-headings *"Proposed Exclusion of Routine In-Process Testing of [redacted]"* and *"Proposed Exclusion of [redacted] Analysis of [redacted] and Final Blend"* under Synthon's response to FDA Observation/Comment #3 above. b(4)

FDA Observation/Comment:

5. *Justify the exclusion of blend uniformity, moisture by Karl Fischer analysis, particle size and tablet diameter from the in-process testing of commercial lots, based on the formulation and manufacturing development data reported in this NDA.*

Synthon's Response:

Exclusion of Blend Uniformity

Information on blend uniformity will be recorded as part of manufacturing process validation. Synthon proposes to exclude testing for blend uniformity from routine in-process testing of commercial lots based on manufacturing data from the qualification batches and the NDA registration batches. For additional information, please refer to the sub-heading *"Proposed Exclusion of Blend Uniformity Testing of Final [redacted] Blend"* under Synthon's response to FDA Observation/Comment #3 above. b(4)

Exclusion of Moisture by Karl Fisher Analysis

Information on moisture content by Karl Fisher analysis was collected as part of in-process controls testing for the manufacture of the NDA registration batches. Please refer to Table 14, which presents the water content in the [redacted] and final blends obtained by LOD (IR) and by Karl Fisher Analysis for the NDA registration batches of Simvastatin Orally Disintegrating Tablets. The information indicates that the IR method and Karl Fisher Analysis method yielded similar results. Therefore, Synthon proposes to exclude the Karl Fisher analysis from the in-process testing of commercial lots. b(4)

Table 14: Comparison of [redacted] Water Content Results Determined by LOD (IR) and Karl Fisher Analysis

Water Content Test Method	Specification	[redacted] Batch Numbers		
		3117750V1	3117752V2	3117752V3
LOD (IR) [%]	≤ [redacted]	[redacted]	[redacted]	[redacted]
KF [%]	< [redacted]	[redacted]	[redacted]	[redacted]

b(4)

Exclusion of Particle Size

Information on particle size will be recorded as part of manufacturing process validation. Synthon proposes to exclude testing for particle size from routine in-process testing of commercial lots based on manufacturing data from the qualification batches and the NDA registration batches. For additional information, please refer to the sub-heading *"Proposed Exclusion of [redacted] Analysis of [redacted] and Final Blend"* under the response to FDA Observation/Comment #3 above. b(4)

Exclusion of Tablet Diameter

Information on tablet diameter was collected as part of in-process controls testing for the manufacture of the NDA registration batches; the results are provided in the executed manufacturing batch records which are provided in Volumes 13 – 22, Module 3, Section 2.R, Exhibits 1 – 51 of the original application. A summary of the results for the NDA registration batches is provided in Table 15.

Table 15: Summary of In-Process Testing of Tablet Diameter During the Manufacture of the NDA Registration Batches of Simvastatin ODTs

Strength and Batch	Target [mm]	Specification [mm]	Min. Value [mm]	Max. Value [mm]	Avg. Value [mm]
10 mg, Batch 3117701V1	[redacted]				
10 mg, Batch 3117702V2					
10 mg, Batch 3117703V3					
20 mg, Batch 3117901V1					
20 mg, Batch 3117902V2					
20 mg, Batch 3117903V3					
40 mg, Batch 3118201V1					
40 mg, Batch 3118202V2					
40 mg, Batch 3118203V3					
80 mg, Batch 3118401V1					
80 mg, Batch 3118402V2					
80 mg, Batch 3118402V2					

b(4)

The information provided in Table 15 indicates that tablet diameter was very consistent for the manufacture of the NDA registration batches, and all batches were well within the specification for tablet diameter. Additionally, [redacted] is verified as part of the manufacturing process for all batches to ensure that the correct [redacted] in place to produce tablets of the appropriate diameter. Therefore, Synthon proposes to exclude tablet diameter from routine in-process control testing of commercial lots. b(4)

FDA Observation/Comment:

6. *Include testing for disintegration time, friability, and hardness as part of the lot release testing for the ——— commercial batches as part of the manufacturing process validation.* b(4)

Synthon's Response:

Acknowledged. Synthon will perform the requested testing as part of manufacturing process validation.

FDA Observation/Comment:

7. *Include microbial testing, for the monitoring of adventitious agents, as part of routine drug product log release testing.*

Synthon's Response:

Acknowledged. Synthon will perform the requested testing as part of routine drug product lot release testing.

As per 21 CFR 314.60(c), Synthon hereby submits two copies of this **Amendment 003** and certifies that a **true and exact copy** of this amendment has been forwarded as a Field Copy to the FDA District Office at the address below:

Mary H. Woleske, District Director
Atlanta District Office
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA, 30309

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

Sincerely,

Michael H. Hinckle
VP and General Counsel

Enclosures

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: 1/19/06

To: Kamali Chance, PhD	**From:** Margaret Simoneau
Company: Synthon	Division of Metabolism and Endocrinology Products
Fax number: 919-493-6104	**Fax number:**
Phone number: 919-536-1310	**Phone number:** (301) 796-1295

Subject: NDA 21-961

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☒ YES ☒ NO

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-961

DISCIPLINE REVIEW LETTER

Synthon Pharmaceuticals, Inc.
Attention: Kamali Chance, MPH, Ph.D., RAC
Director of Regulatory Affairs
9000 Development Drive
P.O. Box 110487
Research Triangle Park, NC 27709

Dear Dr. Chance:

Please refer to your July 28, 2005, 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.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1.

