

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

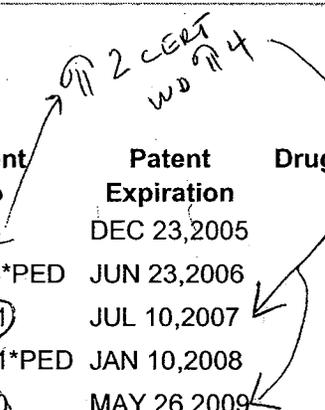
21-961

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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>U-59</u>
019766	001	4444784*PED	JUN 23,2006			<u>U-59</u>
019766	001	RE36481	JUL 10,2007			<u>U-300</u>
019766	001	RE36481*PED	JAN 10,2008			<u>U-300</u>
019766	001	RE36520	MAY 26,2009			<u>U-300</u>
019766	001	RE36520*PED	NOV 26,2009			<u>U-300</u>



Exclusivity Data

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

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE36481 and RE36520 are being relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v. Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents will remain listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act have been triggered and run, unless the agency's appeal of the decision to the U.S. Court of Appeals for the District of Columbia is decided in the agency's favor before the exclusivity periods have expired. While the patents remain listed, any new or pending ANDA referencing Zocor must contain patent certifications to these patents. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046.

Janice Weiner ORP

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

Patent Data

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019766	001	4444784*PED	JUN 23,2006			<u>U-59</u>
019766	001	RE36481	JUL 10,2007	✓		<u>U-300</u>
019766	001	RE36481*PED	JAN 10,2008			<u>U-300</u>
019766	001	RE36520	MAY 26,2009	✓		<u>U-300</u>
019766	001	RE36520*PED	NOV 26,2009			<u>U-300</u>

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
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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.
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8/18/06

[View a list of all patent use codes](#)

[View a list of all exclusivity codes](#)

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FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through July, 2006

Patent and Generic Drug Product Data Last Updated: August 17, 2006

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Patent Use Codes

This page defines the patent use codes.

Code Definition

U-300 INDICATED FOR THE REDUCTION OF ELEVATED TOTAL AND LDL CHOLESTEROL LEVELS IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA

[View a list of all patent use 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**

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Patent and Generic Drug Product Data Last Updated: August 17, 2006

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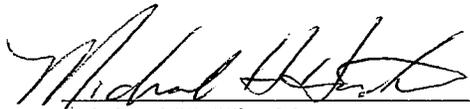
Synthon

Paragraph II Certification

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

Synthon hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 4,444,784 (the "'784 patent") held by Merck & Co., Inc. expired on December 23, 2005, and that the period of pediatric exclusivity assigned to the '784 patent expired on June 23, 2006. Therefore, in accordance with FDCA § 505(c)(3)(A) and 21 C.F.R. § 314.107(b)(1)(iii), the '784 patent has no effect on the final approval of Synthon's NDA.

Synthon Pharmaceuticals, Inc.



Michael H. Hinckle
V.P. & General Counsel

5-23-07
Date

Appears This Way
On Original

Synthon Pharmaceuticals, Inc.

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Synthon

Withdrawal of Patent Certification

Synthon Pharmaceuticals, Inc. ("Synthon") hereby withdraws its "Paragraph IV" patent certifications for U.S. Patent Nos. RE36481 and RE36520 that were submitted to NDA 21-961 on June 30, 2006. The withdrawal of these patent certifications is appropriate because the aforementioned patents are no longer listed in FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" and therefore do not cover the Zocor[®] drug product that is referenced in NDA 21-961. Therefore, U.S. Patent Nos. RE36481 and RE36520 have no effect on the final approval of NDA 21-961.

Synthon Pharmaceuticals, Inc.



Michael H. Hinckle
V.P. & General Counsel

5-23-07

Date

Appears This Way
On Original

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EXCLUSIVITY SUMMARY

NDA # 21-961

SUPPL #

HFD # 510

Trade Name None

Generic Name Simvastatin Orally Disintegrating Tablet

Applicant Name Synthron

Approval Date, If Known October 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505b2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Sponsor submitted a single fasting study to bridge their formulation to the RLP (Zocor). No clinical studies of efficacy or safety were conducted.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No. Pediatric exclusivity was granted to the RLP (Zocor).

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: M. Simoneau

Title: RPM

Date: October 3, 2007

Name of Office/Division Director signing form: Eric Colman, MD

Title: Deputy Division Director/Team Leader

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Eric Colman

10/18/2007 02:56:00 PM

This document was mistakenly overlooked until 10/18/2007

Appears This Way
On Original

Common Technical Document
Simvastatin
10 mg, 20 mg, 40 mg and 80 mg
Orally Disintegrating Tablets

Module 1, Section 3.11
Claimed Exclusivity

page 1 of 1

1.3.11 Claimed Exclusivity

Synthon Pharmaceuticals, Inc. does not claim any period of market exclusivity for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets.

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EXCLUSIVITY STATEMENT

According to the information published in the list of Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), 25th Edition, cumulative supplement 05 (May, 2005), Zocor[®] is entitled to market exclusivity under section 505(c)(3)(D)(iv) of the Federal Food, Drug, and Cosmetic Act for new indications that does not expire until April 18, 2006. Synthon Pharmaceuticals, Inc. does not intend to introduce the Simvastatin 10 mg, 20 mg, 40 mg, 80 mg orally disintegrating tablets that are the subject of this NDA prior to the expiration of this exclusive marketing period.

Synthon Pharmaceuticals, Inc.

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

July 19, 2005
Date

Appears This Way
On Original

Common Technical Document
Simvastatin
10 mg, 20 mg, 40 mg and 80 mg
Orally Disintegrating Tablets

Module 1, Section 3.2
Patent/Market Exclusivity Information

page 1 of 1

1.3.2 Summary of Zocor[®] Patent Listing and Market Exclusivity

Listed Patents: According to the information published in the list of Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), 25th Edition, cumulative supplement 05 (May, 2005), U.S. Patent # 4,444,784 is the only patent that is listed for the Zocor[®] (simvastatin) 5 mg, 10 mg, 20 mg, 40 mg and 80 mg tablets (NDA # 019766). This patent expires on December 23, 2005, but has received an additional six months of listing in the Orange Book pursuant to a grant of “pediatric exclusivity” under section 505A of the Federal Food, Drug, and Cosmetic Act (“FDCA”). Therefore, for the purposes of Synthon Pharmaceuticals Inc.’s (Synthon) Patent Certification to patent number 4,444,784, the applicable “expiration date” is June 23, 2006. Synthon is filing a patent certification to this listed patent pursuant to FDCA § 505(b)(2)(A)(iii) (i.e., a “Paragraph III Certification”). The Paragraph III Patent Certification for US Patent #4,444,784 is provided in Exhibit 1 to this section.

