CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208400Orig1s000
208400Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208400/Original-2 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Xatmep Established/Proper Name: Methotrexate Dosage Form: Oral solution, 2.5 mg/mL		Applicant: Silvergate Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Sadaf Nabavian		Division: Division of Pulmonary, Allergy, and Rheumatology Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes ☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is 4/25/2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Complete Response (6/29/2016)
❖ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] 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.
[2] 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).
[3] 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):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes Orphan
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval (April 25, 2017) Complete Response (6/29/2016)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 4/18/2017
• Original applicant-proposed labeling	☒ Included 8/31/2015
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 2/6/2017
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters: Acceptable 1/18/17, Acceptable 2/29/16, Denied 11/27/15 Reviews: 1/17/17, 2/29/16, 11/24/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 11/12/2015 None DMEPA: ☒ 2/10/17, 3/28/16; 2/17/16 None DMPP/PLT (DRISK): ☒ None OPDP: ☒ 3/21/17, 6/8/2016 None SEALD: ☐ None CSS: ☐ None Product Quality ☒ None Other: ☒ DPMH 4/13/2017, 6/20/16 None
Administrative / Regulatory Documents	

❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Filing Review: 10/30/15 ☐ Not a (b)(2) Clearance obtained on 3/22/17 and 6/23/16 (see emails)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC NA If PeRC review not necessary, explain: Orphan drug exclusivity	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(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)*	IRs: 4/20/17, 4/18/17, 4/7/17, 3/30/17, 3/3/17, 2/27/2017, 11/9/16, 5/31/16, 5/26/16, 4/15/16, 3/15/16, 2/25/16, 1/14/16, 1/8/16, 11/18/15, 11/13/15, 9/14/15
❖ 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)	Labeling 505(b)(2) Assessment (4/25/17) Methods Verification Report Summary (3/7/16)
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None Second Cycle (refer to CDTL Review dated 4/25/17), first cycle 6/29/2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4/25/2017 (2nd cycle), 1st cycle 6/4/2016
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Clinical review(s) *(indicate date for each review)*	3/28/17, 7/1/16, 5/26/16, 10/15/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review: 7/1/2016 (also included in the clinical review field)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • 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)*	☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested March 7 and 8, 2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None

[5] 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).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 3/31/17, 6/2/16, 10/27/15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested OSIS Memos: 3/8/16, 3/7/16, and 12/14/15
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5/26/16, 10/28/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None Cycle 2: 4/21/2017 Cycle 1: 6/15/16, 6/3/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☒ Review & Environmental Impact Statement *(indicate date of each review)*	Page 11 of Quality Review dated 4/21/2017 and Section 1.12.14, page 53-54, from 6/3/2016 Product Review

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

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 4/20/2017 ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done N/A *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done 4/25/2017
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done N/A
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done N/A
❖ Ensure Pediatric Record is accurate	☐ Done N/A
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done 4/25/2017

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

/s/

SADAF NABAVIAN
05/01/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208400/Original-1 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Xatmep Established/Proper Name: methotrexate Dosage Form: oral solution, 2.5 mg/mL.		Applicant: Silvergate Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Michael Gwathmey, RN		Division: Division of Hematology Products/OHOP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is April 25, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ CR, 6/29/16
❖ 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 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain	☐ Received
❖ Application Characteristics[3]	

[1] 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.
[2] 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).
[3] 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)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP, 4/25/17; CR, 6/29/16
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 4/24/17
• Original applicant-proposed labeling	☒ Included 8/31/15
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters: 1/18/17, 2/29/16, 11/27/15 Reviews: 1/17/17, 2/29/16, 11/24/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 11/12/2015 DMEPA: ☒ 2/10/17, 3/28/16, 2/17/16 DMPP/PLT (DRISK): ☒ None OPDP: ☒ 3/21/17, 6/8/2016, SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ DPMH 4/13/17, 6/20/16 ☒ ADL 3/7/17
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review: 10/30/15 ☐ Not a (b)(2) Clearance obtained on 3/28/17, 6/23/16
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan drug	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(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)*	IRs: 4/20/17, 4/18/17, 4/7/17, 3/30/17, 3/3/17, 2/27/17, 5/31/16. 5/26/16, 4/15/16, 3/15/16, 2/25/16, 1/22/16, 1/14/16, 1/8/16, 11/18/15, Filing Letter: 11/13/15 Acknowledgement Letter: 11/9/16, 9/14/15
❖ 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	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 5/21/13
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	4/7/15

