

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-961

CHEMISTRY REVIEW(S)

Simvastatin
10 mg, 20 mg, 40 mg, 80 mg
Orally Disintegrating Tablets
NDA 21-961

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: Synthron Pharmaceuticals, Inc
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Indication: Treatment of hypercholesterolemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, dysbetalipoproteinemia.

Presentation: Orally disintegrating tablet (ODT) containing 10 mg (yellow), 20 mg (peach), 40 mg (pink), or 80 mg (white) of simvastatin for oral administration. The tablets are round, biconvex with the product strength debossed on one side and "ODT" on the other side. The tablets are packaged in ~~_____~~ bottles: 7 count, 75 ml (professional sample); 30 count, 75 mL; or 90 count, 150 ml.

b(4)

EER Status: Acceptable 16-MAY-2006

Consults: DMETS – Not Requested by clinical division (HFD-510)
EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency not requested

Original Submission: 28-JUL-2005

Post-Approval Agreements:

The applicant agrees to place _____ batch of each strength, in the approved container/closure, annually, in the post-approval stability program, if any batches are manufactured.

b(4)

The applicant agrees to place the manufacturing process validation batches on stability per the bracketing schedule outlined in Volume 11, Module 3, Section 2.P.8.2, Exhibit 6.

The applicant agrees, in a postmarketing commitment letter of May 18, 2006, to develop a dissolution method and specification to assure characteristics of Simvastatin Orally Disintegrating Tablets.

Drug Substance

Simvastatin is a lipid-lowering agent that is derived synthetically from lovastatin, a fermentation product of *Aspergillus terreus*. Simvastatin is an inactive lactone that is hydrolyzed, after ingestion, to the corresponding beta-hydroxy acid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyses an early step in the biosynthesis of cholesterol, and thereby limits the rate of overall cholesterol biosynthesis.

The chemistry, manufacturing, and controls information for the drug substance is appropriately referenced, is described in Synthon BV's Type II DMF 18384, has been reviewed, and is concluded to be adequate.

Conclusion: Drug substance is acceptable.

Drug Product

The drug product is an orally disintegrating tablet (ODT) containing 10 mg, 20 mg, 40 mg, or 80 mg of simvastatin. The tablets are round, biconvex, with the product strength debossed on one side and "ODT" on the other side. Product strength debossed on tablet for 10 mg (yellow) reads "S10", for 20 mg (peach) reads "S20", 40 mg (pink) reads "S40", and 80 mg (white) reads "S80."

The tablets are formulated with butylated hydroxyanisole, Povidone, Crospovidone, hydroxypropylcellulose, silicified microcrystalline cellulose, mint menthol sucralose, glyceryl behenate and iron oxide-based colorant.

b(4)

Specifications for the drug product include: visual description, identification by HPLC, assay by HPLC, purity, impurity and content uniformity by HPLC, antioxidant, residual water content, dissolution and microbial testing. All tests methods have been appropriately validated for their intended purpose. The dissolution data demonstrate that the subject drug and the listed drug are comparable.

Submitted stability data support the proposed storage is at 25°C (room temperature) for _____ is for drug product packaged in the proposed bottle. The label claim for storage will be "Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [See USP]. Avoid exposure to excessive heat or light".

b(4)

Conclusion: Drug product is satisfactory.

Additional Items:

As the analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry, revalidation by Agency laboratories will not be requested

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
5/19/2006 03:28:51 PM
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NDA 21-961

Simvastatin

Synthon

**John C. Hill, Ph.D.
ONDQA/DPA I/DMEP/HFD-510**

Chemistry Review #4

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Chemistry Review Data Sheet

1. NDA # 21-961
2. REVIEW # 4
3. REVIEW DATE: 21-JUN-2007
4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA Filing	28-JUL-2005
BC Amendment	13-OCT-2005
BC Amendment	03-FE2006
BC Amendment	09-FEB-2006
BL Amendment	23-FEB-2006
BM Amendment (DMF Correspondence)	27-MAR-2006
BC Amendment	16-MAY-2006
BC Amendment	19-MAY-2006
BL Amendment	24-MAY-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
AZ Amendment	16-APR-2007
BZ Amendment	23-MAY-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Synthon Pharmaceuticals, Inc.
Address: 9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709