Market Exclusivity: The Zocor[®] drug product is entitled to two periods of “three year” market exclusivity under FDCA § 505(c)(3)(D)(iv) that cover the following indications for use: (1) “use in patients at high risk of coronary events due to existing coronary heart disease, diabetes, peripheral vessel disease, stroke history, or other cardiovascular disease to reduce risk and total mortality by reducing coronary death, reduce nonfatal myocardial infarction, stroke, etc.”; and (2) “treatment of heterozygous familial hypercholesterolemia in adolescent boys and girls at least one year postmenarchal, ages 10 to 17 years, with a recommended dosing range of 10 to 40mg once daily” These periods of exclusivity expire on April 16, 2006 and April 18, 2006 (including the applicable pediatric exclusivity extension), respectively. Synthon’s proposed drug product will be labeled for these protected indications for use. Therefore, Synthon has included an Exclusivity Statement in this NDA stating that the proposed drug product will not be introduced into the market prior to the expiration of the latest expiring period of market exclusivity (i.e., April 18, 2006). The Exclusivity Statement is provided in Exhibit 2 to this section.

The relevant Orange Book pages are presented in Exhibit 3 to this section.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-961 Supplement Type (e.g. SE5): _____ Supplement Number: _____

amp Date: July 29, 2005 PDUFA Goal Date: October 17, 2007

HFD 510 Trade and generic names/dosage form: Simvastatin Orally Disintegrating Tablets

Applicant: Synthon Pharmaceuticals, Inc. Therapeutic Class: 505b2 lipid altering agent

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 3

Indication #1: Reductions in Risk of CHD Mortality and CV Events

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 21-961

Page 3

This page was completed by: Margaret Simoneau

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles and
Indication #3: Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- ❖ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ❖ Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❖ Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Margaret Simoneau

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)



July 18, 2005

GENERIC DRUG ENFORCEMENT ACT OF 1992
DEBARMENT CERTIFICATION STATEMENT

Synthon Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 (k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992 under subsection (a) or (b) in connection with this NDA for Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg orally disintegrating tablets.

Synthon Pharmaceuticals, Inc. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, to the best of Synthon Pharmaceuticals, Inc.'s knowledge, no person affiliated with Synthon Pharmaceuticals, Inc. that was responsible for the development or submission of this application has been convicted of an offense described in (a) or (b) of the Generic Drug Enforcement Act of 1992.

A handwritten signature in black ink, appearing to read "Michael H. Hinckle", written over a horizontal line.

Michael H. Hinckle
Vice President and General Counsel

A handwritten date "7/18/05" written in black ink over a horizontal line.

Date

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July 07, 2005

GENERIC DRUG ENFORCEMENT ACT OF 1992
DEBARMENT CERTIFICATION STATEMENT

Synthon B.V. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 (k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992 under subsection (a) or (b) in connection with this (A)NDA which would support a NDA for Simvastatin Oral Disintegrating Tablets 10, 20, 40 and 80 mg or an ANDA.

Synthon B.V. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, to the best of Synthon B.V.'s knowledge, no person affiliated with Synthon B.V. that was responsible for the development or submission of this application has been convicted of an offense described in (a) or (b) of the Generic Drug Enforcement Act of 1992.

Drs. G. W. Klein Kranenburg
Director QA/Qualified Person Synthon B.V.

07 JULI 2005

Date

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7 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

[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 August, 2007

Patent and Generic Drug Product Data Last Updated: October 01, 2007

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10/2/07

ORIGINAL

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

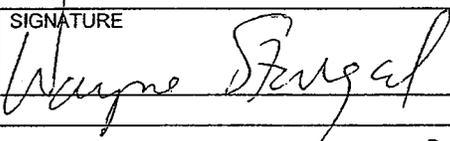
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list of Clinical Investigators for Study No. CSP.US01.SVT.ODT80.001	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME W. Wayne Stargel, Pharm.D.	TITLE Vice President of Medical Affairs
FIRM / ORGANIZATION Synthon Pharmaceuticals, Ltd.	
SIGNATURE 	DATE 18, Feb. 2005

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-961	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Simvastatin Established Name: Dosage Form: Orally Disintegrating Tablets		Applicant: Synthron Pharmaceuticals, Inc.
RPM: M. Simoneau		Division: 510 Phone # 301-796-1295
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Zocor</p> <p>Provide a brief explanation of how this product is different from the listed drug. Orally Disintegrating</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed <input checked="" type="checkbox"/> Corrected</p> <p>Date: 10/2/07 There are no unexpired patents and exclusivity for this product in the Orange Book Database.</p>
❖ User Fee Goal Date ❖ Action Goal Date (if different)		10.16.07
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None NA on 5.25.06
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

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❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• OC clearance for approval (<i>file communication in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire June 23, 2006
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	October 5, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	September 18, 2007
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	July 28, 2005
❖ Patient Package Insert	None
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide	None
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	September 4, 2007
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	10/24/05 and 4/18/06
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	8/29/07 email by Kim Colangelo
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable Section 306 (k)
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	May 23, 2007
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	none <input type="checkbox"/> No mtg <input checked="" type="checkbox"/> No mtg AD comments 7.15.05 9.21.06 Office of Compliance
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	<input checked="" type="checkbox"/> No AC meeting
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	none
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	#1:1.3.06/#2:5.3.06#3 5.19.06 #4:6.22.07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	July 19, 2005
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection <ul style="list-style-type: none"> NDAs: Facilities inspections (include EER printout) 	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	2.14.06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	none
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested 5.18.07Memo with NDA 22-026 Amlodipine
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	Dr. Lubas 2.7.06/E. Colman 10.07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	2.18.05 submission
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None ODS for container and PI labeling
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	none
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	none
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> • Clinical Studies • Bioequivalence Studies • Clin Pharm Studies 	6.7.2006
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5.19.06 & 10.2.07

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Appendix A to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**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
10/4/2007 10:02:20 AM

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On Original

Simoneau, Margaret A

From: Colangelo, Kim M
Sent: Thursday, October 04, 2007 4:12 PM
Subject: Simoneau, Margaret A
RE: 505b2 info request

You bet!