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	4/24/17, 6/29/16
Cross-Discipline Team Leader Review *(indicate date for each review)*	6/9/16
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ 5/27/16
• Clinical review(s) *(indicate date for each review)*	3/20/17, 5/24/16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review: see page 14 of the clinical review dated 5/24/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • 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)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None

[5] 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).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 3/31/17, 6/2/16, 4/15/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ OSIS Memos: 3/8/16, 3/7/16, 12/14/15
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 5/27/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ 4/21/17, 6/15/16, 6/3/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☒ Review & Environmental Impact Statement *(indicate date of each review)*	Page 53, 5/31/16 (Reviewer Sam Bain)
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 4/20/17 ☐ Withhold recommendation ☐ Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done n/a *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done n/a
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done n/a
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done n/a
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

MICHAEL V GWATHMEY
04/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400, Original-1
NDA 208400, Original-2

INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION

Silvergate Pharmaceuticals, Inc.
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Attention: Susan J. Prather
Director, Regulatory Affairs

Dear Ms. Prather:

Please refer to your New Drug Application (NDA) dated October 25, 2016, received October 25, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xatmep (methotrexate) Oral Solution, 2.5 mg/mL.

We also refer to your amendments dated February 6, March 17, April 7 and 18, 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letters for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendments dated February 6, March 17, April 7 and 18, 2017.

If you have any questions, call me, Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, PharmD
Sr. Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SADAF NABAVIAN
04/20/2017

From: Gwathmey, Michael
To: "Michael Beckloff"
Cc: Susan Prather; Nabavian, Sadaf
Subject: RE: NDA 208400 Xatmep (methotrexate) Oral Solution
Date: Tuesday, April 18, 2017 5:38:00 PM

Mr. Beckloff,

This e-mail is in reference to NDA 208400 and the request (via e-mail) for a tele-conference regarding the concerns that you had expressed on 4/14/17. The Agency feels that a tele-conference will not be necessary at this time, given that the responses that you provided are still in review. However we will contact you if any additional information relating to the approval of the application is needed. Thank you and feel free to contact either Sadaf Nabavian or myself if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Michael Beckloff [mailto:michael.beckloff@silvergatepharma.com]
Sent: Monday, April 17, 2017 1:54 PM
To: Gwathmey, Michael
Cc: Susan Prather
Subject: Re: NDA 208400 Xatmep (methotrexate) Oral Solution

Michael:

Thank you very much.

Michael

Michael C. Beckloff
Chief Development Officer
Silvergate Pharmaceuticals, Inc.
7300 West 110th Street, Suite 950
Overland Park, Kansas 66210

Mobile: (b) (6)
michael.beckloff@silvergatepharma.com

From: "Gwathmey, Michael" <Michael.Gwathmey@fda.hhs.gov>
Date: Monday, April 17, 2017 at 6:19 AM
To: Michael Beckloff <michael.beckloff@silvergatepharma.com>
Cc: "Iser, Robert" <Robert.Iser@fda.hhs.gov>, " (b) (4) Susan Prather <susan.prather@silvergatepharma.com>, "Nabavian, Sadaf" <Sadaf.Nabavian@fda.hhs.gov> **Subject:** RE: NDA 208400 Xatmep (methotrexate) Oral Solution

Mr. Beckoff,

Regarding NDA 208400, we acknowledge receipt of your e-mail below and will forward your request to the reviewing team for a response. Thank you and feel free to contact either Sadaf or myself if you have any further questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Michael Beckloff [mailto:michael.beckloff@silvergatepharma.com]
Sent: Friday, April 14, 2017 4:01 PM
To: Gwathmey, Michael; Nabavian, Sadaf
Cc: Farrell, Ann T; Chowdhury, Badrul A; Iser, Robert; (b) (4); Susan Prather
Subject: NDA 208400 Xatmep (methotrexate) Oral Solution

Michael/Sadaf:

We have a very urgent situation regarding our Xatmep NDA and respectfully request a meeting or telephone conference to discuss the impact on our NDA of the recent Pre-Approval Inspection (PAI) conducted at (b) (4) and the resulting (b) (4), Form FDA
483.