CHEMISTRY REVIEW



Representative: Kamali Chance, MPH, Ph.D. RAC, Director Regulatory Affairs
Telephone: 919-493-6066

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Simvastatin
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) Listed Drug: Zocor (Merck) NDA #19-766

10. PHARMACOL. CATEGORY: Hypercholesterolemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, dysbetalipoproteinemia.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10, 20, 40, and 80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



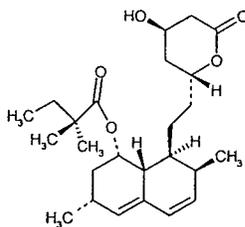
CHEMISTRY REVIEW



Name: Simvastatin

Molecular Formula: C₂₅H₃₈O₅

Molecular Weight: 418.57



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
18384	II	Synthon BV	Simvastatin API	4	Adequate	08-FEB-2006	LOA 08-JUL-2005
					Adequate	13-JAN-2006	LOA 27-MAY-2005
					Adequate	30-AUG-2005	LOA 11-JUL-2005
					Acceptable	Acceptable as NF	LOA 23-JUN-2005
					Acceptable	21-SEP-2003	LOA 30-JUN-2005
					Acceptable	01-JAN-2003	LOA 28-JUN-2005
					Acceptable	01-AUG-2003	LOA 30-JUN-2005
					Acceptable	30-AUG-2001	LOA 27-JUN-2005

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	70,964	Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	17-MAY-2006	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		
OPDRA			
EA	Acceptable	22-DEC-2005	John C. Hill, Ph.D.
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes
 No If no, explain reason(s) below:

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The Chemistry Review for NDA 21-961

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The Agency requests that Synthron commit to concurrently validating the more discriminating dissolution method QC.WO.SVT.odt.020.C/12.02 (submitted as a BC amendment 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, Synthron 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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Product

The drug product presented in this NDA is an orally disintegrating tablet containing either 10, 20, 40 or 80 mg of simvastatin. The tablets are round, biconvex with the

product strength debossed on one side and "ODT" on the other side. Following is a detailed description of appearance for each tablet strength.

10 mg Tablets

Yellow, round, biconvex tablets. These tablets are debossed with "S10" on one side and "ODT" on the other side.

20 mg Tablets

Peach, round, biconvex tablets. These tablets are debossed with "S20" on one side and "ODT" on the other side.

40 mg Tablets

Pink, round, biconvex tablets. These tablets are debossed with "S40" on one side and "ODT" on the other side.

80 mg Tablets

White to off-white, round, biconvex tablets. These tablets are debossed with "S80" on one side and "ODT" on the other side.

The individual components used to manufacture Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets are listed in the following table.

Ingredients	Function	Quality
Simvastatin	lipid altering agent	USP / Ph. Eur.
Burlyated hydroxybenzoinole		NF
Povidone		USP
Crospovidone		NF
hydroxypropylcellulose*		USP / NF
Silicified microcrystalline cellulose*		NF
Mint menthol*		in house
Sucralose		in house
Iron oxide yellow		NF
Iron oxide red		NF
Glyceryl behenate*		NF

b(4)

Excipients used to manufacture the drug product are of USP/NF quality with the exception of mint menthol and Silicified microcrystalline cellulose, which are tested in-house for quality. The drug product is composed of:

b(4)

During formulation development of the drug product, careful evaluation of excipients, particle size and stability were conducted to develop a stable, rapidly disintegrating tablet. Initial formulation development, conducted with a simvastatin particle, provided fundamental information about interactions with excipients, development of a suitable optimization of

_____ parameters, evaluation of tablet size and _____ forces on disintegration and dissolution times. The desire for increased bioavailability of simvastatin resulted in the use of a _____ simvastatin particle. This formulation change required additional optimization of the _____ and the _____ formulations. Additionally, initial stability data indicated that basic excipients used in the formulation _____ of simvastatin on stability _____ resolved this stability issue.

b(4)

2. Drug Substance:

The drug substance is simvastatin {[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 α] β]}, _____

_____ The manufacture of this compound is described in DMF# 18384. This DMF contains complete information on the manufacture, control of materials, control of critical steps and intermediates, process validation, manufacturing process development, elucidation of structure, impurities, control of the drug substance, drug substance specifications, analytical procedures, batch analyses, justification of specifications, reference standards and materials, release testing, container closure system, drug substance stability, and stability summary and conclusions.

b(4)

Simvastatin is a lipid-lowering agent that is derived synthetically from lovastatin, a fermentation product of *Aspergillus terreus*. Simvastatin is an inactive lactone, which is hydrolyzed after ingestion to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which catalyses an early step in the biosynthesis of cholesterol, limiting the rate of the total reaction.