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

From: Simoneau, Margaret A
Sent: Thursday, October 04, 2007 4:09 PM
To: Colangelo, Kim M
Subject: 505b2 info request

Kim,

We received clearance to approve the 505b2 NDA 22-026 Simvastatin Orally Disintegrating tablets on August 29, 2007. The Division will sign the AP letter tomorrow. Are we still legally cleared to take an approval action?

Thanks
Margaret

Appears This Way
On Original

Memo to File

NDA #: 21-961
Sponsor: Synthron Pharmaceuticals, Inc.
Drug: Simvastatin Orally Disintegrating Tablets (simvastatin)
Submission Date: April 16, 2007
Memo Date: October 1, 2007

This submission responds to the Not Approval (NA) letter issued by the Agency on May 25, 2006 based on deficiencies documented by the Division of Scientific Investigations (DSI).

The DSI concluded that this submission is a complete response to the Agency's action letter issued on May 25, 2006. There are no pending issues related to clinical pharmacology.

The follow labeling proposal related to pharmacokinetics under Clinical Pharmacology section has been accepted by the sponsor and reflected in the final labeling. (Red bold underlined text denotes the Agency's changes).

Pharmacokinetics

The pharmacokinetics of simvastatin and simvastatin acid, following administration of the 80 mg Simvastatin Orally Disintegrating tablet and 240 mL water at 1 minute post-dosing, were comparable to those following administration of the simvastatin immediate release 80 mg tablet taken with 240 mL water.

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/s/

Sang Chung
10/2/2007 02:38:52 PM
BIOPHARMACEUTICS

Sally Choe
10/2/2007 02:40:26 PM
BIOPHARMACEUTICS

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On Original

MEMORANDUM

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

DATE: 24-SEP-2006
TO: NDA 21-961 Review File
FROM: John Hill, Ph.D., Chemistry Reviewer, Branch II/DPA-I/ONDQA
Through: Ali Al-Hakim, Ph.D., Chief, Branch II/DPA-I/OMDQA
SUBJECT: NDA 21-965: Final Review

SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BL Amendment	24-MAY-2007
BL Amendment	4-SEP-2007

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

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

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

The Agency requests that Synthon commit to concurrently validating the more discriminating dissolution method QC.WO.SVT.odt.020.C/12.02 (submitted as a BC amendment 16-MAY-2006, e-mail dated 15-MAY-2006) to NDA 21-961 while performing Simvastatin lot release testing using dissolution method QC.US01.SVT.020.C/6. The new dissolution test method (QC.WO.SVT.odt.020.C/12.02) will be validated to support a lot release specification of Q_{∞} 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.

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

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

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

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/s/

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

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

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On Original

Simoneau, Margaret A

From: Bridges, Todd
nt: Tuesday, September 18, 2007 4:14 PM
Subject: Simoneau, Margaret A
NDA 21-961 Simvastatin ODT

Hi Margaret,

Regarding the revised container label colors used to designate the 10 mg, 20 mg, and 40 mg product strengths, we recognize that these colors do not reflect the actual color of the tablets. However, we continue to recommend that the sponsor utilize the revised colors to designate the aforementioned strengths. We do not believe this will pose any safety risks and will help to reduce the potential for product selection errors which could result in the dispensing or administration of the incorrect strength.

Thanks,
Todd

Todd D. Bridges, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
The Federal Research Center at White Oak
Building 22, Rm. #4408
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Office 301.796.0120
Fax 301.796.9865

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On Original

Simoneau, Margaret A

From: Choe, Sally
nt: Friday, September 14, 2007 12:59 PM
Subject: Simoneau, Margaret A; Colman, Eric C; Chung, Sang
RE: DFS Email - N 021961 N 000 28-Jul-2005 - Review

Hello!
Both Sang and I are fine with the proposed change.
Thanks.

Sally-

-----Original Message-----

From: Simoneau, Margaret A
Sent: Friday, September 14, 2007 9:49 AM
To: Colman, Eric C; Choe, Sally; Chung, Sang
Subject: FW: DFS Email - N 021961 N 000 28-Jul-2005 - Review

Sang & Sally,

Dosage and Administration PI concerns...label doesn't look final yet! I'll wait for your recommendation.

Eric,

I spoke with Todd Bridges, the consult reviewer, and asked him for an official response regarding the consult question that was submitted. Info was asked on the labeling container and we received info on the PI. Nice...

Thanks

-----Original Message-----

From: cderdocadmin@cder.fda.gov [mailto:cderdocadmin@cder.fda.gov]
Sent: Thursday, September 13, 2007 4:58 PM
To: Simoneau, Margaret A; Lubas, William (CDER); Holquist, Carol A; Bridges, Todd; Beam, Sammie; Campbell, Cheryl; Parks, Mary H; Toyer, Denise P
Subject: DFS Email - N 021961 N 000 28-Jul-2005 - Review

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
N 021961 N 000 28-Jul-2005	E13	13-Sep-2007	CM

Document Type: Review

Submission Description: Medication Error Label and Labeling Review for Simvastatin ODT
PM activity: PM activity required

Author(s)/Discipline(s)

1. Todd Bridges, DRUG SAFETY OFFICE REVIEWER

Signer(s)

1. Todd Bridges
13-Sep-2007
2. Carol Holquist
13-Sep-2007

Simoneau, Margaret A

From: Simoneau, Margaret A
nt: Thursday, September 13, 2007 9:22 AM
'Richard.Almond@synthon.com'
Cc: Chung, Sang; Choe, Sally; Colman, Eric C
Subject: FW: NDA 21-961 Simvastatin Orally Disintegrating Tablets/ Labeling comments

Mr. Almond,

In reference to my voice message today, we have the following labeling recommendation:

(red underlined text indicates addition.)

