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RESEARCH**

*APPLICATION NUMBER:*

**206679Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206679

Trade Name Simvastatin Oral Suspension

Generic Name simvastatin

Applicant Name Rosemont Pharmaceuticals Limited, a Perrigo Company

Approval Date, If Known April 21, 2016

### 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

505(b)(2)

b) 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.

The clinical basis for the US application is a comparative bioavailability study, PRG-NY-14-010, that compared an 80 mg dose of Simvastatin Oral Suspension, 40 mg/5 mL strength (test article) versus 80 mg of Zocor Tablets (reference article) under fasted conditions. Pharmacokinetic measurements were taken for simvastatin and the major active form,  $\beta$ -hydroxyacid simvastatin.

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:

NA

c) Did the applicant request exclusivity?

YES  NO

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

NA

d) 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?

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#	019766	Zocor (simvastatin)
NDA#	022078	Simcor (simvastatin and Niacin)
NDA#	021687	Vytorin (simvastatin and ezetimibe)

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 similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # YES  ! NO   
! Explain:

Investigation #2  
IND # YES  ! NO   
! Explain:



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/s/  
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RICHARD E WHITEHEAD  
04/21/2016

JAMES P SMITH  
04/21/2016

**From:** [Maureen Rath](#)  
**To:** [Whitehead, Richard](#)  
**Subject:** RE: NDA 206679 simvastatin oral susp: Information request  
**Date:** Thursday, February 25, 2016 10:55:55 AM

---

Richard,  
Confirming receipt of this email. Will submit a response by February 29, 2016 officially to the application.  
Best regards,

Maureen

Maureen Rath, RAC  
Senior Manager, Regulatory Affairs  
Paddock Laboratories LLC, a Perrigo Company  
  
3940 Quebec Ave N  
Minneapolis, MN 55427  
[maureen.rath@perrigo.com](mailto:maureen.rath@perrigo.com)  
phone: 763-732-0235 (extension 32-0235)

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**From:** Whitehead, Richard [mailto:[Richard.Whitehead@fda.hhs.gov](mailto:Richard.Whitehead@fda.hhs.gov)]  
**Sent:** Thursday, February 25, 2016 9:21 AM  
**To:** Maureen Rath  
**Subject:** NDA 206679 simvastatin oral susp: Information request

Maureen,

The report of Study PRG-NY-14-010 (Page 43/589) states that the Reference Product, 80 mg simvastatin tablets, were manufactured by (b) (4). Please confirm that the 80 mg simvastatin tablets (Lot No. J 008788) used in Study PRG-NY-14-010 are the United States approved and marketed 80 mg Zocor tablets.

Provide your response to me via email by February 29, 2016, and officially submit to your application. Let me know if you have any questions and please confirm receipt of this email.

**Regards,**  
**Rich**

---

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;

(t) 301.796.4945; (f) 301.796.9712; [richard.whitehead@fda.hhs.gov](mailto:richard.whitehead@fda.hhs.gov)

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RICHARD E WHITEHEAD  
02/25/2016



NDA 206679

**GENERAL ADVICE**

Rosemont Pharmaceuticals Limited, a Perrigo Company  
Attention: Maureen Rath, RAC  
Sr. Manager, Regulatory Affairs  
3940 Quebec Avenue North  
Minneapolis, MN 55427

Dear Ms. Rath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for simvastatin oral suspension.

We also refer to your January 22, 2016, submission, containing updated draft carton and container labels.

We recommend the following be implemented prior to approval of this NDA:

- A. Carton labeling
  1. On the side panel combine the usual dosage and administration to state, "Usual Dosage and Administration: Read the Package insert before use. For oral administration."
  2. Remove the statement " [REDACTED] (b) (4) " as the intent of this statement is not clear.
- B. Container label
  1. See A.1 and revise the container label accordingly.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JAMES P SMITH  
02/10/2016

**From:** [Maureen Rath](#)  
**To:** [Whitehead, Richard](#)  
**Subject:** RE: NDA 206679 simvastatin suspension: Information Request  
**Date:** Friday, October 23, 2015 2:01:29 PM

---

Good afternoon Richard,  
Confirming receipt of this email.  
Best regards,

Maureen

Maureen Rath, RAC  
Senior Manager, Regulatory Affairs  
Paddock Laboratories LLC, a Perrigo Company