Some of the key characteristics of Simvastatin drug substance that may influence the performance of the drug product, and were evaluated during product development include solubility, potential isomerism/polymorphism, exposure to light, alkaline media and oxidation. In order to increase the bioavailability, the simvastatin drug substance was _____ the mean particle size from around _____ to around _____

b(4)

B. Description of How the Drug Product is Intended to be Used

Hypercholesterolemia:

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

Coronary Heart Disease:



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

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. However, certain CMC deficiencies remain to be addressed. The CGMP facility inspections are pending.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

John C. Hill, Ph.D., Review Chemist: Same date as electronic review
Ali Al-Hakim, Ph.D., Branch Chief: Same date as electronic review

C. CC Block

Margaret A Simoneau, RPH, Project Manager: Same date as electronic review

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Ali Al-Hakim
6/22/2007 02:30:58 PM
CHEMIST

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NDA 21-961

Simvastatin

Synthon

**John C. Hill, Ph.D.
ONDQA/DPA I/DMEP/HFD-510**

Chemistry Review #3

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CHEMISTRY REVIEW



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Chemistry Review Data Sheet

1. NDA # 21-961
2. REVIEW # 3
3. REVIEW DATE: 17-May-2006
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA Filing	28-JUL-2005
BC Amendment	03-FEB-2006
BC Amendment	09-FEB-2006
BL Amendment	23-FEB-2006
Amendment (DMF Correspondence)	27-MAR-2006
Amendment # 09	19-MAY-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Synthon Pharmaceuticals, Inc.
Address: 9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709
Representative: Kamali Chance, MPH, Ph.D. RAC, Director Regulatory
Affairs
Telephone: 919-493-6066

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Simvastatin
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S



CHEMISTRY REVIEW



9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Listed Drug: Zocor (Merck) NDA #19-766

10. PHARMACOL. CATEGORY: Hypercholesterolemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, dysbetalipoproteinemia.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10, 20, 40, and 80 mg

13. ROUTE OF ADMINISTRATION: Oral

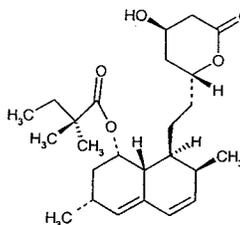
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Simvastatin
Molecular Formula: $C_{25}H_{38}O_5$
Molecular Weight: 418.57



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
18384	II	Synthon BV	Simvastatin API	4	Adequate	08-FEB-2006	LOA 08-JUL-2005
					Adequate	13-JAN-2006	LOA 27-MAY-2005
					Adequate	30-AUG-2005	LOA 11-JUL-2005
					Acceptable	Acceptable as NF	LOA 23-JUN-2005
					Acceptable	21-SEP-2003	LOA 30-JUN-2005
					Acceptable	01-JAN-2003	LOA 28-JUN-2005
					Acceptable	01-AUG-2003	LOA 30-JUN-2005
Acceptable	30-AUG-2001	LOA 27-JUN-2005					

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – _____

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

b(4)



CHEMISTRY REVIEW



DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	70,964	Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	16-MAY-2006	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		
OPDRA			
EA	Acceptable	22-DEC-2005	John C. Hill, Ph.D.
Microbiology			

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The Chemistry Review for NDA 21-961

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

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.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Synthon agrees (amendment 09, dated May 18, 2006) to concurrently validate the more discriminating dissolution method QC.WO.SVT.odt.020.C/12.02 (submitted as amendment 08 dated 16-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 C at 15 minutes.

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 _____ of approval of NDA 21-961

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**1. Drug Product

The drug product presented in this NDA is an orally disintegrating tablet containing either 10, 20, 40 or 80 mg of simvastatin. The tablets are round, biconvex with the product strength debossed on one side and "ODT" on the other side. Following is a detailed description of appearance for each tablet strength.