Pharmacokinetics

The pharmacokinetics of simvastatin and simvastatin acid, following administration of the 80 mg Simvastatin Orally Disintegrating tablet and 240 mL water at 1 minute post-dosing, were comparable to those following administration of the simvastatin immediate release 80 mg tablet taken with 240 mL water.

Thank you,
Margaret

From: Simoneau, Margaret A
Sent: Tuesday, September 11, 2007 9:06 AM
'Richard.Almond@synthon.com'
Colman, Eric C; Chung, Sang
subject: NDA 21-961 Simvastatin Orally Disintegrating Tablets/ Labeling comments

Mr. Almond,

In reference to the draft package insert submitted by email September 5, 2007, we have the following labeling comments to the **CLINICAL PHARMACOLOGY, *Pharmacokinetics* subsection:**

Recommendation: (red underlined text indicates addition.)

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

The pharmacokinetics of simvastatin and simvastatin acid, following administration of the **80 mg** Simvastatin Orally Disintegrating tablet **and 240 mL water at 1 minute post-dosing**, were comparable to those following administration of the simvastatin immediate release **80 mg** tablet **taken with 240 mL water**.

Please feel free to contact me with any questions.

ank you,
Margaret



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 10, 2007

To: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products

Thru: Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

From: Todd Bridges, R.Ph., Team Leader
Division of Medication Errors and Technical Support

Subject: Medication Error Label and Labeling Review

Drug Name(s): Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg, 80 mg

Application Type/Number: NDA #: 21-961

Submission Number: Not applicable

Applicant/sponsor: Synthon Pharmaceuticals, Inc.

OSE RCM #: 2007-1912

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1 INTRODUCTION

This memorandum is in response to a September 6, 2007, request from the Division of Metabolism and Endocrinology Products for a review of the revised container labels and insert labeling for Simvastatin Orally Disintegrating Tablets. The label revisions were made in response to OSE Review # 2007-1421, dated August 15, 2007.

2 MATERIAL REVIEWED

DMETS reviewed revised container labels and insert labeling submitted August 29, 2007 and September 5, 2007, respectively.

3 DISCUSSION

DMETS acknowledges that the sponsor has addressed most of our recommendations. However, in the Dosage and Administration section of the insert labeling, reference is made regarding the Administration of Simvastatin Orally Disintegrating Tablets. In its current location, this information may easily be overlooked and the patient and provider may not be aware that the tablet is intended to be placed on the tongue and dissolved. Proper placement maybe critical to the absorption of the drug product. Ambiguity in proper placement could lead to medication errors in which the patient may swallow (whole), chew, or crush the tablet.

4 RECOMMENDATION

DMETS recommends implementation of the labeling revision to the Dosage and Administration section of the package insert labeling outlined below.

- 4.1 DOSAGE AND ADMINISTRATION SECTION - DMETS recommends that the sponsor relocate the two sentences contained in the subsection concerning the administration of Simvastatin Orally Disintegrating Tablets, to appear as the second paragraph of this section. Below is an excerpt from the Dosage and Administration section of the insert labeling with this revision incorporated and noted with underlining.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, Simvastatin Orally Disintegrating Tablets can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see NCEP Treatment Guidelines. For the reduction in risks of major coronary events, see CLINICAL PHARMACOLOGY, *Clinical Studies in Adults*.) The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. The orally disintegrating tablet should be placed on the tongue where it will dissolve and then be swallowed with the saliva. If necessary, follow with water.

Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (i.e., homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (i.e., cyclosporine, danazol, amiodarone, verapamil, or gemfibrozil).

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. We would be willing to meet with the Division for further discussion, if needed. If you have any questions or need clarification, please contact Cheryl Campbell, OSE Project Manager, at 301-796-0723.

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/s/

Todd Bridges
9/13/2007 04:47:33 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/13/2007 04:57:18 PM
DRUG SAFETY OFFICE REVIEWER

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On Original

Simoneau, Margaret A

From: Davis Bruno, Karen L
Sent: Wednesday, September 12, 2007 3:01 PM
To: Simoneau, Margaret A
Subject: RE: NDA 21-961 Simvastatin Orally Disintegrating Tablets/ Labeling comments
Attachments: FW: NDA 21-961 Simvastatin Orally Disintegrating Tablets/ Labeling comments

I don't see any track changes proposed to the nonclinical sections of the label and therefore I am OK with this version.

Thanks,
Karen

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9/13/2007

Simoneau, Margaret A

From: Simoneau, Margaret A
nt: Tuesday, September 11, 2007 9:06 AM
'Richard.Almond@synthon.com'
cc: Colman, Eric C; Chung, Sang
Subject: NDA 21-961 Simvastatin Orally Disintegrating Tablets/ Labeling comments

Mr. Almond,

In reference to the draft package insert submitted by email September 5, 2007, we have the following labeling comments to the **CLINICAL PHARMACOLOGY, Pharmacokinetics subsection:**

Recommendation: (red underlined text indicates addition.)

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

The pharmacokinetics of simvastatin and simvastatin acid, following administration of the **80 mg** Simvastatin Orally Disintegrating tablet **and 240 mL water at 1 minute post-dosing**, were comparable to those following administration of the simvastatin immediate release **80 mg** tablet **taken with 240 mL water.**

ase feel free to contact me with any questions.

Thank you,

Margaret

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 10, 2007
To: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
Thru: Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support
From: Todd Bridges, R.Ph., Team Leader
Division of Medication Errors and Technical Support
Subject: Medication Error Label and Labeling Review
Drug Name(s): Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg, 80 mg
Application Type/Number: NDA #: 21-961
Submission Number: Not applicable
Applicant/sponsor: Synthon Pharmaceuticals, Inc.
OSE RCM #: 2007-1912

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1 INTRODUCTION

This memorandum is in response to a September 6, 2007, request from the Division of Metabolism and Endocrinology Products for a review of the revised container labels and insert labeling for Simvastatin Orally Disintegrating Tablets. The label revisions were made in response to OSE Review # 2007-1421, dated August 15, 2007.

2 MATERIAL REVIEWED

DMETS reviewed revised container labels and insert labeling submitted August 29, 2007 and September 5, 2007, respectively.