3940 Quebec Ave N  
Minneapolis, MN 55427  
[maureen.rath@perrigo.com](mailto:maureen.rath@perrigo.com)  
phone: 763-732-0235 (extension 32-0235)

Maureen

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**From:** Whitehead, Richard [mailto:[Richard.Whitehead@fda.hhs.gov](mailto:Richard.Whitehead@fda.hhs.gov)]  
**Sent:** Friday, October 23, 2015 12:59 PM  
**To:** Maureen Rath  
**Subject:** NDA 206679 simvastatin suspension: Information Request

Maureen:

In reference to NDA206679 simvastatin oral suspension, we have the following request for information:

“Provide the location in NDA 206679 or submit the datasets for adverse events, laboratory values, demographics, and treatment for Protocol PRG-NY-14-010 and Protocol PRG-NY-14-011.”

Please provide this information by November 6, 2015. Let me know if you have any questions and confirm receipt of this email.

**Regards,**  
**Rich**

---

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;  
(t) 301.796.4945; (f) 301.796.9712; [richard.whitehead@fda.hhs.gov](mailto:richard.whitehead@fda.hhs.gov)

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RICHARD E WHITEHEAD  
10/23/2015

**From:** [Maureen Rath](#)  
**To:** [Whitehead, Richard](#)  
**Subject:** RE: NDA206679 simvastatin: Information Request  
**Date:** Wednesday, September 30, 2015 11:59:19 AM

---

Hello Richard,  
Confirming receipt of your email.

Thank you,  
Maureen

Maureen Rath, RAC  
Senior Manager, Regulatory Affairs  
Paddock Laboratories LLC, a Perrigo Company



3940 Quebec Ave N  
Minneapolis, MN 55427  
[maureen.rath@perrigo.com](mailto:maureen.rath@perrigo.com)  
phone: 763-732-0235 (extension 32-0235)

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**From:** Whitehead, Richard [mailto:[Richard.Whitehead@fda.hhs.gov](mailto:Richard.Whitehead@fda.hhs.gov)]  
**Sent:** Wednesday, September 30, 2015 9:53 AM  
**To:** Maureen Rath  
**Subject:** NDA206679 simvastatin: Information Request

Maureen:

In reference to NDA206679 simvastatin oral suspension, we have the following request for information:

“Provide the location in NDA 206679 or submit the programming codes that you used to assess scaled bioequivalence for simvastatin and b-hydroxyacid simvastatin in the pivotal Study PRG-NY-14-010.”

Please provide this information by October 16, 2015. Let me know if you have any questions and please confirm receipt of this email.

**Regards,**  
**Rich**

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Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;

(t) 301.796.4945; (f) 301.796.9712; [richard.whitehead@fda.hhs.gov](mailto:richard.whitehead@fda.hhs.gov)

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RICHARD E WHITEHEAD  
10/01/2015

MEMORANDUM

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

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DATE: 8/27/2015

TO: Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 206679

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

**Rationale**

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	(b) (4)	(b) (4)

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/s/  
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SHILA S NKAH  
08/27/2015

**From:** [Nkah, Shila](#)  
**To:** [Whitehead, Richard](#)  
**Subject:** Acknowledgment of Receipt of Bioequivalence Audit Request (FRM-CONSULT-09)  
**Date:** Wednesday, August 05, 2015 4:40:00 PM  
**Attachments:** [NDA206679 OSIS Bioequivalence Audit Request \(FRM-CONSULT-09\).pdf](#)

Dear Richard,

This email acknowledges receipt of the Bioequivalence Audit Request Consult for NDA 206679 submitted on August 3, 2015. I am the OSIS PM assigned to this NDA. The consult has been sent for assessment. I will be updating you on the site inspection decision as soon as the information is available.

Feel free to contact me if you have any questions.  
 Thanks.