2.

3.

b(4)

4.

5.

6.

7.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should

not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Blair Fraser
1/18/2006 12:28:20 PM

Simoneau, Margaret A

From: Hill, John
nt: Monday, November 28, 2005 9:30 AM
: Simoneau, Margaret A
Subject: FW: "Report sent from Report Builder"

Report.txt (14 KB)

eggy:

FYI. Attached is the EES status update for this NODE. If all goes well I should have most of the review done before Christmas.

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

-----Original Message-----
From: Hill, John
Sent: Monday, November 28, 2005 9:28 AM
To: Hill, John
bject: "Report sent from Report Builder"

8 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: October 25, 2005

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: (Required for international inspections)
Director, Review Division, HFD-510 or

Director, Division of Pharmaceutical Evaluation, HFD-510

FROM: Margaret Simoneau, Regulatory Project Manager, HFD-510

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-961
(Simvastatin Orally Disintegrating Tablets)

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
Synthon Study No.: CSP.US01.SVT.ODT80.001 Study No.: 099/226/05	[redacted]	[redacted]

b(4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

__X__ There is a lack of domestic data that solely supports approval;

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **April 3, 2006**. We intend to issue an action letter on this application by **May 22, 2006**.

Should you require any additional information, please contact Margaret Simoneau at 301-796-1295.

Concurrence:

Mary Parks, MD Medical Team Leader
William Lubas, MD Medical Reviewer
Hae-Young Ahn, Biopharm Team Leader
Sang Chung, Biopharm Reviewer

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

/s/

Mary Parks
10/26/2005 05:55:04 AM

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#1
10/24/05

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-961 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name:
Established Name: Simvastatin Orally Disintegrating Tablets
Strengths: 10, 20, 40 and 80 mg

Applicant: Synthon Pharmaceuticals, Inc
Agent for Applicant: Kamali Chance

Date of Application: July 28, 2005
Date of Receipt: July 29, 2005
Date clock started after UN: N/A
Date of Filing Meeting: September 19, 2005
Filing Date: September 27, 2005
Action Goal Date (optional): User Fee Goal Date: May 29, 2006

Indication(s) requested: Reductions in Risk of CHD Mortality and CV Events; Pts with Hypercholesterolemia Req. modifications of Lipid Profiles; Adolescent Pts with HeFH

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☒ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification (1,2,3 etc.):
Other (orphan, OTC, etc.):

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: Zocor/ April 18, 2006 (ped)

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒

  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Is the submission complete as required under 21 CFR 314.50? YES ☒ NO ☐

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.

  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Was the patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Was exclusivity requested? YES, _____ Years NO ☒

NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO ☒

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☒

- Were financial disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- Are the PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Are the trade, established, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
  Is the established name correct in COMIS IND(s) file(s): YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- List referenced IND numbers: PIND 70,964

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) Advice lt and t-con with User Fee NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☐ NO ☒

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☒
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☒
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☒
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/19/05

NDA #: 21-961

DRUG NAMES: Simvastatin ODT

APPLICANT: Synthon Pharmaceuticals, Inc.

BACKGROUND: Synthon's Simvastatin ODT is a new dosage form of the lipid-lowering drug product Zocor tablets, NDA 19-766, by Merck & Co., Inc.

(Provide a brief background of the drug, e.g., the molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: M. Parks, W. Lubas, H. Ahn, S. Chung, J. Hill and M. Simoneau

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline	**Reviewer**
Medical:	W. Lubas
Secondary Medical:	M. Parks
Statistical:	nn
Pharmacology:	Davis-Bruno
Statistical Pharmacology:	nn
Chemistry:	J. Hill
Environmental Assessment (if needed):	nn
Biopharmaceutical:	S. Chung
Microbiology, sterility:	nn
Microbiology, clinical (for antimicrobial products only):	nn
DSI:	nn
Regulatory Project Management:	M. Simoneau
Other Consults:	Biopharm Consult

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	☒	FILE	☐	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐
• Biopharm. inspection needed?					YES ☒	NO ☐
PHARMACOLOGY	N/A	☐	FILE	☒	REFUSE TO FILE	☐
• GLP inspection needed?					YES ☐	NO ☒
CHEMISTRY			FILE	☒	REFUSE TO FILE	☐
• Establishment(s) ready for inspection?					YES ☐	NO ☒
• Microbiology					YES ☐	NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional): Request sponsor to develop a new dissolution method for the ODT.

ACTION ITEMS:

1.☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g, orphan, OTC) are correctly entered into COMIS.

2.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4.☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☐ Convey document filing issues/no filing issues to applicant by Day 74.

Sent 10/4/05

Margaret Simoneau
Regulatory Project Manager, HFD-510

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Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Phone call on 4/18/06 R. Peat re edit #3 + #4

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Zocor, NDA 19-766

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☒ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). Merck is tablet formulation; Synthon is orally disintegrating tablets

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference? YES ☒ NO ☐
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES ☒ NO ☐
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A ☐ YES ☒ NO ☐
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
N/A ☐ YES ☒ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES ☐ NO ☒

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted? YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application? YES ☒ NO ☐

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

/s/

Margaret Simoneau
10/24/2005 11:31:19 AM
CSO

Synthon
Pharmaceuticals, Inc.