10 mg Tablets

Yellow, round, biconvex tablets. These tablets are debossed with "S10" on one side and "ODT" on the other side.

20 mg Tablets

Peach, round, biconvex tablets. These tablets are debossed with "S20" on one side and "ODT" on the other side.



CHEMISTRY REVIEW



40 mg Tablets

Pink, round, biconvex tablets. These tablets are debossed with "S40" on one side and "ODT" on the other side.

80 mg Tablets

White to off-white, round, biconvex tablets. These tablets are debossed with "S80" on one side and "ODT" on the other side.

The individual components used to manufacture Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets are listed in the following table.

Ingredients	Function	Quality
Simvastatin	lipid altering agent	USP / Ph. Eur.
Butylated hydroxyanisole		NF
Povidone		USP
Crossovidone		NF
hydroxypropylcellulose*		USP / NF
Silicified microcrystalline cellulose*		NF
Mint menthol* ¹		in house
Sucralose		in house
Iron oxide yellow		NF
Iron oxide red		NF
Glyceryl behenate*		NF

b(4)

Excipients used to manufacture the drug product are of USP/NF quality with the exception of mint menthol and Silicified microcrystalline cellulose, which are tested in-house for quality. The drug product is composed of _____ 1

b(4)

During formulation development of the drug product, careful evaluation of excipients, particle size, _____ and stability were conducted to develop a stable, rapidly disintegrating tablet. Initial formulation development, conducted with a _____ simvastatin particle, provided fundamental information about interactions with excipients, development of a suitable _____ optimization of _____ parameters, evaluation of tablet size and _____ forces on disintegration and dissolution times. The desire for increased bioavailability of simvastatin resulted in the use of a _____ simvastatin particle. This formulation change required additional optimization of the _____ and the _____ formulations. Additionally, initial stability data indicated that basic excipients used in the formulation _____ simvastatin on stability. _____ resolved this stability issue.

b(4)

2. Drug Substance:

The drug substance is simvastatin _____

_____ The manufacture of this compound is described in DMF# 18384. This DMF contains complete information on the manufacture, control of materials, control of critical steps and intermediates, process validation, manufacturing process development, elucidation of structure, impurities, control of the drug substance, drug substance specifications, analytical procedures, batch analyses, justification of specifications, reference standards and materials, release testing, container closure system, drug substance stability, and stability summary and conclusions.

Simvastatin is a lipid-lowering agent that is derived synthetically from lovastatin, a fermentation product of *Aspergillus terreus*. Simvastatin is an inactive lactone, which is hydrolyzed after ingestion to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which catalyses an early step in the biosynthesis of cholesterol, limiting the rate of the total reaction.

Some of the key characteristics of Simvastatin drug substance that may influence the performance of the drug product, and were evaluated during product development include solubility, potential isomerism/polymorphism, exposure to light, alkaline media and oxidation. In order to increase the bioavailability, the simvastatin drug substance was ~~the mean particle size from around ~~to around~~~~ the mean particle size from around ~~to around~~

b(4)

B. Description of How the Drug Product is Intended to be Used

Hypercholesterolemia:

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

Coronary Heart Disease:

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

C. Basis for Approvability or Not-Approval Recommendation

This application may be approved (AP) from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product.

III. Administrative

A. Reviewer's Signature

John C. Hill, Ph.D., Review Chemist: Same date as electronic review

B. Endorsement Block

Blair A. Fraser, Ph.D., Branch Chief: Same date as electronic review

C. CC Block

Margaret A Simoneau, RPH, Project Manager: Same date as electronic review

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Xavier Ysern
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CHEMIST
Xavier Ysern, PhD signing for John Hill, PhD

Blair Fraser
5/19/2006 03:17:29 PM
CHEMIST

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P. Simoneau

DMF: 18384 DMF Type:II
TITLE: Simvastatin

MAY - 5 2006

1. CHEM REVIEW No. 2

2. REVIEW DATE: 03-MAY-2006

3. ITEM REVIEWED:

A. IDENTIFICATION

USAN: Simvastatin
Ingredient Dictionary name: Simvastatin
Trade name:
Manufacturer's code: SVT
Chemical name:

[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 α β]]

b(4)

~~2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenylester,~~
[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 α β]]

b(4)

CAS number, if available: [79902-63-9]

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Amendment 001	23-MAR-2006	Volume 1.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location	Description
Original Submission	21-JUN-2005	Volume 1.1	Original Submission

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME: Synthon BV
Dr. Ing. H. M. Hultman

ADDRESS:
Microweg 22
6545 CM Nijmegen
The Netherlands
Tel: +31 (0) 24 3727700; Fax: +31 (0) 24 3727739

REPRESENTATIVE or U.S. AGENT (if applicable):

NAME: Synthon Pharmaceuticals Inc.