Shila Nkah, M.S.  
 Project Manager  
 Office of Study Integrity & Surveillance  
 Office of Translational Sciences  
 Center for Drug Evaluation and Research  
 Food & Drug Administration  
 White oak Bldg. 51, Rm. 5318  
 Phone: (301)- 796- 8347  
 Email: [shila.nkah@fda.hhs.gov](mailto:shila.nkah@fda.hhs.gov)  
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**From:** oasfda@fda.gov [mailto:oasfda@fda.gov]  
**Sent:** Monday, August 03, 2015 12:29 PM  
**To:** CDER OSI; Tran, Suong T; ct.viswanathan@fda.hhs.gov; Craig, Eileen; Hampp, Christian; Jain, Ritesh; Elmore, Calvin (Lee); Ou, Mei; Whitehead, Richard; CDER OSIS BEQ; Garrison, Nicole; Chen, Tien Mien; Hamilton-Stokes, Deveonne; ddrdsi@cder.fda.gov; Hanan, Elisabeth  
**Subject:** Finalized - NDA-206679 Biopharmaceutical Inspections Request (FRM-CONSULT-09)



[Proceed to DARRTS Welcome Screen](#)

## Finalized - Biopharmaceutical Inspections Request (FRM-CONSULT-09)

The following communication has been signed and finalized.

Functions	Communication	Communication Group	Communication Name
	FRM-CONSULT-09	CONSULT	Biopharmaceutical Inspections Request

Linked

Supporting Documents

Application Type and Number	Sponsor	Product Name (Preferred)	Submission Type and Number	Group ID	Supporting Document Number	Category/Subcategory	Submit Date	Receive Date
NDA-206679	ROSEMONT	Simvastatin Oral	ORIG-1		10	New/NDA	06/22/2015	06/22/2015
	LTD	Suspension 20 mg/5 mL and 40 mg/5 mL						

Linked Submissions

Application Type and Number	Sponsor	Preferred Product Name	Submission Type and Number	Submission Classification	Group ID

Signers

Signer	Proxy Signer	Signed Status	Signed Date
WHITEHEAD, RICHARD E.		signed	08/03/2015





APPEARS THIS WAY ON ORIGINAL

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/s/  
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SHILA S NKAH  
08/05/2015

**From:** (b) (4)  
**To:** [Whitehead, Richard](#)  
**Subject:** RE: NDA206679 Perrigo simvastatin: DMF information Request  
**Date:** Tuesday, August 04, 2015 3:12:08 PM

---

Hello.

In safe receipt of the below message, Richard.

Will be back in touch when I get some paperwork pulled together for you, as we discussed. Thank you.

Kind regards  
Lorna

(b) (4)  
[Redacted]

Stay Connected: (b) (4) | [LinkedIn](#) | [Facebook](#) | [YouTube](#)

*"Always try to be a little kinder than is necessary."*

-- J.M. Barrie

Scottish writer and dramatist

---

**From:** Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]  
**Sent:** Tuesday, August 04, 2015 2:39 PM  
**To:** (b) (4)  
**Subject:** FW: NDA206679 Perrigo simvastatin: DMF information Request

Dear (b) (4)

In reference to Perrigo's NDA 2066679, oral Simvastatin oral suspension, you are listed as the regulatory contact for the Drug Manufacturing File (DMF). We have a request for information that needs immediate response. Please respond by **noon Wednesday, August 5, 2015**. Provide your response to me via email.

Is there any Pharm/Tox information for the strawberry flavoring (Strawberry Flavoring (b) (4) [Redacted]; to be used in simvastatin oral solution) in DMF (b) (4)? If so, where this information is located in the DMF. DMF (b) (4) is held by (b) (4)

Please confirm receipt of this email and let me know if you have any questions.

**Regards,  
Rich**

---

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology  
Products;

(t) 301.796.4945; (f) 301.796.9712; [richard.whitehead@fda.hhs.gov](mailto:richard.whitehead@fda.hhs.gov)

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/s/  
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RICHARD E WHITEHEAD  
08/04/2015

**From:** [Maureen Rath](#) on behalf of [RegulatoryAffairs\\_USA](#)  
**To:** [Whitehead, Richard](#)  
**Subject:** RE: NDA206679 Simvastatin Oral Suspension: request for information  
**Date:** Thursday, July 16, 2015 2:54:20 PM

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Dear Richard,

This email is to confirm receipt of the information request. I will look into this and respond within one week of receipt.