October 13, 2005

N-000(BC)

VIA FEDERAL EXPRESS

David G. Orloff, 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

ORIG AMENDMENT

RE: NEW DRUG APPLICATION
NDA # 21-961 / Amendment 002
Simvastatin Orally Disintegrating Tablets
Dissolution Data

Dear Dr. Orloff:

Synthon Pharmaceuticals, Inc. ("Synthon") hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets for the purpose of correcting inadvertent transcription errors that have been discovered on the dissolution data provided in Volume 1, Module 1, Section 3.9, pages 16 – 18 on the innovator drug product, Zocor® tablets (Biowaiver section). Please note that correct dissolution data on Zocor tablets and Simvastatin orally disintegrating tablets was provided in Module 5, Section 3.1.2.1.1 on Bioequivalence Summary Tables, more specifically Table 4, "Summary of In-Vitro Dissolution Studies."

Synthon is submitting replacement pages with corrected in-vitro dissolution tables and graphs for Volume 1, Module 1, Section 3.4, pages 16 – 18 as well a copy of Table 4 from Module 5, Section 3.1.2.1.1 (for reference). A completed Form FDA 356h is also being provided.

ORIGINAL

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

S. Chung

As per 21 CFR 314.60(c), Synthon hereby submits two copies of this **Amendment 002** and certifies that a complete copy of this amendment has been forwarded as a Field Copy to the FDA District Office at the address below:

Mary H. Woleske, District Director
Atlanta District Office
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA 30309

Should you have any questions or comments concerning this NDA, please do not hesitate to contact me at (919) 536-1310.

Sincerely,

Kamali Chance

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

Enclosures

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-961

Synthon Pharmaceuticals, Inc.
Attention: Kamali Chance, MPH, Ph.D., RAC
Director of Regulatory Affairs
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Ms. Chance:

Please refer to your July 28, 2005, 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, 40mg and 80 mg.

We also refer to your submissions dated August 12 and September 16, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 27, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

The Orally Disintegrating Tablet (ODT) is a substantially different formulation compared to Merck's marketed Zocor® (simvastatin) Tablets, your comparator. Dissolution study results were submitted using a dissolution method for simvastatin Tablets. This dissolution method is not considered discriminative enough for your ODT formulation. Therefore, you should develop a new dissolution method for the ODT. Paddle speed and [redacted] concentration should be the major factors to be considered in developing the new dissolution method. It is recommended that you use a lower paddle speed (e.g., 50RPM) with lower [redacted] concentration. b(4)

Additionally, we note that your proposed "patient package insert" is considered a consumer brief summary. You must submit a request for advisory comments to the Division of Drug Marketing, Advertising, and Communication (DDMAC) if you would like them to review the brief summary. Please note that DDMAC will only review the brief summary after approval of the package insert.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Margaret Simoneau, S.S. R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolism and Endocrinology
Drug Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Mary Parks
10/4/2005 08:58:16 AM
for Dr. Orloff

Simoneau, Margaret A

Subject:	NDA 21-961 Simvastatin Orally Disintegrating Tablet Filing Meeting
Location:	CDER 510 Calendar; CDER PKLN 14B39 Conf Room -AR
Start:	Mon 9/19/2005 2:00 PM
End:	Mon 9/19/2005 3:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Parks, Mary H; Lubas, William (CDER); Hill, John; ~~Moore, Stephen K;~~ Davis Bruno, Karen L; Ahn, Hae Young; Chung, Sang
Resources:	CDER 510 Calendar; CDER PKLN 14B39 Conf Room -AR

File date: 27 September 2005
User Fee: 29 May 2006

Total (6)

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Simoneau, Margaret A

From: Tran, Debi Nhu
Sent: Friday, September 16, 2005 8:25 AM
To: Simoneau, Margaret A
Subject: simvastatin ODT

Hi Margaret,

The proposed "patient package insert" submitted by Synthon Pharmaceuticals is a consumer brief summary. I attached a guidance if you would like more information about brief summaries. Please instruct the sponsor to submit a request for advisory comments to DDMAC if they would like us to review the brief summary.

guidance consumer brief summar...

Thanks!

Debi Tran, Pharm.D.
Regulatory Review Officer
Food and Drug Administration
Division of Drug Marketing Advertising & Communications
Tel: 301-827-2831
Fax: 301-594-6771

Appears This Way
On Original

Synthon
Pharmaceuticals, Inc.

FAX COVER

DATE: September 16, 2005 **NUMBER OF PAGES (including cover): 3**

TO: Margaret Simoneau
FDA – Division of Metabolic & Endocrine Drug Products

FROM: Michael H. Hinckle
Tel: (919) 493-6006
Fax: (919) 493-6104

RE: NDA#21-961 Amendment 001
PREA Statement

Ms. Simoneau:

Per your request of September 15th the following PREA Statement is being submitted to you via fax. A hard copy of this statement and Form 356h are being shipped FEDEX Priority Overnight to the Division Director, David Orloff.

Please contact me if you have any questions.