3 DISCUSSION

DMETS acknowledges that the sponsor has addressed most of our recommendations. However, in the Dosage and Administration section of the insert labeling, reference is made regarding the Administration of Simvastatin Orally Disintegrating Tablets. In its current location, this information may easily be overlooked and the patient and provider may not be aware that the tablet is intended to be placed on the tongue and dissolved. Proper placement maybe critical to the absorption of the drug product. Ambiguity in proper placement could lead to medication errors in which the patient may swallow (whole), chew, or crush the tablet.

4 RECOMMENDATION

DMETS recommends implementation of the labeling revision to the Dosage and Administration section of the package insert labeling outlined below.

- 4.1 DOSAGE AND ADMINISTRATION SECTION - DMETS recommends that the sponsor relocate the two sentences contained in the subsection concerning the administration of Simvastatin Orally Disintegrating Tablets, to appear as the second paragraph of this section. Below is an excerpt from the Dosage and Administration section of the insert labeling with this revision incorporated and noted with underlining.

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The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, Simvastatin Orally Disintegrating Tablets can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see NCEP Treatment Guidelines. For the reduction in risks of major coronary events, see CLINICAL PHARMACOLOGY, *Clinical Studies in Adults*.) The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. The orally disintegrating tablet should be placed on the tongue where it will dissolve and then be swallowed with the saliva. If necessary, follow with water.

Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (i.e., homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (i.e., cyclosporine, danazol, amiodarone, verapamil, or gemfibrozil).

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. We would be willing to meet with the Division for further discussion, if needed. If you have any questions or need clarification, please contact Cheryl Campbell, OSE Project Manager, at 301-796-0723.

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/s/

Todd Bridges
9/13/2007 04:47:33 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/13/2007 04:57:18 PM
DRUG SAFETY OFFICE REVIEWER

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Simoneau, Margaret A

From: Chung, Sang
Sent: Friday, September 07, 2007 4:36 PM
To: Colman, Eric C
Cc: Choe, Sally; Simoneau, Margaret A
Subject: RE: NDA 21-961 / A-016 / Simvastatin ODT Labeling

Dr. Colman,

I have labeling recommendation as follows and let me know if you have any comments.

Thanks,

Sang

Sponsor's proposal:

b(4)

Recommendation: (red underlined text indicates addition.)

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

The pharmacokinetics of simvastatin and simvastatin acid, following administration of the **80 mg** Simvastatin Orally Disintegrating tablet **and 240 mL water at 1 minute post-dosing**, were comparable to those following administration of the simvastatin immediate release **80 mg** tablet **taken with 240 mL water**.

From: Simoneau, Margaret A
Sent: Wednesday, September 05, 2007 11:48 AM
To: Chung, Sang

9/11/2007

Subject: FW: NDA 21-961 / A-016 / Simvastatin ODT Labeling

From: Kim Bartakovits [mailto:kim.bartakovits@synthon.com]

Sent: Wednesday, September 05, 2007 11:46 AM

To: Simoneau, Margaret A

Cc: Richard Almond

Subject: NDA 21-961 / A-016 / Simvastatin ODT Labeling

Dear Ms. Simoneau:

Per your telephone request today to Richard Almond of Synthon Pharmaceuticals, Inc., I am forwarding the revised package insert (PI) for NDA 21-961, Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg and 80 mg (Word and PDF).

To better assist with the review process, I have attached the tracked changes document in Word format. Please note that the source document used was the package insert included in our original submission to the Agency (based on ZOCOR's PI dated November 2004). The tracked changes include revisions from two (2) amendments (A-005 & A-010) as well as the latest innovator PI dated August 2006 as requested.

Please contact us should you have any questions.

Best regards,

Kim Bartakovits

Regulatory Affairs Specialist

Synthon Pharmaceuticals, Inc.

9000 Development Drive

P.O. Box 110487

R.T.P., NC 27709

(tel) 919.536.1319

kim.bartakovits@synthon.com

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9/11/2007

Simoneau, Margaret A

From: Campbell, Cheryl
nt: Thursday, September 06, 2007 3:55 PM
Subject: Simoneau, Margaret A
FW: DFS Email - N 021961 N 000 BZ 23-May-2007 - Forms
Attachments: 09001464807fd044.pdf



09001464807fd044.pdf (475 KB)

Hi Margaret,

The RCM for this is 2007-1912.

Thx! CC

Cheryl L. Campbell, M.S.
Project Manager
CDER
Office of Surveillance and Epidemiology
10903 New Hampshire Avenue
WO Building #22, Room 3417
Silver Spring, MD 20993
301-796-0723
Cheryl.Campbell@fda.hhs.gov

-----Original Message-----

From: CDER OSE CONSULTS
Sent: Thursday, September 06, 2007 11:07 AM
To: Campbell, Cheryl
Cc: Beam, Sammie
Subject: FW: DFS Email - N 021961 N 000 BZ 23-May-2007 - Forms

-----Original Message-----

From: cderdocadmin@cder.fda.gov [mailto:cderdocadmin@cder.fda.gov]
Sent: Thursday, September 06, 2007 9:56 AM
To: CDER OSE CONSULTS; CDER DDR510 Public Folder
Subject: DFS Email - N 021961 N 000 BZ 23-May-2007 - Forms

Document room update the following:

	Decision Date	Decision Code
N 021961 N 000 BZ 23-May-2007	06-Sep-2007	:

Document Type: Forms
Form Group: CONSULT
Form Name: OSE Consult Request
Submission Description: F/up OSE consult regarding colors of container label

Author(s)/Discipline(s)

Margaret Simoneau, CSO

Signer(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: ODS		FROM: Margaret Simoneau, RPM, DMEP		
DATE Sept. 6, 2007	IND NO.	NDA NO. 21-961	TYPE OF DOCUMENT New 505b2 NDA(2 nd review cycle)	DATE OF DOCUMENT August 29, 2007 (email)
NAME OF DRUG Simvastatin Orally Disintegrating Tablet	PRIORITY CONSIDERATION Type 2 resubmission (6- mo clock)	CLASSIFICATION OF DRUG Statin	DESIRED COMPLETION DATE September 14, 2007	
NAME OF FIRM: Synthron Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>This is a follow-up non-trade name consult for OSE Review # 2007-1421. Regarding the revised labeling container colors used to designate the 10 mg, 20 mg, and 40 mg strengths, these labels do not reflect the actual color of the tablets. Please evaluate. All labeling is attached.</p> <p>Please call me (796-1295) if you have any questions or problems. Thank you.</p>				
SIGNATURE OF REQUESTER Margaret Simoneau		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Margaret Simoneau
9/6/2007 09:54:32 AM

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DUPLICATE

RECEIVED

SEP 06 2007

Synthon

September 4, 2007

CDER/WHITE OAK/DRI

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
SEP - 5 2007
GDR / CDER

RE: NDA # 21-961 / Amendment 016
Simvastatin Orally Disintegrating Tablets
Labeling revision

Dear Dr. Parks:

Reference is made to the August 8, 2007 telecon between Richard Almond of Synthon Pharmaceuticals, Inc. ("Synthon") and Margaret Simoneau (FDA/CDER/OND/ODEII/DMEP) regarding the package insert for Synthon's New Drug Application ("NDA") for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets (NDA # 21-961). Ms. Simoneau requested that Synthon update the proposed package insert based on the latest revisions made to the innovator's package insert.