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

CONTACT PERSON'S NAME, TITLE, DEPARTMENT: Kamali Chance, MPH,
Ph.D., RAC

ADDRESS: As noted above

TELEPHONE NUMBER: 919 493-6006

FAX NUMBER: 919 493-6104

6. DMF REFERENCED FOR:

NDA\ANDA\AADA\IND: NDA 21-961

PRIMARY DMF (as needed)

APPLICANT NAME: Synthron Pharmaceuticals Ltd.

LOA DATE: 08-JUL-2005

DRUG PRODUCT NAME: Simvastatin

DOSAGE FORM: Tablet

CODE:

ROUTE OF ADMINISTRATION: Oral

CODE:

STRENGTH: 10, 20, 40 and 80 mg orally disintegrating tablets

7. SUPPORTING DOCUMENTS:

NA

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: 23-MAR-2006

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE
BEEN PROVIDED: 19-JUL-2005

9. CONSULTS:

NA

10. COMMENTS: The DMF holder has adequately addressed the deficiencies
communicated 23-FEB-2006.

11. CONCLUSION/RECOMMENDATION: Acceptable

John C. Hill 5/9/06
John C. Hill, Ph.D.
Review Chemist, HFD-510

Blair A. Fraser 5/3/06
Blair A. Fraser, Ph.D.
Branch Chief, DPA-1, ONDQA

cc: DMF 18384
ONDQA/Valerie Jimenez
HFD-510/Division File NDA 21-961
HFD-510/Hillj/BFraser/PSimoneau

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Deliberative Process (b5)



NDA 21-961

Simvastatin

Synthon

**John C. Hill, Ph.D.
ONDQA/DPA I/DMEP/HFD-510**

Chemistry Review #2

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Chemistry Review Data Sheet

1. NDA # 21-961
2. REVIEW # 2
3. REVIEW DATE: 03-May-2006
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

BC Amendment	03-FEB-2006
BC Amendment	09-FEB-2006
BL Amendment	23-FEB-2006
C Amendment (DMF Correspondence)	27-MAR-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Synthon Pharmaceuticals, Inc.
Address:	9000 Development Drive P.O. Box 110487 Research Triangle Park, North Carolina 27709
Representative:	Kamali Chance, MPH, Ph.D. RAC, Director Regulatory Affairs
Telephone:	919-493-6066

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
b) Non-Proprietary Name (USAN): Simvastatin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
Listed Drug: Zocor (Merck) NDA #19-766

10. PHARMACOL. CATEGORY: Hypercholesterolemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, dysbetalipoproteinemia.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10, 20, 40, and 80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

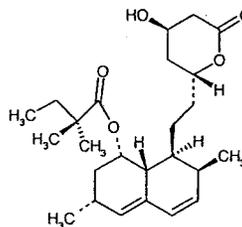
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Simvastatin

Molecular Formula: $C_{25}H_{38}O_5$

Molecular Weight: 418.57





17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
18384	II	Synthon BV	Simvastatin API	4	Adequate	08-FEB-2006	LOA 08-JUL-2005
					Adequate	13-JAN-2006	LOA 27-MAY-2005
					Adequate	30-AUG-2005	LOA 11-JUL-2005
					Acceptable	Acceptable as NF	LOA 23-JUN-2005
					Acceptable	21-SEP-2003	LOA 30-JUN-2005
					Acceptable	01-JAN-2003	LOA 28-JUN-2005
					Acceptable	01-AUG-2003	LOA 30-JUN-2005
					Acceptable	30-AUG-2001	LOA 27-JUN-2005

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	70,964	Simvastatin Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg,



CHEMISTRY REVIEW



_____ and 80 mg.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		
OPDRA			
EA	Acceptable	22-DEC-2005	John C. Hill, Ph.D.
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes
 No If no, explain reason(s) below:

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The Chemistry Review for NDA 21-961

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC viewpoint this NDA is approvable (AE). The outstanding issue is:

- 1.) Acceptable CGMP status for pending pre-approval establishment inspections.