It is our understanding that approval of our NDA may be withheld pending resolution of the four (4) findings cited in the (b) (4), Form FDA 483. It is also our understanding that (b) (4) provided a written response to each of the Form FDA 483 observations on (b) (4). For the reasons discussed below, we believe that our NDA is ready for approval.

Because of the critical nature of the situation and the very short timeline associated with our April

25, 2017, PDUFA date for NDA 208400, I have taken the liberty to copy Ann Farrell, M.D., Badrul Chowdhury, M.D., Ph.D., Robert Iser, OPQ/Process and Facilties, (b) (4) (b) (4) District Office on this e-mail.

The following is the background information we would like to discuss with the Agency:

1. There have been two PAIs conducted for our Xatmep NDA No. 208400. The first occurred on (b) (4), and the most recent on (b) (4), (b) (4). It is very important to note that no specific deficiencies were identified for any aspect of our Xatmep product during either of the FDA Pre-Approval Inspections.

   During the most recent PAI, four (4) deficiencies were identified. A copy of the FDA 483, redacted by (b) (4) is attached. Although the investigators noted that significant progress has been made by (b) (4) to improve GMP compliance since the inspections conducted in (b) (4), it is our understanding that approval of Xatmep may be withheld.

   On (b) (4) provided a complete written responses to each of the items listed on the FDA 483.

2. (b) (4) has implemented organizational and procedural changes to enhance GMP compliance and to help eliminate these types of findings from occurring in the future.

3. There were no specific deficiencies noted for Xatmep product during either of the two FDA PAI inspections.

   - The Xatmep oral formulation is a (b) (4) solution produced using a (b) (4) (b) (4) process. The process is tightly controlled and produces a very high- quality product.

   - All inquiries from reviewers were responded to promptly and fully during the review.

   - We are not aware of any other outstanding questions or issues pending with either of the NDA reviewing divisions. Minor edits to the prescribing information were emailed to the Agency yesterday.

4. Silvergate is aware that other drug products manufactured by (b) (4) have received marketing approval by FDA between the (b) (4) and most recent inspections, i.e., (b) (4) and (b) (4) We have not been able to identify the specific ANDA or NDA number, but it is our understanding that (b) (4) also received approval for an (b) (4) product in (b) (4).

5. Our Xatmep product has been designated as an Orphan Drug for each of the two pediatric indications provided in NDA 208400. There is a significant unmet medical need as no other

oral liquid pediatric formulation is available for methotrexate.

&#8226 The patient population for acute lymphoblastic leukemia (ALL) is approximately 3,000 patients (0 – 14), with most patients 2 - 5 years of age.

&#8226 The patient population for polyarticular juvenile idiopathic arthritis (pJIA) is approximately 118,000 patients. Typical patients are 5 - 16 years of age.

&#8226 Many of these patients suffer from needle phobia.

6. In the absence of a methotrexate oral solution such as Xatmep, patients are prescribed compounded methotrexate suspension or instructed to crush methotrexate tablets, raising significant safety concerns for patients and caregivers.

&#8226 There are significant product quality/safety concerns associated with compounded methotrexate formulations provided to pediatric patients.

&#8226 There are significant product quality/safety concerns when pediatric patients are dosed with crushed tablets.

&#8226 There are very significant safety/environment concerns for caregivers and their families associated with crushing tablets that can produce cytotoxic dust contaminating the home setting.

7. As an Orphan drug, Xatmep is expected to be a very low-volume product as compared to other non-Orphan drug pediatric formulations. Silvergate will continue to provide independent review over all steps of manufacture, sampling, and testing.

&#8226 At present, process validation is scheduled to begin the 3rd week of May and will be completed by the end of July. This is well after the (b) (4) commitment to resolve the existing backlogs cited in the FDA 483 observation 2.

&#8226 The total number of units produced for process validation (3 batches) will be (b) (4), totaling (b) (4) units.

&#8226 Using April 25th as the approval date, the projected launch date will be (b) (4) Again, well after the (b) (4) commitment.