Thank you,  
Maureen

---

**From:** Whitehead, Richard [mailto:[Richard.Whitehead@fda.hhs.gov](mailto:Richard.Whitehead@fda.hhs.gov)]  
**Sent:** Thursday, July 16, 2015 1:15 PM  
**To:** Maureen Rath  
**Subject:** NDA206679 Simvastatin Oral Suspension: request for information

Maureen:

In reference to NDA 206679 simvastatin oral suspension, we have questions regarding your 2 Form 3455 financial disclosure forms. You state that 10 investigators participated in financial arrangements or hold financial interest but did not provide an explanation on what this financial arrangement was or what steps were taken to minimize potential bias. Please explain what the financial disclosure is for these investigators. Resubmit updated forms with the requested information within one week of receipt of this information request. Let me know if you have any questions and please confirm receipt of this email.

**Regards,**  
**Rich**

---

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology  
Products;

(t) 301.796.4945; (f) 301.796.9712; [richard.whitehead@fda.hhs.gov](mailto:richard.whitehead@fda.hhs.gov)

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/s/  
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RICHARD E WHITEHEAD  
07/16/2015



NDA 206679

**NDA ACKNOWLEDGMENT**

Rosemont Pharmaceuticals Limited, a Perrigo Company  
Attention: Maureen L. Rath, RAC  
Senior Manager, Regulatory Affairs  
3940 Quebec Avenue North  
Minneapolis, MN 55427

Dear Ms. Rath:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: simvastatin 20 mg/5 mL and 40 mg/5 mL oral suspension

Date of Application: June 22, 2015

Date of Receipt: June 22, 2015

Our Reference Number: NDA 206679

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **Friday, August 21, 2015**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4945.

Sincerely,

*{See appended electronic signature page}*

Richard Whitehead, M.S.  
Senior Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RICHARD E WHITEHEAD  
07/14/2015



NDA 206679

**GENERAL ADVICE**

Rosemont Pharmaceuticals Limited, a Perrigo Company  
Attention: Maureen L. Rath, RAC  
Senior Manager, Regulatory Affairs  
3940 Quebec Avenue North  
Minneapolis, MN 55427

Dear Ms. Rath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for simvastatin oral suspension.

We also refer to your June 22, 2015, submission, containing proposed labeling for your original NDA application.

We have reviewed the referenced material and recommend the following be implemented prior to approval of this NDA:

- A. Container labels (20 mg/5 mL and 40 mg/5 mL)
  1. Provide adequate space between the numerical dose and the unit of measure for increased readability.
  2. Remove the statement “(b)(4)” from the principle display panel (PDP) since the importance of this information is not communicated in the insert labeling.
  3. Relocate the statement “Shake the bottle well before use” to the principle display panel under the strength to increase the prominence of this statement as this is important administration information.
  4. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 201.17 and 21 CFR 201.10(i)(1).
  5. Increase the prominence of the statement “Use within 1 month of opening” by using bold font as this important information needed for safe administration of the product.
  6. Add “Usual Dosage” statement to the side panel in accordance with 21 CFR 201.55.
  7. Consider providing additional differentiation between the two product strengths using color, boxing, or other means to prevent selection errors.
- B. Carton labeling
  1. See A.1 through A.5 and revise carton labeling accordingly.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JAMES P SMITH  
12/01/2015

**Office of New Drug Quality Assessment**  
**For**  
**Division of Metabolism and Endocrinology Products (DMEP)**  
**Pre-NDA Meeting Request - Written Response**

**NDA 206679**

**Submission date:** 24-FEB-2014

**Sponsor:** Paddock Laboratories

**Product Name:** simvastatin

**Dosage Form & Route of Administration:** oral suspension, (b) (4)

**Pharmacological Category & Principal Indication:** treatment of hyperlipidemia and mixed dyslipidemia

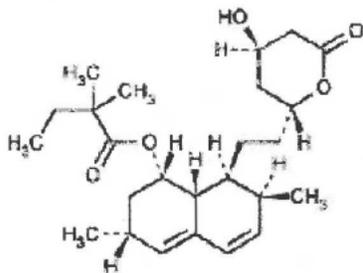
**Background:**

The sponsor proposes a 505(b)(2) application for simvastatin, which has been approved in many new and generic products. All of the approved simvastatin products are oral tablets (immediate release and extended release). The sponsor proposes an oral suspension dosage form, in two dosage strengths: 20 mg/5 mL and 40 mg/5 mL.

Butanoic acid, 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-naphthalenyl ester, [1S-[1 $\alpha$ ,3 $\alpha$ ,7 $\beta$ ,8 $\beta$  (2S\*,4S\*),8 $\alpha$  $\beta$ ]].