Appears This Way
On Original

If you have problems receiving this fax, please call (919) 493-6006
9000 Development Dr. • P.O. Box 110487 • RTP, NC • 27709

Synthon
Pharmaceuticals, Inc.

September 16, 2005

VIA FEDERAL EXPRESS

David G. Orloff, M.D.
Division Director (HFD-510)
Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA # 21-961 Amendment 001
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg, and 80 mg
PREA Statement

Dear Dr. Orloff:

Synthon Pharmaceuticals, Inc. ("Synthon") hereby amends the above referenced New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg orally disintegrating tablets for the purpose of requesting a "full waiver" of the pediatric assessment requirement of the Pediatric Research Equity Act ("PREA") pursuant to Section 505B(a)(4)(A) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. 314.55 (c)(2)(i). The basis for our request is provided below.

Zocor® (simvastatin) is approved for the treatment of heterozygous familial hypercholesterolemia in adolescents age 10-17 years. Synthon's Simvastatin orally disintegrating tablet contains the same active ingredient as Zocor (i.e., simvastatin) and therefore would not offer a meaningful therapeutic benefit over the currently marketed product. Consequently, no new safety or efficacy information would be obtained from additional simvastatin studies in the 10-17 year old patient population in light of what is already known about simvastatin in this population. Therefore, Synthon believes that a full waiver of pediatric assessment requirement in the 10-17 year old patient population is warranted in this instance.

With respect to treatment of children under 10 years of age, we note that the medical community recommends that drug therapy for cholesterol management in this younger patient population be undertaken in only very rare instances. Addressing this very issue, the American Academy of Pediatrics ("AAP") in accordance with the National

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

NDA # 21-961
Synthon Pharmaceutical, Inc.
Simvastatin Orally Disintegrating Tablets
PREA Statement
Page 2 of 2

Cholesterol Education Program issued a statement for the management of cholesterol in childhood. In relevant part, the AAP's statement recommends that,

> drug therapy should be considered only for children > 10 years of age after an adequate trial of diet therapy (for 6 to 12 months) and whose LDL-cholesterol level remains ≥ 190 mg/dL or whose LDL-cholesterol level remains ≥ 160 mg/dL and there is a family history of premature cardiovascular disease (≤55 years of age) or two or more other risk factors ... are present in the child or adolescent after vigorous attempts have been made to control these risk factors. The recommended drugs for the treatment of hypercholesterolemia and high LDL-cholesterol levels in children are the bile acid sequestrants cholestyramine and colestipol, which bind bile acids in the intestinal lumen. They have documented efficacy, relative freedom from adverse effects, and are apparently safe when administered to children. Other pharmacologic agents are not recommended for routine use in children and adolescents except in consultation with a lipid specialist.

Cholesterol in Childhood. Pediatrics. 1998; 101:141-147 (available at http://www.pediatrics.org/cgi/content/full/101/1/141).

Consequently, there is a very limited population of less than 10 year old patients who would qualify for statin drug therapy under the AAP recommendations. This fact, combined with the lack of a meaningful therapeutic benefit conferred by Synthon's proposed drug product, warrants a full waiver of the PREA requirement for the under 10 years population. See FDCA 505B(a)(4)(A)(iii).

Based on the forgoing, Synthon hereby requests a full waiver of the PREA requirements pertaining to all indications and all age groups for NDA No. 21-961.

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

Sincerely,

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

cc: Margaret Simoneau, FDA (via fax)

Synthon
Pharmaceuticals, Inc.

RECEIVED
AUG 15 2005
FDR/CDER

August 12, 2005

VIA FEDERAL EXPRESS

Margaret Simoneau, R.Ph.
Project Manager
Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: New Drug Application
Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg
Orally Disintegrating Tablets
NDA# 21-961

Dear Ms. Simoneau:

Pursuant to your request, Synthon Pharmaceutical, Inc. hereby submits a true copy of Module 1 of the New Drug Application for Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg Orally Disintegrating Tablets.

Should you have any questions concerning the information provided in this NDA, please do not hesitate to contact me directly at (919) 536-1310.

Sincerely,

Kamali Chance

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

Enclosures

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-961

Synthon Pharmaceuticals, Inc.
Attention: Kamali Chance, MPH, Ph.D., RAC
Director of Regulatory Affairs
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Dr. Chance:

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

Name of Drug Product: Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40mg and 80 mg

Review Priority Classification: Standard

Date of Application: July 28, 2005

Date of Receipt: July 29, 2005

Our Reference Number: NDA 21-961

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 27, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 29, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until January 31, 2006. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with

the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room #8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Margaret Simoneau
8/11/05 02:30:17 PM

Appears This Way
On Original

Simoneau, Margaret A

From: Colangelo, Kim M
Sent: Monday, August 08, 2005 4:26 PM
To: Simoneau, Margaret A
Cc: Chen, Andrea; Peat, Raquel
Subject: RE: Notification of a new 505b2 NDA

Good afternoon Margaret,

Thank you very much for the email. We do try to pull this information from the filing review, but the email notification is helpful to us, so please continue sending them.