&#8226 Silvergate anticipates that the three validation batches will supply commercial needs until (b) (4). Approximately, (b) (4) units will be distributed in (b) (4) with (b) (4) units distributed in (b) (4) for a total of (b) (4) units through the end of (b) (4).

&#8226 Silvergate will continue to provide manufacturing and quality oversight for the validation and commercial batches manufactured by (b) (4) Specifically, Silvergate

will be present during manufacture and will review all raw laboratory data. Final approval and release is the responsibility of Silvergate Pharmaceuticals.

Based on the information provided above, as well as our understanding that (b) (4) has provided the Agency with complete, thorough, and adequate responses to the (b) (4), FDA 483 observations, we respectfully request that the manufacturer, (b) (4), and the manufacture and control of our Xatmep product be recommended for approval.

Please let us know if a meeting or teleconference will be possible. We will make ourselves available at any time. If a teleconference is best, we are happy to schedule the call at 12:00 noon or 5:00 pm if this time is more convenient for the Agency.

Thank you in advance for your consideration. We look forward to meeting with the Agency to resolve this urgent and very important matter.

Best regards.

Michael

Michael C. Beckloff
Chief Development Officer
Silvergate Pharmaceuticals, Inc.
7300 West 110th Street, Suite 950
Overland Park, Kansas 66210

Mobile: (b) (6)
michael.beckloff@silvergatepharma.com

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/s/

MICHAEL V GWATHMEY
04/18/2017

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2017

To: Michael C. Beckloff Chief Development Officer	**From:** CDR Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager
Company: Silvergate Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: NA	**Fax number:** 301-796-9728
Phone number: (b) (6) **Email Address:** michael.beckloff@silvergatepharma.com	**Phone number:** 301-796-2777

Subject: NDA 208400; FDA Labeling Comments

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES xNO

NDA 208400, Original-1
NDA 208400, Original-2
Methotrexate Oral Solution
Silvergate Pharmaceuticals, Inc.

Dear Ms. Prather:

Your NDA submission dated October 25, 2016, for methotrexate oral solution is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by noon, Wednesday, April 12, 2017, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777, or contact Michael Gwathmey, Regulatory Project Manager, at 301-796-8498.

Drafted by: SNabavian/4.7.2017

Cleared by: BWheeler (for LJafari)/4.7.2017

Finalized by: SNabavian/4.7.2017

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/s/

SADAF NABAVIAN
04/07/2017

NDA 208400, Original-1
NDA 208400, Original-2
Methotrexate Oral Solution
Silvergate Pharmaceuticals, Inc.

Dear Ms. Prather:

Your NDA submission dated October 25, 2016, for methotrexate oral solution is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by COB, Wednesday, April 5, 2017, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777, or contact Michael Gwathmey, Regulatory Project Manager, at 301-796-8498.

Drafted by: SNabavian/3.28.2017

Cleared by: LJafari/3.28.2017

Finalized by: SNabavian/3.28.2017

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/s/

SADAF NABAVIAN
03/30/2017

(template to be finalized in DARRTS upon action 2nd cycle)

Nabavian, Sadaf

ɔm: Holovac, Mary Ann
ɹt: Wednesday, March 22, 2017 5:03 PM
To: Nabavian, Sadaf; Gwathmey, Michael
Cc: Goldstein, Beth A (Duvall); Sharma, Khushboo; Holovac, Mary Ann; Kim, Tamy; Boehmer, Jessica
Subject: NDA 208400-Methotrexate Solution - cleared for action
Attachments: N208400-ORP bridge.docx

Sadaf/Michael,

We discussed the subject application at last Monday's 505(b)(2) clearance meeting. The application is cleared for action from a 505(b)(2) perspective.

Please make the following changes to the draft assessment before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the resubmission arrives so that we can add it anew to our clearance queue.

- *Q3: Please use the latest version of the bridge (attached) as cleared by ORP and agreed upon by the division in response to this question*

Please let me know if you have any questions.