2,2-Dimethylbutyric acid, 8-ester with (4R,6R)-6-2-[(1S,2S,6R,8S,8 $\alpha$ R)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one [79902-63-9].

**Structural Formula:**



**Sponsor Question (copied from the briefing package) and FDA's response:**

**Question 1:** *Does the Agency agree that the proposed drug substance release tests and specifications, established by Rosemont and provided in Table 3 are appropriate?*

**Table 3: Simvastatin, USP Drug Substance Testing and Specifications**

Test	Specification	Method
Description	White or almost white crystalline powder	visual
Identification A	The IR spectra exhibits maxima at the same wavelength as the standard	USP <197>
Identification B	The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation	HPLC
Specific Rotation	+285° to +298°	USP <781S>
Loss on Drying	NMT 0.5%	USP <731>
Residue on Ignition	NMT 0.1%	USP <281>
Heavy Metals, Method II	NMT 0.002%	USP <231>
Chromatographic Purity:		HPLC
Simvastatin hydroxyacid	NMT 0.4%	
Epiclovastatin and Lovastatin	NMT 1.0%	
Methylene simvastatin	NMT 0.4%	
Acetyl simvastatin	NMT 0.4%	
Anhydro simvastatin	NMT 0.4%	
Simvastatin dimer	NMT 0.4%	
Any other individual impurity	NMT 0.1%	
Total impurities other than lovastatin and epiclovastatin	NMT 1.0%	
Assay	98.0% to 102.0% on dried basis	HPLC
Residual Solvents:		GC
	(b) (4) NMT (b) (4) ppm	
	(b) (4) NMT (b) (4) ppm	
	(b) (4) NMT (b) (4) ppm	
	(b) (4) NMT (b) (4) ppm	
	(b) (4) NMT (b) (4) ppm	
Antioxidant	(b) (4) to (b) (4) %	HPLC
Particle Size	(b) (4)	(b) (4)

NMT = Not More Than

**FDA's Response:** Your proposed drug substance specification that meets the USP monograph requirements for simvastatin is acceptable. The additional non-compendial attributes will be evaluated as part of our NDA review and comments, if any, will be conveyed to you after our review of all available data in the NDA.

**Additional comment for the sponsor:** Regarding the Drug Master File (DMF) (b) (4) for simvastatin that will support your NDA, the following information should be included in the NDA: Authorized references to the applicable DMFs, a brief section on the general properties of the drug substance, regulatory specifications of the drug substance, retest period, and a list of all manufacturing and testing facilities with a readiness statement for FDA's GMP inspections.

**Reviewer's comments for internal use only:** The proposed drug substance specification (b) (4) the USP monograph (b) (4) Residual Solvents, (b) (4). The response above is self-explanatory.

**Question 2:** Table 4 and Table 5 provide the formulations for Simvastatin Oral Suspension, 20 mg/5 mL and 40 mg/5 mL, respectively. Inactive Ingredient Database (IID) Maximum Potency information is presented in Table 6 (20 mg/5 mL) and Table 7 (40 mg/5 mL). All ingredients are within IID maximum potency limits for oral route of administration with the exception of ethylparaben and the strawberry flavor. The amount of ethylparaben used in the formulation is supported by Paddock Laboratories, LLC approved ANDA 090902, Clindamycin Palmitate HCl Granules for Oral Solution, USP (oral route of administration). Formulation information pertaining to the strawberry flavor is proprietary and not available to Rosemont but has been provided directly to Julie Van der Waag, Food and Drug Administration, Chief, Project Management Staff, by the flavor manufacturer. Does the Agency agree that the qualitative and quantitative product formulations are acceptable for filing a 505(b)(2) NDA application?

**Table 6: Simvastatin Oral Suspension 20 mg/5 mL IID Levels**

Ingredient	Formulation (% w/w)	MDI* Amount (mg/day)	IID Maximum Potency Oral Liquid** (%)	IID Maximum Potency Oral Solid** (mg)
Propylene Glycol	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Methylparaben				
Ethylparaben				
Propylparaben				
Magnesium Aluminum Silicate				
Carboxymethylcellulose Sodium				
Simethicone Emulsion				
Sodium Lauryl Sulfate				
Acesulfame Potassium				
Citric Acid Monohydrate				
Sodium Phosphate, Dibasic, Anhydrous				
Strawberry Flavor				
Water		NA	NA	NA
Simvastatin		40	NA	NA

NA = Not Applicable

MDI = Maximum Daily Intake

\*Based on MDI of 40 mg simvastatin per day. The prescribing information includes additional instructions that patients should be prescribed the 40 mg/5 mL strength product for doses of 40 mg or greater per day. \*\*Per FDA's Inactive Ingredient Database (IID) October 24, 2013 update

<sup>1</sup>Approved ANDA 040028, Kionex (sodium polystyrene sulfonate) Suspension, USP MDI equates to a greater content (mg) than the IID lists and is less than the MDI for the proposed formulation.