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

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

- 1.) Synthon agrees to place ∞ batch of each strength on stability per stability protocols provided in Volume 5, Module 3, Section 2.P.8.2, Exhibits 1,3,5 and 7 each year, if manufactured. The results from the ongoing stability studies will be provided to the Agency in the annual reports.

b(4)

- 2.) Synthon agrees to place the manufacturing process validation batches on stability per the bracketing schedule outlined in Volume 11, Module 3, Section 2.P.8.2, Exhibit 6.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Product

The drug product presented in this NDA is an orally disintegrating tablet containing either 10, 20, 40 or 80 mg of simvastatin. The tablets are round, biconvex with the product strength debossed on one side and "ODT" on the other side. Following is a detailed description of appearance for each tablet strength.

10 mg Tablets

Yellow, round, biconvex tablets. These tablets are debossed with "S10" on one side and "ODT" on the other side.

20 mg Tablets

Peach, round, biconvex tablets. These tablets are debossed with "S20" on one side and "ODT" on the other side.

40 mg Tablets

Pink, round, biconvex tablets. These tablets are debossed with "S40" on one side and "ODT" on the other side.

80 mg Tablets

White to off-white,, round, biconvex tablets. These tablets are debossed with "S80" on one side and "ODT" on the other side.

The individual components used to manufacture Simvastatin 10 mg, 20 mg, 40 mg and 80 mg orally disintegrating tablets are listed in the following table.

Ingredients	Function	Quality
Simvastatin	lipid altering agent	USP / Ph. Eur.
Butylated hydroxyanisole		NF
Povidone		USP
Crospovidone		NF
hydroxypropylcellulose*		USP / NF
Silicified microcrystalline cellulose*		NF
Mint menthol*		in house
Sucralose		in house
Iron oxide yellow		NF
Iron oxide red		NF
Glyceryl behenate*		NF

b(4)

Excipients used to manufacture the drug product are of USP/NF quality with the exception of mint menthol and Silicified microcrystalline cellulose, which are tested in-house for quality. The drug product is composed

b(4)

During formulation development of the drug product, careful evaluation of excipients, particle size, and stability were conducted to develop a stable, rapidly disintegrating tablet. Initial formulation development, conducted with a simvastatin particle, provided fundamental information about interactions with excipients, development of a suitable optimization of parameters, evaluation of tablet size and forces on disintegration and dissolution times. The desire for increased bioavailability of simvastatin resulted in the use of a simvastatin particle. This formulation change required additional optimization of the and the formulations. Additionally, initial stability data indicated that basic excipients used in the formulation were simvastatin on stability. resolved this stability issue.

b(4)

2. Drug Substance:

The drug substance is simvastatin {[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 α] β]}. b(4)

The manufacture of this compound is described in DMF# 18384. This DMF contains complete information on the manufacture, control of materials, control of critical steps and intermediates, process validation, manufacturing process development, elucidation of structure, impurities, control of the drug substance, drug substance specifications, analytical procedures, batch analyses, justification of specifications, reference standards and materials, release testing, container closure system, drug substance stability, and stability summary and conclusions.

Simvastatin is a lipid-lowering agent that is derived synthetically from lovastatin, a fermentation product of *Aspergillus terreus*. Simvastatin is an inactive lactone, which is hydrolyzed after ingestion to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which catalyses an early step in the biosynthesis of cholesterol, limiting the rate of the total reaction.