Kind regards,
Kim

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs
CDER/FDA

NEW INFORMATION BEGINNING AUGUST 8, 2005
Phone:
301-796-0700 (OND IO main)
301-796-0140 (direct)
Fax:
301-796-9856
Internal Mail:
White Oak, Bldg #22, Room 6300
External Mail Address:
FDA
10903 New Hampshire Ave.
Bldg #22, Room 6300
Silver Spring, MD 20993

-----Original Message-----
From: Simoneau, Margaret A
Sent: Monday, August 08, 2005 3:29 PM
To: Colangelo, Kim M
Subject: Notification of a new 505b2 NDA

Hi Kim,

A new 505b2 NDA 21-961 for Simvastatin Orally Disintegrating Tablets 10, 20, 40 and 80 mg has been submitted in CTD to this Division on July 29, 2005. Synthon Pharmaceuticals, Inc, is the sponsor.

If you get this information from the filing review template now and this email notification is unnecessary, please let me know.

Thanks.

Margaret Simoneau
FDA/CDER/HFD-510
301-827-6411

Simoneau, Margaret A

From: EDRAdmin@cder.fda.gov
Sent: Monday, August 08, 2005 3:50 PM
To: CHUNGSA@cder.fda.gov; HILLJ@cder.fda.gov; SIMONEAUM@cder.fda.gov; LUBASW@cder.fda.gov; DAVISBRUNOK@cder.fda.gov; GALLIERS@cder.fda.gov; GUILDERSON@cder.fda.gov; JOHNSONKA@cder.fda.gov; PRATHERM@cder.fda.gov; TAGOEI@cder.fda.gov
Cc: schumaker@cder.fda.gov; esub@cder.fda.gov; talastash@cder.fda.gov; emmonsp@cder.fda.gov; langhnojau@cder.fda.gov; Tokoli@cder.fda.gov; EDRAdmin@cder.fda.gov
Subject: EDR - NDA021961 from SYNTHON PHARMS drug name SIMVASTATIN ORALLY DISINTEGRATING TABS,1

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-510:

NDA# N21961
Incoming Document Type: N
Incoming Document Type Sequence Number: 000
Supplement Modification Type:
Letter Date: 7/28/2005

It has sections 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19. The network path location is: \\CDSESUB1\N21961\N_000\2005-07-28
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAdmin@cder.fda.gov

Thanks,
Prentiss

Appears This Way
On Original

Simoneau, Margaret A

From: Galliers, Enid M
Sent: Wednesday, August 03, 2005 6:14 PM
To: Moore, Stephen K; Ahn, Hae Young; Parks, Mary H; Davis Bruno, Karen L; Simoneau, Margaret A; CDER-DRTL-FDR
Cc: Johnson, Kati
Subject: NDA 21-961 SIMVASTATIN ORALLY DISINTEGRATING TABLETS, 10, 20, 40, 80 MG from your friends at SYNTHON PHARM

FDR:

Please change the NAME = SIMVASTATIN ORALLY DISINTEGRATING TABS, 10,20,40,80 MG

THER CODE = 3041600

CHEM CLASS = 3

REV PRIORITY = S

PM = SIMONEAU

TEAM LEADERS:

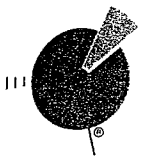
This 505b2 NDA is based on biopharm, chemistry, literature, and reference to Zocor for dyslipidemia indications. The application was submitted in electronic format but is not yet loaded in EDR. Also, the red CMC jackets have not been forwarded yet.

Pharm/tox refers to literature. I can't tell if there's anything associated with the dosage form that needs your attention.

Please make review assignments - if you can - even without access to the submission.

Thanks,

Enid



Synthon
Pharmaceuticals, Inc.

July 28, 2005

VIA FEDERAL EXPRESS

David G. Orloff, M.D.
Division Director (HFD-510)
Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: New Drug Application
Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg
Orally Disintegrating Tablets
NDA# 21-961

Dear Dr. Orloff:

Pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and in accordance with the provisions of 21 C.F.R. § 314.50, Synthon Pharmaceuticals, Inc. (Synthon) hereby submits a new drug application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg orally disintegrating tablets.

The NDA applicant is Synthon Pharmaceuticals, Inc. and the primary contact person is as follows:

Kamali Chance, MPH, Ph.D., RAC
Director of Regulatory Affairs
9000 Development Drive
P.O. Box 110487
Research Triangle Park, NC 27709
919-493-6006
919-536-1310 (direct)
919-493-6104 (fax)

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

The safety and efficacy of simvastatin is well documented in the published literature and in FDA's 1991 approval of the 5 mg to 40 mg strengths of Zocor (NDA # 019766). Additionally, FDA approved the 80 mg dose of Zocor in 1998 (NDA # 019766 /S028). Therefore, Synthon is proposing to support the approval of its 505(b)(2) NDA with a combination of:

(a) published literature concerning the simvastatin active ingredient;
(b) FDA's previous findings of the safety and efficacy of the Zocor drug product (NDA# 019766); and
(c) data from a comparative bioavailablity (i.e., bioequivalence) study comparing the proposed 80 mg simvastatin orally disintegrating tablet with the approved Zocor 80 mg tablet in the fasting condition.

This NDA submission contains 39 volumes in the Common Technical Document (CTD) format. This is a paper submission with the exception of labeling information and bioequivalence data, which are provided in both paper format and in an electronic format pursuant to 21 CFR 314.50(l)(i), FDA Guidance for Industry entitled "Providing Regulatory Submissions in Electronic Format – Content of Labeling" and FDA Guidance for Industry entitled "Providing Regulatory Submissions in Electronic Format – General Considerations".