<sup>2</sup>Paddock Laboratories, LLC approved ANDA 090902, Clindamycin Palmitate HCl Granules for Oral Solution, USP MDI equates to  $\frac{1}{6}$  mg of ethylparaben per 70 kg person.

**Table 7: Simvastatin Oral Suspension 40 mg/5 mL IID Levels**

Ingredient	Formulation (% w/w)	MDI* Amount (mg/day)	IID Maximum Potency Oral Liquid (%)	IID Maximum Potency Oral Solid (mg)
Propylene Glycol	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Methylparaben				
Ethylparaben				
Propylparaben				
Magnesium Aluminum Silicate				
Carboxymethylcellulose Sodium				
Simethicone Emulsion				
Sodium Lauryl Sulfate				
Acesulfame Potassium				
Citric Acid Monohydrate				
Sodium Phosphate, Dibasic, Anhydrous				
Strawberry Flavor				
Water		NA	NA	NA
Simvastatin		80	NA	NA

NA = Not Applicable

MDI = Maximum Daily Intake

\*based on maximum daily intake of 80 mg simvastatin per day

\*\*Per FDA's Inactive Ingredient Database (IID) October 24, 2013 update

<sup>1</sup>Paddock Laboratories, LLC approved ANDA 040028 Kionex (sodium polystyrene sulfonate) Suspension, USP MDI equates to a greater content (mg) than the IID lists and is less than the MDI for the proposed formulation

<sup>2</sup> Paddock Laboratories, LLC approved ANDA 090902 Clindamycin Palmitate HCl Granules for Oral Solution, USP MDI equates to (b) (4) mg of ethylparaben per 70 kg person.

**FDA's Response:** Your proposed formulations are acceptable for the clinical studies in support of the NDA. Comments, if any, regarding the formulations will be conveyed to you after our complete review of all available information in the NDA. We remind you to include a (b) (4) effectiveness report in the NDA in support of the selected (b) (4) and their levels (i.e., stability acceptance criteria).

**Reviewer's comments for internal use only:** There is no safety issue with any excipient in the formulations. There is no IND submitted for this product. Therefore, the suitability of the formulations will be determined as part of the NDA review and will be based on information such as stability data and clinical experience. There is a DMF for the strawberry flavor, which will be reviewed in support of the NDA (or IND if one is submitted).

**Question 3:** *The proposed in-process tests and specifications are presented in Table 8. Does the Agency concur that the proposed in-process tests and specifications are acceptable?*

**FDA's Response:** Comments, if any, regarding the manufacturing process controls will be conveyed to you after our complete review of all available information in the NDA.

**Question 4:** *The proposed drug product release tests and specifications are presented Table 9. The proposed drug product stability tests, specifications, test intervals and storage conditions are presented in Table 11. Does the Agency agree that the stability tests and specifications are adequate and that the test intervals and storage conditions are acceptable?*