Reference is also made to the August 22, 2007 telecon between Mike Hinckle of Synthon and Margaret Simoneau regarding the container labels for Synthons NDA #21-961. Ms. Simoneau requested that Synthon update the container labels as follows:

1. The words "orally disintegrating tablets" should be as prominent as the established name (i.e., Simvastatin).
2. The word "Synthon" is more prominent than the established name and strength. Recommend removing the bold font for "Synthon" and reducing the font size.
3. The Synthon logo is more prominent than the established name. Reduce prominence or remove the logo.
4. The statement of net quantity of contents appears where the tablet strength would normally appear. Move tablet count to bottom of the principle display panel and make it bold.

Synthon Pharmaceuticals, Inc.

9000 Development Drive | P.O. Box 110487 | Research Triangle Park, NC 27709

Phone +1 (919) 493 6006 | Fax +1 (919) 493 6104 | info@synthon.com | www.synthon-usa.com

NDA # 21-961

Amendment 016 – Labeling revision

Page 2 of 2

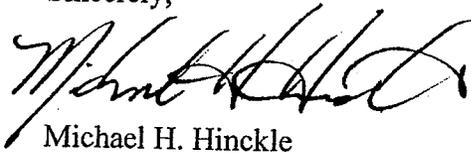
5. The colors used to distinguish the tablet strengths are not sufficiently different so as to avoid medication errors. Use brighter colors that are more easily distinguished. The colors do not have to match the actual tablet colors.

Synthon hereby amends the above referenced New Drug Application (“NDA”) for Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets to update the package insert and container labels. A completed Form FDA-356h is provided in Exhibit 1 to this response. The revised, proposed package insert and updated container labels are provided in Exhibits 2 and 3 respectively. The labeling information submitted in this amendment is being provided in both paper and electronic format (CD provided in Exhibit 4).

Synthon previously submitted an amendment (Amendment 005 dated February 23, 2006) revising the proposed container labels and package insert to remove the proposed trade name and to use only the established name and dosage form (i.e. “Simvastatin Orally Disintegrating Tablets”). Should Synthon decide to add a trade name to the product label or labeling in the future, a Prior Approval Supplement (PAS) will be submitted at that time seeking Agency approval for the proposed trade name.

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

Appears This Way
On Original

56 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Simoneau, Margaret A

From: Colangelo, Kim M
Sent: Wednesday, August 29, 2007 1:59 PM
Subject: Simoneau, Margaret A
RE: ScanDoc.pdf

Hi Margaret,

You are cleared for action on this one!

Have a great day!
Kim

From: Simoneau, Margaret A
Sent: Wednesday, August 22, 2007 2:09 PM
To: Colangelo, Kim M
Subject: FW: ScanDoc.pdf

From: Simoneau, Margaret A
Sent: Wednesday, August 22, 2007 2:08 PM
To: Simoneau, Margaret A
Subject: ScanDoc.pdf

<< File: ScanDoc.pdf >>

Appears This Way
On Original

Simoneau, Margaret A

From: Hill, John
t: Tuesday, August 21, 2007 2:30 PM
Simoneau, Margaret A
Cc: Tran, Suong T
Subject: NDA 21-961 Synthron Simvastatin

Attachments: Picture (Metafile)

From my CMC Review...

P.7 Container Closure System [name, dosage form]

The NDA registration batches of Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets are packaged in white opaque 75 mL or 150 mL round ~~_____~~ bottles. The closure system includes a ~~_____~~ twist-off cap ~~_____~~. The round, white opaque cap is child resistant with a tamper-evident liner ~~_____~~. The tablet count per bottle is 7, 30, or 90 tablets. b(4)

These packaging configurations are summarized in the following table.

Container/Closure System	Number of Tablets per Bottle			
	10 mg	20 mg	40 mg	80 mg
_____ 75 mL round bottles with _____ twist-off closure that is child resistant with tamper evident cap liner. The twist-off cap contain _____	7, 30 and 90 count	7, 30 and 90 count	7, 30 and 90 count	7 and 30 count
_____ 150 mL round bottles with _____ twist-off closure that is child resistant with tamper evident cap liner. The twist-off cap contain _____	-	-	-	90 count
Bulk Packaging - _____	Approximately _____			

b(4)

In short, the caps are child resistant.

One less item to worry about.

John C. Hill, Ph.D., CAPT. 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

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research

To: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products

Through: Todd Bridges, R.Ph, Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

From: Jinhee Jahng Lee, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support

Date: July 20, 2007

Subject: DMETS Labeling Review
Drug: Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg, 80 mg
NDA #: 21-961
Sponsor: Synthon Pharmaceuticals, Inc.

OSE Review #: 2007-1421

This memorandum is in response to a June 25, 2007 request from the Division of Metabolism and Endocrinology Products for a review of the container labels and insert labeling of Simvastatin Orally Disintegrating Tablets. DMETS notes that this NDA was submitted as a 505(b)2 application and the sponsor has not requested a tradename. Additionally, the chemistry reviewer had concerns regarding the appropriateness of the font sizes (e.g. the tablet quantity) on the labels and labeling.

Upon review of the labels and labeling for Simvastatin Orally Disintegrating Tablets, DMETS has identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety.