This NDA submission contains the following sets of documents:

- An archival copy (in blue binders) of the complete NDA - 39 volumes
- A review copy of the complete NDA - 39 volumes
    - Module 1, 2 and 3 - red binders
    - Module 4 - yellow binder
    - Module 5 - orange binders

- A field copy (in green binders) - 25 volumes
  - Module 1
  - Module 3
- A CD-ROM of the complete NDA (a PDF courtesy copy)

The following documents are being provided in an electronic format:

- Proposed package insert (PI)
- Proposed Patient Package Insert (PPI)
- Side-by-Side annotated PI
- Side-by-Side annotated PPI
- Proposed container labels
- Pharmacokinetic data CD in SAS Transport format
- Bioequivalence Study Summary Tables

Synthon commits to resolve any issues identified in the methods validation process after approval in accord with usual FDA practices.

Additionally, concurrently with the filing of this NDA, pursuant to 21 C.F.R. § 314.50(l)(3), a true copy of the technical sections of the NDA (including a copy of Form FDA 356h and a certification that the contents are a true copy of those filed with the Division of Metabolic and Endocrine Drug Products) has been forwarded to Atlanta District Office.

Should you have any questions concerning the information provided in this original NDA, please do not hesitate to contact me directly at (919) 536-1310.

Sincerely,

Kamali Chance

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

Enclosures

Synthon
Pharmaceuticals, Inc.

July 28, 2005

VIA FEDERAL EXPRESS

Ms. Mary Woleske, District Director
Atlanta District Office
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA 30309

Re: New Drug Application
Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg
Orally Disintegrating Tablets
NDA# 21-961

Dear Ms. Woleske:

Pursuant to 21 CFR 314.50 (1)(3), Synthon Pharmaceuticals, Inc. (Synthon) is hereby forwarding a true copy of the technical sections of the New Drug Application (NDA) for Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg orally disintegrating tablets including a completed copy of Form FDA 356h and a certification that the contents are a true copy of those filed with the Division of Metabolic and Endocrine Drug Products.

The NDA applicant is Synthon Pharmaceuticals, Inc. and the primary contact person is as follows:

Kamali Chance, MPH, Ph.D., RAC
Director of Regulatory Affairs
9000 Development Drive
P.O. Box 110487
Research Triangle Park, NC 27709
919-493-6006
919-536-1310 (direct)
919-493-6104 (fax)

Should you have any questions concerning the information presented in this application, please do not hesitate to contact me directly at (919) 536-1310.

Sincerely,

Kamali Chance

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

Enclosures

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA# 21-961

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Synthon Pharmaceuticals, Inc.	7/27/05
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
919-493-6006	919-493-6104
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 9000 Development Drive P.O. Box 110487 Research Triangle Park, North Carolina 27709	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Simvastatin Orally Disintegrating Tablets	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of hypercholesterolemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, dysbetalipoproteinemia.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Zocor (Simvastatin) Holder of Approved Application Merck & Co., Inc.

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
New Drug Application

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 39 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Establishment information is provided in Volume 1, Module 1, Section 3
CD-ROM of the complete drug application is being provided as well as Labeling, bioequivalence tables and SAS transport data in an electronic format.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

PIND# 70-964

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☒	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☒	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kamali Chance ✓	Kamali Chance, MPH, Ph.D., RAC Director of Regulatory Affairs	7/27/05

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
9000 Development Drive P.O. Box 110487 Research Triangle Park, North Carolina 27709	(919) 493-6006

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-961

Synthon Pharmaceuticals, Inc.
Attention: Kamali Chance, MPH, Ph.D., RAC
Director of Regulatory Affairs
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Dr. Chance:

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

Name of Drug Product: Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40mg and 80 mg

Review Priority Classification: Standard

Date of Application: July 28, 2005

Date of Receipt: July 29, 2005

Our Reference Number: NDA 21-961

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 27, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 29, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until January 31, 2006. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with

the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room #8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Margaret Simoneau
8/11/05 02:30:17 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Synthon Pharmaceuticals, Inc.
9000 Development Drive
P. O. Box 110487
Research Triangle Park, North Carolina 27709

2. TELEPHONE NUMBER *(Include Area Code)*
(919) 493-6006

3. PRODUCT NAME
Simvastatin Orally Disintegrating Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
Pre-IND# 70-964

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	V.P. & General Counsel	7/22/05

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 30, 2001, unless specifically exempted below. Form 3397 should be placed in the first volume of the application with the application form.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications

CBER

Any supplement that does not require clinical data for approval
Applications (including supplements) for:

- Products for further manufacturing only
- Whole Blood or Blood Component for Transfusion
- Bovine Blood Product for Topical Application Licensed before September 1, 1992
- A crude Allergenic Extract Product
- An *In-Vitro* diagnostic biological product licensed under section 351 of the PHS Act

ITEM NO.: **INSTRUCTIONS**

1-2. **Self-explanatory**

3. **PRODUCT NAME** - Include generic name and trade name, as applicable.

4. **BLA STN / NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the 6-digit Biologics License Application STN if known.