**Table 9: Drug Product Release Testing and Specifications**

Test	Specification	Method
Description	White to off-white suspension	visual
HPLC Identification	The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation	HPLC
UV Identification	The UV absorption spectra of the test solution are concordant with the Standard solution	USP <197>
Viscosity	TBD <sup>1</sup>	USP <911>
pH	6.5 to 7.0	USP <791>
Density		USP <841> Method I or II
20 mg/5 mL strength	(b) (4) to (b) (4) g/mL	
40 mg/5 mL strength	(b) (4) to (b) (4) g/mL	
Methylparaben Assay	(b) (4) % to (b) (4) %	HPLC
Methylparaben Identification	Corresponds to RRT in standard	HPLC
Ethylparaben Assay	(b) (4) % to (b) (4) %	HPLC
Ethylparaben Identification	Corresponds to RRT in standard	HPLC
Propylparaben Assay	(b) (4) % to (b) (4) %	HPLC
Propylparaben Identification	Corresponds to RRT in standard	
Chromatographic Purity:		HPLC
(b) (4)	≤ (b) (4) %	
Any other individual impurity	NMT (b) (4) %	
Total impurities	NMT (b) (4) %	
Assay	95.0% to 105.0% of label claim	HPLC
Dissolution	NLT (b) (4) % Q of the labeled amount of simvastatin dissolved in (b) minutes	USP <711>
Deliverable Volume	Meets USP requirements	USP <689>
Uniformity of Dosage Unit	L1 ≤ (b) (4) and L2 ≤ (b) (4)	USP <905>
Microbial Limits Tests		USP <61> and USP <62>
Total Aerobic Microbial Count	NMT (b) cfu/g	
Total Molds and Yeasts Count	NMT (b) cfu/g	
Absence of <i>Escherichia coli</i>	Meets USP for Absence of <i>Escherichia coli</i>	

<sup>1</sup>TBD = To Be Determined (data currently being collected on submission batches, specification will be finalized prior to NDA submission)

NLT = Not Less Than; NMT=Not More Than

**Table 11: Proposed Stability Requirements**

Test*	Specification	Method
Description	White to off-white suspension	visual
Resuspendability	The suspension is readily dispersed after shaking. (b) (4)	visual
Sedimentation	The clear liquid is not more than (b) (4)	visual
Viscosity	TBD†	USP <912>
pH	6.4 to 7.2	USP <791>
Density		
20 mg/5 mL strength	(b) (4) to (b) (4) g/mL	USP <841>
40 mg/5 mL strength	(b) (4) to (b) (4) g/mL	Method I or II
Methylparaben Assay	(b) (4) to (b) (4) %	HPLC
Ethylparaben Assay	(b) (4) to (b) (4) %	HPLC
Propylparaben Assay	(b) (4) to (b) (4) %	HPLC
Chromatographic Purity:		HPLC
(b) (4)	≤ (b) (4) % (b) (4)	
Any other individual impurity	NMT (b) (4) % (b) (4)	
Total impurities	NMT (b) (4) % (b) (4)	
Assay	(b) (4) to (b) (4) % of label claim	HPLC
Deliverable Volume	Meets USP requirements	USP <689>
Uniformity of Dosage Unit	L1 ≤ (b) (4) and L2 ≤ (b) (4)	USP <905>
Dissolution	NLT (b) (4) % (Q) of the label claim of Simvastatin dissolved in (b) (4) minutes.	USP <711>
Microbial Limits Tests		USP <61> and USP <62>
Total Aerobic Microbial Count	NMT (b) (4) cfu/g	
Total Molds and Yeasts Count	NMT (b) (4) cfu/g	
Absence of <i>Escherichia coli</i>	Meets USP for Absence of <i>Escherichia coli</i>	
Anti-Microbial Effectiveness Testing**	Meets USP	USP <51>

†TBD = To Be Determined (data currently being collected on submission batches, specification will be finalized prior to NDA submission)

NLT = Not Less Than; NMT=Not More Than

\*All tests performed at each time point (0, 3, 6, 9, 12, and 24 months shelf conditions and 0, 3, and 6 months accelerated) after storage inverted and upright unless otherwise noted.

\*\*performed at time 0, 12, and 24 months (shelf conditions) and 0, 3, and 6 months (accelerated conditions) on-side orientation, on submission batches only.

**FDA's Response:** Your proposed drug product specifications are acceptable for the clinical studies in support of the NDA. As your product is an oral suspension, Particle Size Distribution should be added to the release and stability testing program, and Leachables should be added to the stability testing program, or a justification for the omission of either attribute should be included in the NDA. We note that you propose two separate specifications, for release and for stability. As there can be only one regulatory specification for the drug product in the NDA, you should combine the two specifications into one and note the specific tests that are conducted only at release or only during stability testing. Comments, if any, regarding the specification will be conveyed to you after our complete review of all available information in the NDA.

**Additional comment for the sponsor:** In support of your proposed acceptance criteria for degradants, provide the following in the NDA:

- Information on the potential impurities arising from the drug interaction with excipients and/or container closure system, and from potential degradation pathways.
- Safety information to qualify any proposed impurity/degradants limit that exceeds the applicable ICH qualification threshold for the maximum daily dose of your product (we refer

you to ICH Q3B(R2) Impurities in New Drug Products at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf>.