A. GENERAL COMMENT

DMETS is concerned about the lack of prominence of the dosage form "Orally Disintegrating Tablets". With current "regular" simvastatin tablets available on the market, we are concerned that the "ODT" dosage form would be confused and incorrectly substituted with the existing "regular" simvastatin tablets, especially since they have overlapping strengths. Thus, we request you revise the font size of the dosage form so that it is commensurate with the size and font type of the simvastatin portion of the name.

B. CONTAINER LABEL

1. See GENERAL COMMENT.

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

/s/

Jinhee Jahng
8/15/2007 03:51:12 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/15/2007 05:18:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/16/2007 07:19:55 AM
DRUG SAFETY OFFICE REVIEWER

Appears This Way
On Original

Simoneau, Margaret A

From: Beam, Sammie
nt: Monday, June 25, 2007 10:02 AM
Simoneau, Margaret A
Subject: FW: DFS Email - N 021961 N 000 BZ 23-May-2007 - Forms
Attachments: 09001464807b1e75.pdf



09001464807b1e75.pdf (19 KB)

Assigned 2007-1421 in OSE tracking system

CDR Sammie Beam
Project Manager Team Leader
Office of Surveillance and Epidemiology
301-796-0080

10903 New Hampshire Avenue
CDER Building #22, Room 3422
Silver Spring, MD 20993

-----Original Message-----

From: CDER OSE CONSULTS
Sent: Friday, June 22, 2007 12:36 PM
To: Beam, Sammie
Subject: FW: DFS Email - N 021961 N 000 BZ 23-May-2007 - Forms

-----Original Message-----

From: cderdocadmin@cder.fda.gov [mailto:cderdocadmin@cder.fda.gov]
Sent: Friday, June 22, 2007 11:13 AM
To: CDER OSE CONSULTS; CDER DDR510 Public Folder
Subject: DFS Email - N 021961 N 000 BZ 23-May-2007 - Forms

Document room update the following:

	Decision Date	Decision Code
N 021961 N 000 BZ 23-May-2007	22-Jun-2007	:

Document Type: Forms
Form Group: CONSULT
Form Name: ODS Consult (Except Tradename Reviews)
Submission Description: ODS consult regarding container labels

Author(s)/Discipline(s)

1. Margaret Simoneau, CSO

Signer(s)

1. Margaret Simoneau
22-Jun-2007

Supervisory Signer(s)

1. Margaret Simoneau

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

O (Division/Office):

Mail: ODS

FROM: Margaret Simoneau, RPM, DMEP

DATE
June 22, 2007

IND NO.

NDA NO.
21-961

TYPE OF DOCUMENT New 505b2
NDA(2nd review cycle)

DATE OF DOCUMENT
May 23, 2007

NAME OF DRUG Simvastatin
Orally Disintegrating Tablet

PRIORITY CONSIDERATION
Type 2 resubmission (6-
mo clock)

CLASSIFICATION OF DRUG
Statin

DESIRED COMPLETION DATE
September 1, 2007

NAME OF FIRM: Synthron Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We are requesting a non-tradename consult of labels for bottles. This is an electronic 505b2 NDA. All labeling is in the EDR. The chemistry reviewer has concern regarding the appropriateness of the font sizes (for example, the tablet quantity).

Please call me (796-1295) if you have any questions or problems. Thank you.

SIGNATURE OF REQUESTER Margaret Simoneau

METHOD OF DELIVERY (Check one)
 MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Margaret Simoneau
6/22/2007 11:11:50 AM

Appears This Way
On Original

Simoneau, Margaret A

From: Chandra, Savithri*
nt: Monday, June 11, 2007 12:35 PM
Simoneau, Margaret A
Cc: CDER-DRTL-ALL
Subject: RE: Request COMIS change

Hi,

It's done.

Thanks-Savithri.

From: Simoneau, Margaret A
Sent: Monday, June 11, 2007 11:24 AM
To: CDER-DRTL-ALL
Subject: Request COMIS change

For NDA 21-961, Simvastatin Orally Disintegrating Tablets, the "AZ" April 17, 2007, re-submission is considered Class 2. Can you please change this entry from a 2-month to a 6-month goal date.

Thank you.

Margaret Simoneau
FDA/CDER/DMEP
301-796-1295

Appears This Way
On Original

Synthon

May 23, 2007

VIA FEDERAL EXPRESS

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

RECEIVED

MAY 24 2007

CDER CDR

**RE: NDA # 21-961 / Amendment 015
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
AMENDMENT – Update on NDA 21-961**

Dear Ms. Woleske:

Pursuant to 21 CFR 314.96(3)(b), Synthon Pharmaceuticals, Inc. (Synthon) is hereby forwarding a **true and exact copy** of Amendment 015 to NDA 21-961 that was forwarded to the Division of Metabolic and Endocrine Drug Products. This amendment provides a summary of NDA 21-961 post approval commitments, currently proposed labeling and an update (amendment and withdrawal) on patent certifications.

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

Sincerely,



Michael H. Hinckle
VP and General Counsel

Enclosure

Appears This Way
On Original

Synthon Pharmaceuticals, Inc.

9000 Development Drive | P.O. Box 110487 | Research Triangle Park, NC 27709

Phone +1 (919) 493 6006 | Fax +1 (919) 493 6104 | info@synthon.com | www.synthon-usa.com

July 28, 2005
Submitted
originally

DUPLICATE

long d'ed



RECEIVED

May 23, 2007

MAY 25 2007

VIA FEDERAL EXPRESS

CDER White Oak DT1

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

MAY 24 2007

CDER CDR

RE: NDA # 21-961 / Amendment 015
Simvastatin Orally Disintegrating Tablets
10 mg, 20 mg, 40 mg and 80 mg
AMENDMENT - Update on NDA# 21-961

ORIGINAL AMENDMENT
N(BZ)

Dear Dr. Parks:

Synthon Pharmaceuticals, Inc. ("Synthon") is amending its New Drug Application ("NDA") 21-961 for Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg and 80 mg to list the Chemistry Manufacturing and Controls ("CMC") post approval commitments, to provide Synthon's currently proposed Labeling and to amend/withdraw patent certifications. A completed Form FDA-356h is provided as Exhibit 1 to this amendment.

CMC post approval commitments:

Synthon made the following CMC post approval commitments to NDA 21-961.

1. *r*

7

u

5

b(4)

2. *r*

7

u

5

Synthon Pharmaceuticals, Inc.