FOR DRUG PRODUCTS - Indicate the NDA number, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

EXAMPLE: For NDA 99999, the number would be: N099999.

5. **CLINICAL DATA** - The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on CDER's web site: http://www.fda.gov/cder/pdufa/default.htm.

6. **USER FEE I.D. NUMBER - PLEASE INCLUDE THIS NUMBER ON THE APPLICATION PAYMENT CHECK.** If the application is exempted from a fee, a User Fee I.D. Number is not required. To obtain the appropriate User Fee I.D. Number, read and complete the following:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210. Questions regarding the CDER User Fee I.D. Number should be directed to CDER's User Fee Staff at (301) 594-2041.

FOR BIOLOGIC PRODUCTS - The User Fee I.D. Number is the applicant's four digit U.S. License Number, followed by a sequential number for each fee paying submission from the applicant; starting with number 1. If the firm is unlicensed, a number may be obtained by calling CBER's Regulatory Information Management Staff (RIMS) at (301) 827-3503. Questions regarding the CBER User Fee I.D. number should also be directed to RIMS.

EXAMPLE: For U.S. License Number 0222, the fifth submission would be given the User Fee I.D. Number: 0222-5.

7. **EXCLUSIONS:**

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); and NOT a new indication for a use.

The application is for an orphan product. Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement.

8. **WAIVER** - Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. *A copy of the official FDA notification that the waiver has been granted must be provided with the submission.*

Synthon
Pharmaceuticals, Inc.

REQUEST FOR EXCLUSION FROM REQUIREMENT FOR ENVIRONMENTAL IMPACT ANALYSIS STATEMENT

Pursuant to 21 C.F.R. § 25.31(a) Synthon Pharmaceuticals, Inc. ("Synthon") hereby requests a categorical exclusion from the requirements of an Environmental Impact Analysis Statement.

Under 21 C.F.R. § 25.31(a), a categorical exclusion exists for:

Action on an NDA if the action does not increase the use of the active moiety.

Synthon is requesting FDA to take action by approving its application for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets. This is an action specified in 21 C.F.R. §25.31(a). Synthon meets the other requirements of 21 C.F.R. § 25.31(a) because Synthon's Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets will be administered at the same dosage level, for the same duration, and for the same indications as other currently approved forms of simvastatin (e.g., Zocor®) and thus will not increase the use of the active moiety at issue. Synthon also certifies that, to the best of its knowledge, no extraordinary circumstances exist, that would require an Environmental Assessment per 21 C.F.R § 25.15.

Kamali Chance — July 19 2005

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

Date

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 70,964

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

Dear Mr. Hinckle:

Please refer to your Pre-Investigational New Drug Application (PIND) for Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40mg, and 80 mg Tablets.

We also refer to your June 13, 2005 correspondence, received June 14, 2005, containing additional detailed information concerning Synthon's bioequivalence study. This information was requested by the Agency to provide responses to your April 29, 2005 questions. We have completed the review of your submission and have the following comments.

1. Is Synthron's bioequivalence data adequate to support approval of the proposed drug product?

Agency response: *The study design appears adequate.*

2. Will the Division grant a "biowaiver" for the 10 mg, 20 mg, and 40 mg tablet strengths based on proportional formulation, linear kinetics, and dissolution testing?

Agency response: *Yes, based on the information provided.*

3. Does the Division agree with Synthon's conclusion that the application will be exempt from user fees because it involves a "molecular entity" that has been previously approved for the same "indications of use"?

Synthon was advised to contact Mr. Michael Jones, of CDER's User Fee staff, for comments and recommendation.

4. Will the Division accept the application for filing with 6 months of accelerated and real time stability data?

Agency response: *Yes, this amount of stability data is acceptable for filing; however, the Agency customarily grants only a 6-month extension beyond the real time stability data for the drug product's expiry dating.*

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
7/15/05 09:52:01 AM
for Dr. Orloff

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 70,964

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

Dear Mr. Hinckle:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

We also refer to your April 29, 2005 correspondence, received May 2, 2005, requesting a meeting to discuss your development plan. We have considered your request and concluded that the meeting is unnecessary. However, in order to assist you, in a separate letter, we will provide written responses to the questions included in your meeting request.

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
5/16/05 03:30:51 PM
for Dr. Orloff

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Synthon
Pharmaceuticals, Inc.

April 29, 2005

VIA FEDERAL EXPRESS

David G. Orloff, M.D.
Division Director (HFD-510)
Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Pre-NDA Meeting Request – Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg, and 80 mg

Dear Mr. Orloff:

Synthon Pharmaceuticals, Inc. ("Synthon") has developed an orally disintegrating tablet ("ODT") formulation of the simvastatin active ingredient that is currently marketed by Merck & Co., Inc. under the Zocor® trade name. The ODT dosage form was developed in order to provide patients with a convenient and easily administered form of simvastatin, especially for adolescent patients (ages 10-17 years) and the elderly, who have traditionally had difficulties swallowing more conventional dosage forms. Synthon intends to submit a new drug application ("NDA") under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA") seeking approval of this new dosage form of simvastatin for the same indications as the currently marketed Zocor drug product and in the 10 mg, 20 mg, 40 mg, and 80 mg strengths.