Some of the key characteristics of Simvastatin drug substance that may influence the performance of the drug product, and were evaluated during product development include solubility, potential isomerism/polymorphism, exposure to light, alkaline media and oxidation. In order to increase the bioavailability, the simvastatin drug substance was ~~_____~~ mean particle size from around ~~_____~~ to around ~~_____~~. b(4)

B. Description of How the Drug Product is Intended to be Used

Hypercholesterolemia:

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

Coronary Heart Disease:

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

C. Basis for Approvability or Not-Approval Recommendation



This application is approvable (AE) from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. However, certain CMC deficiencies remain to be addressed. The CGMP facility inspections are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist: Same date as electronic review
Blair A. Fraser, Ph.D., Branch Chief: Same date as electronic review

C. CC Block

Margaret A Simoneau, RPH, Project Manager: Same date as electronic review

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/s/

John C. Hill
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Blair Fraser
5/3/2006 12:28:31 PM
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NDA 21-961

Simvastatin

Synthon

John C. Hill, Ph.D.
ONDQA/DPA I/DMEP/HFD-510

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III. Administrative.....10

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b(4)



CHEMISTRY REVIEW



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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					Adequate	Pending Review	27-MAY-2005
					Adequate	30-AUG-2005	LOA 11-JUL-2005
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					Acceptable	21-SEP-2003	LOA 30-JUN-2005
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CHEMISTRY REVIEW



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CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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EES	Pending		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		
OPDRA			
EA	Acceptable	22-DEC-2005	John C. Hill, Ph.D.
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes
 No If no, explain reason(s) below:

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The Chemistry Review for NDA 21-961

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC viewpoint this NDA is approvable (AE). The outstanding issues are:

- 1.) Acceptable responses to CMC review deficiencies,
- 2.) Acceptable CGMP status for pending pre-approval establishment inspections.
- 3.) Acceptable status of outstanding DMF ~~_____~~ reviews.

b(4)

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

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1.) Synthon agrees to place ~~_____~~ batch of each strength on stability per stability protocols provided in Volume 5, Module 3, Section 2.P.8.2, Exhibits 1,3,5 and 7 each year, if manufactured. The results from the ongoing stability studies will be provided to the Agency in the annual reports.

b(4)

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CHEMISTRY REVIEW



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Povidone		USP
Crospovidone		NF
hydroxypropylcellulose*		USP / NF
Silicified microcrystalline cellulose*		NF
Mint menthol* ¹		in house
Sucralose		in house
Iron oxide yellow		NF
Iron oxide red		NF
Glyceryl behenate*		NF

b(4)

Excipients used to manufacture the drug product are of USP/NF quality with the exception of mint menthol and Silicified microcrystalline cellulose, which are tested in-house for quality. The drug product is composed of the _____

b(4)

During formulation development of the drug product, careful evaluation of excipients, particle size, _____ and stability were conducted to develop a stable, rapidly disintegrating tablet. Initial formulation development, conducted with a _____ simvastatin particle, provided fundamental information about interactions with excipients, development of a suitable _____, optimization of _____ parameters, evaluation of tablet size and _____ forces on disintegration and dissolution times. The desire for increased bioavailability of simvastatin resulted in the use of a _____ simvastatin particle. This formulation change required additional optimization of the _____ and the _____ formulations. Additionally, initial stability data indicated that basic excipients used in the formulation _____ of simvastatin on stability. _____ resolved this stability issue.

b(4)

2. Drug Substance:

The drug substance is simvastatin {[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 α]]} _____

_____ The manufacture of this compound is described in DMF# 18384. This DMF contains complete information on the manufacture, control of materials, control of critical steps and intermediates, process validation, manufacturing process development, elucidation of structure, impurities, control of the drug substance, drug substance specifications, analytical procedures, batch analyses, justification of specifications, reference standards and materials, release testing, container closure system, drug substance stability, and stability summary and conclusions.

b(4)

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Some of the key characteristics of Simvastatin drug substance that may influence the performance of the drug product, and were evaluated during product development include solubility, potential isomerism/polymorphism, exposure to light, alkaline media and oxidation. In order to increase the bioavailability, the simvastatin drug substance was _____ mean particle size from around _____ to around _____

b(4)

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**C. Basis for Approvability or Not-Approval Recommendation**

This application is approvable (AE) from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. However, certain CMC deficiencies remain to be addressed. The CGMP facility inspections are pending.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

John C. Hill, Ph.D., Review Chemist: Same date as electronic review
Blair A. Fraser, Ph.D., Branch Chief: Same date as electronic review

C. CC Block

Margaret A Simoneau, RPH, Project Manager: Same date as electronic review

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/s/

John C. Hill
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