9000 Development Drive | P.O. Box 110487 | Research Triangle Park, NC 27709

Phone +1 (919) 493 6006 | Fax +1 (919) 493 6104 | info@synthon.com | www.synthon-usa.com

Synthon

3. Synthon made a commitment to concurrently validate 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 Q~~_____~~ at 15 minutes.
1. The new dissolution test method (QC.WO.SVT.odt.020.C/12.02) will also be included in the stability protocol.
 2. 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.
 3. These stability data can be updated in the annual report to support the proposed dating period.
- Please refer to amendment 009, to NDA #21-961 sent to FDA on May 18, 2006. A copy of the cover letter to amendment 009 is provided in Exhibit 3 to this amendment.

b(4)

Labeling:

Synthon's proposed labels and package insert for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg is provided in Exhibits 4 and 5 respectively. No labeling revisions have occurred since Synthon's amendment 010 to NDA 21-961 dated May 24, 2006. A copy of the cover letter to amendment 010 is provided in Exhibit 6. Labeling in electronic format (Microsoft word and pdf) is provided in Exhibit 7.

Withdrawal of Patent Certifications:

Synthon is converting its "Paragraph III" patent certification for patent number 4,444,784 (the '784 patent) to a "Paragraph II" certification to reflect the fact that the '784 patent, and associated period of pediatric exclusivity, expired on June 23, 2006. See Patent Certification enclosed as Exhibit 8. Likewise, Synthon is withdrawing the "Paragraph IV" patent certifications that were submitted in NDA 21-961 for patent numbers RE36481 and RE36520 because both of these patents have been removed from FDA's "Orange Book." See Patent Certification Withdrawal enclosed as Exhibit 9.

The current edition of the "Orange Book" includes no patent listings for the Zocor® reference listed drug. Consequently, there are no remaining patent issues that block the final approval of NDA 21-961.

As per 21 CFR 314.60(c), Synthon hereby submits two copies of this **Amendment 015** 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:

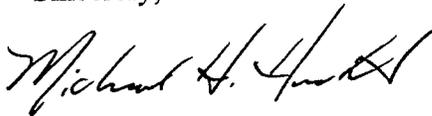
Page 3 of 3
NDA No. 21-961
Amendment 015

Synthon

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

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

Sincerely,



Michael H. Hinckle
Vice President & General Counsel

Enclosure(s)

Appears This Way
On Original

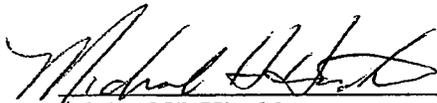
Synthon

Paragraph II Certification

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

Synthon hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 4,444,784 (the "'784 patent") held by Merck & Co., Inc. expired on December 23, 2005, and that the period of pediatric exclusivity assigned to the '784 patent expired on June 23, 2006. Therefore, in accordance with FDCA § 505(c)(3)(A) and 21 C.F.R. § 314.107(b)(1)(iii), the '784 patent has no effect on the final approval of Synthon's NDA.

Synthon Pharmaceuticals, Inc.



Michael H. Hinckle
V.P. & General Counsel

5-23-07
Date

Appears This Way
On Original

Synthon Pharmaceuticals, Inc.

9000 Development Drive | P.O. Box 110487 | Research Triangle Park, NC 27709

Phone +1 (919) 493 6006 | Fax +1 (919) 493 6104 | info@synthon.com | www.synthon-usa.com

Synthon

Withdrawal of Patent Certification

Synthon Pharmaceuticals, Inc. ("Synthon") hereby withdraws its "Paragraph IV" patent certifications for U.S. Patent Nos. RE36481 and RE36520 that were submitted to NDA 21-961 on June 30, 2006. The withdrawal of these patent certifications is appropriate because the aforementioned patents are no longer listed in FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" and therefore do not cover the Zocor[®] drug product that is referenced in NDA 21-961. Therefore, U.S. Patent Nos. RE36481 and RE36520 have no effect on the final approval of NDA 21-961.

Synthon Pharmaceuticals, Inc.



Michael H. Hinckle
V.P. & General Counsel

5-23-07

Date

Appears This Way
On Original

Synthon Pharmaceuticals, Inc.

9000 Development Drive | P.O. Box 110487 | Research Triangle Park, NC 27709

Phone +1 (919) 493 6006 | Fax +1 (919) 493 6104 | info@synthon.com | www.synthon-usa.com

Simoneau, Margaret A

Subject: NDA 21-961 Simvastatin ODT/Discussion of DMETS labeling review comments
Location: CDER WO 3376 conf rm Bldg22

Start: Tue 8/21/2007 2:00 PM
End: Tue 8/21/2007 2:30 PM

Recurrence: (none)

Meeting Status: Meeting organizer

Required Attendees: Simoneau, Margaret A; Tran, Suong T; Hill, John
Resources: CDER WO 3376 conf rm Bldg22

Appears This Way
On Original

Simoneau, Margaret A

From: Chandra, Savithri*
nt: Monday, May 21, 2007 4:40 PM
CDER-OBPS-DRM-COMIS Changes
Cc: CDER-DRTL-ALL; CDER-EDRADMIN; Simoneau, Margaret A
Subject: N21-961 - Request to Modify a Record in COMIS / ECH

Please change the following entry per CSO's request:

	MUST INCLUDE	COMPLETE ONLY
APPLICATION TYPE	N	
APPLICATION NUMBER	21-961	
LETTER_DATE	16-APR-07	
STAMP_DATE	17-APR-07	
IN_DOC_TYPE_SEQ_NO	000	
INCOMING_DOC_TYPE	N	
SUP_MODIFICATION_TYPE	BZ	AZ
STATUS_CODE		
STATUS_DATE		
DOCUMENT ID #	3086130	
ELECTRONIC SUBMISSION	NO	
VOLUME NUMBER	A19.1	

Thanks-Savithri.

From: Simoneau, Margaret A
Monday, May 21, 2007 12:24 PM
CDER-DRTL-ALL
Cc: Galliers, Enid M
Subject: Request COMIS change

For NDA 21-961 Simvastatin Orally Disintegrating Tablets, submission dated April 16, 2007, please change the code from BZ to AZ.

Thank you,

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

Appears This Way
On Original