The safety and efficacy of simvastatin is well documented in the published literature and in FDA's 1991 approval of the 5 mg to 40 mg strengths of Zocor (NDA # 19-766). Additionally, FDA approved the 80 mg dose of Zocor in 1998 (NDA # 19-766 /S028). Therefore, Synthon is proposing to support the approval of its 505(b)(2) NDA with a combination of:

(a) published literature concerning the simvastatin active ingredient;
(b) FDA's previous findings of the safety and efficacy of the Zocor drug product (NDA# 19-766); and
(c) data from a comparative bioavailablity (i.e., bioequivalence) study comparing the proposed 80 mg simvastatin ODT tablet with the approved Zocor 80 mg tablet in the fasting condition.

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

Synthon plans to principally rely upon FDA's previous determination of the safety and effectiveness of simvastatin (i.e., Zocor). The "bridge" between the previously approved drug product and Synthon's proposed ODT product would be spanned by data demonstrating that the proposed and approved products are "bioequivalent." As the Agency is well aware, bioequivalence studies are generally accepted as the most appropriate proof of establishing therapeutic equivalence. It may be inferred that an equivalent plasma concentration profile will result in essentially similar concentrations at the site of action. Based on this assumption, an equivalent rate and extent of absorption will predict an essentially similar efficacy and safety profile.

Because the active ingredient in the proposed and previously approved drug products is the same, an investigational new drug ("IND") application was not required for Synthon's bioequivalence study. See 21 C.F.R. § 320.31. Accordingly, the biostudy was conducted in March, 2005 in th[redacted]pursuant to an approval of the study by the [redacted]authorities. We expect to receive the final study report within the next few weeks. Once the final study report is received (assuming that the data support a finding of bioequivalence), we will submit a full briefing book to the agency and request a meeting date at least four weeks after the briefing book is received by the agency. Currently, we anticipate requesting a meeting date sometime during the last week of June, 2005. b(4)

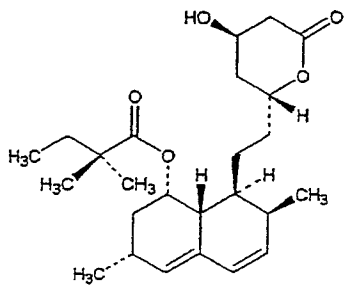
In accordance with the FDA Guidance Document entitled "Formal Meetings with Sponsors and Applicants of PDUFA Products," Synthon provides the following specific information concerning its meeting request:

Product Name:

Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg Orally Disintegrating Tablets (Tradename to be determined).

Chemical Name and Structure:

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Proposed Indications:

Synthon is seeking approval for all of the indications that are currently approved for the Zocor drug product (see list below). We intend to file a "paragraph III" patent certification for the patent listed in the "Orange Book" for Zocor. Therefore, Synthon's proposed NDA will not be eligible for final FDA approval until June 23, 2006 (the expiration date, with pediatric exclusivity extension, of the Orange Book listed patent), at which time the 3-year and pediatric exclusivity for all of the currently approved Zocor indications will have expired.

Type of Meeting Requested:

Type B (Pre-NDA)

Purpose of the Meeting:

To receive the Division of Metabolic and Endocrine Drug Product's (the "Division's") input as to the approvability of Synthon's proposed 505(b)(2) NDA and, if necessary, to receive the Division's guidance on any additional data or information that may be needed to support approval.

Preliminary Proposed Agenda:

I. Brief background information on Synthon Pharmaceuticals, Inc. (2 minutes)
II. Discussion of the regulatory approach for approval (3 minutes)
III. Summary of the clinical plan (5 minutes)
IV. Summary of the clinical data and study results (20 minutes)
V. Agency response to Synthon's specific questions and discussion of any Agency questions (30 minutes)

List of Specific Questions:

1. Is Synthon's bioequivalence data adequate to support approval of the proposed drug product?
2. Will the Division grant a "biowaiver" for the 10mg, 20mg, and 40mg tablet strengths based on proportional formulation, linear kinetics, and dissolution testing?
3. Does the Division agree with Synthon's conclusion that the application will be exempt from user fees because it involves a "molecular entity" that has been previously approved for the same "indications of use"?
4. Will the Division accept the application for filing with 6 months of accelerated and real time stability data?

List of Individuals Who will Attend This Meeting:

1. Peter van Straelen, President
2. Wayne Stargel, Pharm.D., Vice President of Medical Affairs
3. Michael Hinckle, Vice President of Regulatory Affairs/General Counsel
4. Kamali Chance, Director of Regulatory Affairs
5. Po Lui, Director of Quality Control
6. [redacted] b(4)

List of Agency Staff Requested by the Sponsor to Participate in this Meeting

Synthon requests the participation of all Agency personnel that are necessary to achieve the aforementioned objectives of the meeting.

Approximate Date on which Supporting Documentation (Briefing Books) will be Sent to Reviewing Division

We anticipate submitting the Briefing Books to the Division no later than the last week in May, 2005.

* * * *

Thank you for your attention to this matter. We look forward to meeting with the Division and receiving the Agency's input and recommendations.

Should you have any questions concerning the proposed drug product or this meeting request, please feel free to contact me at (919) 493-6006.

Sincerely,

Michael H. Hinckle
Vice President of Regulatory Affairs/General Counsel

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