Reviewer's comments for internal use only: The proposed drug product specifications follow ICH guidelines. There is no justification for any attribute or acceptance criteria in the specification. The response above is self-explanatory.

**Question 5:** *Rosemont proposes to include 6 months of accelerated ( $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ ) and 6 months of long term shelf ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ ) stability data from three batches of each strength of drug product (at upright and inverted orientations) in the initial NDA application. Additional supportive stability data from one batch of Simvastatin Oral Suspension 20 mg/5 mL and two batches of Simvastatin Oral Suspension 40 mg/5 mL will also be submitted. Supportive stability data will include long term shelf stability data ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /ambient humidity) for all three lots through 24 months and 6 months accelerated ( $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ /ambient humidity) stability data on one lot of Simvastatin Oral Suspension 40 mg/5 mL. It is noted that the flavor used for the 40 mg/5 mL supportive stability batches contains (b) (4) flavor; the proposed formulation contains strawberry flavor. The 20 mg/5 mL supportive stability batch and the 20 mg/5 mL exhibit batches both contain the same strawberry flavor as will be used in the proposed 40 mg/5 mL formulation. Does the Agency agree to accept the proposed primary and supportive stability data for the initial 505(b)(2) NDA application?*

**FDA's Response:** You have not provided sufficient information in support of your question. For the filing of the NDA, submit a minimum of 12 months of long term stability data on at least three primary batches drug product. These primary batches will be of the same formulation and packaged in the same container closure system as proposed for marketing, and their manufacturing process should adequately simulate that of the to-be-marketed product. Any difference should be discussed and justified. We refer you to ICH Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products (<http://www.fda.gov/cder/guidance/5635fnl.htm>) for additional guidelines on product stability testing. Stability testing should be performed on product stored in both the upright and inverted positions. Testing for leachables may be required based on findings from the extraction studies of the container closure components (using the drug product or placebo vehicle).

Reviewer's comments for internal use only: The sponsor did not provide any information on the supportive stability batches that can adequately bridge them to the proposed product of the NDA. (b) (4)

**Additional comments for the sponsor:** We remind you to include a complete list of all testing and manufacturing facilities used for the commercial drug substances and drug product in Form 356h of the NDA, with contact information and a statement that all facilities will be ready for the GMP inspection at the time of the NDA submission.

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SUONG T TRAN  
03/12/2014

DANAE D CHRISTODOULOU  
03/12/2014

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 206679		
Proprietary Name: Simvastatin Oral Suspension Established/Proper Name: simvastatin Dosage Form: oral suspension		Applicant: Rosemont Pharmaceuticals, LTD Agent for Applicant (if applicable): Perrigo Pharmaceuticals
RPM: Richard Whitehead, M.S.		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p> <input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)                      Date of check:                 </p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
<b>Actions</b>		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>April 21, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 3- New dosage form  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information were issued</li> </ul>	<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
❖ Exclusivity	
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?</li> <li>• If so, specify the type</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>	
Copies of all action letters <i>(including approval letter with final labeling)</i>	Approval; 4-21-16
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included see final PI in Approval Letter
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included see final carton and container labeling in Approval Letter
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>Review(s) <i>(indicate date(s))</i></li> </ul>	None requested
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: PLR review 4-7-16; 9-17-15 DMEPA: 4-08-16; 1-29-16; 2-17-16 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> None SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: see OPQ review Other: <input checked="" type="checkbox"/>
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	9-11-15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	505(b)(2) assessment: 4-20-16
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>2-17-16</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i> )	7-14-15; 7-16-15; 8-04-15; 10-01-15; 10-23-15; 12-01-15; 2-10-16; 2-25-16
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    Written Responses issued 3-12-14
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    4-21-16
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    see Division Director Summary Review
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	

❖ <b>Clinical Reviews</b>	
• Clinical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)	4-08-16; 8-13-15
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	See clinical review dated 4-8-16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) <sup>5</sup>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</li> <li>• REMS Memo(s) and letter(s) (indicate date(s))</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 3-17-16; 8-17-15
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3-22-16; 8-18-15
❖ 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	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested 8-27-15; 8-5-15
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3-17-16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input 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> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

<b>Day of Approval Activities</b>	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done