ɹry Ann

From: Holovac, Mary Ann
Sent: Monday, March 20, 2017 8:58 AM
To: Nabavian, Sadaf
Cc: Gwathmey, Michael
Subject: RE: NDA 208400-Methotrexate Solution

Hi Sadaf/Michael,

Please see attached comments from ORP with respect to the bridge on the Methotrexate NDA. Does the division have any comments on the revised bridge? Please advise.

Thank you.
Mary Ann

From: Nabavian, Sadaf
Sent: Wednesday, March 08, 2017 10:29 AM
To: Holovac, Mary Ann
Cc: Gwathmey, Michael
Subject: RE: NDA 208400-Methotrexate Solution

ɹ Mary Ann,

Thank you for your feedback. The labeling is currently in the negotiation stage and attaching the recent labeling communication issued to the applicant on 2/27 (as track changes) in which they plan to submit the updated label by end of this week which we can forward it your way as well. Please let me know if any additional information is needed. Thanks so much, Sadaf

---

From: Holovac, Mary Ann
Sent: Wednesday, March 08, 2017 10:06 AM
To: Nabavian, Sadaf
Cc: Gwathmey, Michael
Subject: RE: NDA 208400-Methotrexate Solution

Hi Sadaf,
It appears everything is in order for these applications for review by the committee. I noted in the last cycle that labeling was still under discussion. Do you have updated annotated labeling? What is the status of the labeling?
Thank you.
Mary Ann

From: Nabavian, Sadaf
Sent: Tuesday, March 07, 2017 1:46 PM
To: Holovac, Mary Ann
Cc: Gwathmey, Michael
Subject: NDA 208400-Methotrexate Solution

Hello CAPT Holovac,

Please find the attached 505(b)(2) template for the split NDA 208400-Original 1 (DHP) and Original 2 (DPARP) for methotrexate oral solution that was resubmitted to the FDA on October 25, 2016, with the PDUFA date of April 25, 2017. As you recall, we took a CR action back in June 29, 2016 (due to facility issues), and you and your dear committee had cleared the template but advised that we resend you the updated form during the second review cycle. Of note, we are gearing towards an approval action unless something new arises between now and April 25th. Please let me know if you need any additional information.

I have also cc'd LCDR Gwathmey, the RPM from DHP, to keep him in the loop.

Thanks and Happy Tuesday!

Sadaf

Sadaf Nabavian, Pharm.D.
CDR, U.S Public Health Service
Senior Regulatory Project Manager
FDA/CDERII/OND/DPARP

10903 New Hampshire Ave
Bldg. 22, Rm. 3306
Silver Spring, MD 20993-0002
Phone: (301) 796-2777

Cc: Gwathmey, Michael
Subject: RE: NDA 208400-Methotrexate Solution

Hi Sadaf/Michael,

. ıease see attached comments from ORP with respect to the bridge on the Methotrexate NDA. Does the division have any comments on the revised bridge? Please advise.

Thank you.
Mary Ann

From: Nabavian, Sadaf
Sent: Wednesday, March 08, 2017 10:29 AM
To: Holovac, Mary Ann
Cc: Gwathmey, Michael
Subject: RE: NDA 208400-Methotrexate Solution

Hi Mary Ann,

Thank you for your feedback. The labeling is currently in the negotiation stage and attaching the recent labeling communication issued to the applicant on 2/27 (as track changes) in which they plan to submit the updated label by end of this week which we can forward it your way as well. Please let me know if any additional information is needed. Thanks so much, Sadaf

---

ɒm: Holovac, Mary Ann
ɹent: Wednesday, March 08, 2017 10:06 AM
To: Nabavian, Sadaf
Cc: Gwathmey, Michael
Subject: RE: NDA 208400-Methotrexate Solution

Hi Sadaf,
It appears everything is in order for these applications for review by the committee. I noted in the last cycle that labeling was still under discussion. Do you have updated annotated labeling? What is the status of the labeling?
Thank you.
Mary Ann

From: Nabavian, Sadaf
Sent: Tuesday, March 07, 2017 1:46 PM
To: Holovac, Mary Ann
Cc: Gwathmey, Michael
Subject: NDA 208400-Methotrexate Solution

Hello CAPT Holovac,

Please find the attached 505(b)(2) template for the split NDA 208400-Original 1 (DHP) and Original 2 (DPARP) for methotrexate oral solution that was resubmitted to the FDA on October 25, 2016, with the PDUFA date of April 25, ?017. As you recall, we took a CR action back in June 29, 2016 (due to facility issues), and you and your dear committee d cleared the template but advised that we resend you the updated form during the second review cycle. Of note, we ɹre gearing towards an approval action unless something new arises between now and April 25th. Please let me know if you need any additional information.

From: Gwathmey, Michael
To: "Susan Prather"
Cc: Nabavian, Sadaf
Subject: RE: NDA 208400 Labeling Comments
Date: Friday, March 03, 2017 4:39:00 PM

Ms. Prather,

This e-mail is in reference to NDA 208400. Regarding the question stated below, your plan ("we intend to add them to the references included in Section 5.4") is acceptable. Thank you and feel free to contact us if you have any further questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Susan Prather [mailto:susan.prather@silvergatepharma.com]
Sent: Friday, March 03, 2017 10:42 AM
To: Gwathmey, Michael; Nabavian, Sadaf
Cc: Michael Beckloff
Subject: NDA 208400 Labeling Comments

Good morning Michael and Sadaf,

We are preparing our response to your comments.
Regarding the request to have the dosing references you've presented submitted to our NDA, we intend to add them to the references included in Section 5.4.
Please advise if this will be acceptable?

Thank you and feel free to call me if that is more convenient.

Best regards,
Susan

Susan J. Prather
Director Regulatory Affairs
Silvergate Pharmaceuticals, Inc.
7300 W. 110th Street, Suite 950
Overland Park, KS 66210

913.871.1230 (o)
(b) (6) **(m)**

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/s/

MICHAEL V GWATHMEY
03/03/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400-Original 1
NDA 208400-Original 2

LABELING COMMENTS

Silvergate Pharmaceuticals, Inc.
Attention: Susan J. Prather
Director, Regulatory Affairs
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Dear Ms. Prather

Please refer to your New Drug Application (NDA) dated October 25, 2016, received October 25, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xatmep (methotrexate) Oral Solution, 2.5 mg/mL.

On June 22, 2016, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by March 10, 2017. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Based on FDA's review of published literature in connection with FDA's Prescription Drug Labeling Improvement and Enhancement Initiative and independent of your 505(b)(2) application, FDA has modified your draft proposed labeling to reflect the Agency's current recommended dose and dose regimen for orally administered methotrexate products indicated for

treatment of pediatric patients with ALL as part of a multi-phase, combination chemotherapy maintenance regimen, and to make other methotrexate labeling updates. We note that these proposed labeling revisions are not specific to Silvergate's proposed methotrexate oral solution product. FDA intends to consider recommending these proposed updates, to the extent applicable, to labeling for other methotrexate drug products as well. With respect to the recommended dose and dose regimen, the appropriateness of the 20 mg/m^2 dose and weekly dose regimen is apparent to FDA from published literature, including the following published studies:

- Hunger S, Mullighan C, 2015, Acute Lymphoblastic Leukemia in Children, N Engl J Med, 373:1541-1552.
- Angiolillo AL, Schore RJ, Devidas M, Borowitz MJ, et al., 2014, Pharmacokinetic and pharmacodynamic properties of calaspargase pegol E. coli L-asparaginase in the treatment of patients with acute lymphoblastic leukemia: Results from Children's Oncology Group Study AALL07P4, J Clin Oncol, 32:3874-3882.
- Borowitz MJ, Wood BL, Devidas M, Loh ML, et al., 2015, Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232, Blood.126:964-97.
- Bowman WP, Larsen EC, Devidas M, Linda SB, et al., 2011 Augmented therapy improves outcome for pediatric high risk acute lymphocytic leukemia: Results of Children's Oncology Group trial P9906, Pediatr Blood Cancer; 57:569-577.
- Dreyer Z, Dinndorf P, Camitta BM, Sather H, et al., 2011, Analysis of the role of hematopoietic stem-cell transplantation in infants with acute lymphoblastic leukemia in first remission and MLL gene rearrangements: A report from the Children's Oncology Group, J Clin Oncol, 29:214-222. PMCID: PMC3058277. 1953/CCG-1953, P9407 (POG-9407);
- Riehm H, Gadner H, Henze G, Langermann H-J, Odenwald E,1980, The Berlin Childhood Acute Lymphoblastic Leukemia Therapy Study, 1970-1976, Am J Pediatr Hematol Oncol, 2:299-306.
- Schultz KR, Bowman WP, Aledo A, Slayton WB et al., 2009, Improved early event-free survival with imatinib in philadelphia chromosome-positive acute lymphoblastic leukemia: A Children's Oncology Group study, J Clin Oncol, 27:5175-5181.

We request that you amend your 505(b)(2) application to include the published studies that we have identified.

If you have any questions, call me at (301) 796-8498 or Dr. Sadaf Nabavian at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Michael Gwathmey, RN
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

31 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MICHAEL V GWATHMEY
02/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Silvergate Pharmaceuticals, Inc.
7300 W 110th Street
Suite 950
Overland Park, KS 66210

ATTENTION: Michael C. Beckloff
Chief Development Officer

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated and received August 31, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Oral Solution, 2.5 mg per mL.

We also refer to your correspondence, dated and received December 6, 2016, requesting review of your proposed proprietary name, Xatmep.

We have completed our review of the proposed proprietary name, Xatmep, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 6, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application for the Division of Hematology Products, contact Michael Gwathmey, Regulatory Project Manager in the Office of New Drugs, at (301) 796-8498. For any other information regarding this application for the Division of Pulmonary, Allergy, and Rheumatology, contact Sadaf Nabavian, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
01/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400, Original-1
NDA 208400, Original-2

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Silvergate Pharmaceuticals, Inc.
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Attention: Susan J. Prather
Director, Regulatory Affairs

Dear Ms. Prather:

We acknowledge receipt on October 25, 2016, of your October 25, 2016, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Xatmep (methotrexate) Oral Solution, 2.5 mg/mL.

We consider this a complete, class 2 response to our June 29, 2016, action letter. Therefore, the user fee goal date is April 25, 2017.

If you have any questions, please contact the regulatory project managers listed below.

NDA 208400/Original-1	Michael Gwathmey, Division of Hematology Products, 301-796-8498
NDA 208400/Original-2	Sadaf Nabavian, Division of Pulmonary, Allergy, and Rheumatology Products, 301-796-2777

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SADAF NABAVIAN
11/09/2016

1st cycle

Nabavian, Sadaf

From: Holovac, Mary Ann
Sent: Thursday, June 23, 2016 12:36 PM
To: Boehmer, Jessica
Cc: Nabavian, Sadaf; Kim, Tamy; Stradley, Sara; Goldstein, Beth A (Duvall); Holovac, Mary Ann
Subject: NDA 208400 (MTX oral solution) orig1 and orig2- cleared for complete response

Follow Up Flag: Follow up
Flag Status: Flagged

Jessica/Sadaf,

We discussed this application at Monday's 505(b)(2) clearance meeting and you provided input (email below) based upon the committee discussion. This application is **cleared for ~ complete response (CR) action ~** from a 505(b)(2) perspective.

Please make the following changes to the draft assessment before archiving in DARRTS. As you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the RS arrives so that we can add it anew to our clearance queue.

- *Q3: Please add additional bridge information in response to this question as provided to me via 6/22/16 email from Jessica Boehmer.*
- *Q11: Add N204824, N205776 as additional pharm alternatives.*

Please let me know if you have any questions.

Mary Ann

From: Boehmer, Jessica
Sent: Wednesday, June 22, 2016 3:43 PM
To: Holovac, Mary Ann
Cc: Kim, Tamy; Goldstein, Beth A (Duvall); Nabavian, Sadaf; Maynard, Janet; Deisseroth, Albert
Subject: Responses from DHP & DPARP: NDA 208400 (MTX oral solution) - additional clarity needed

Dear Mary Ann,

Please find our teams' responses (in blue, below) regarding NDA 208400 for Methotrexate Oral Solution. Please contact Sadaf and me if further clarification is needed.

- The committee noted the food effect delay in tmax and 50% decrease in cmax as part of the bridge description. The committee does not opine on scientific decisions but would like the division to assure that it is documented WHY the 50% difference is acceptable/allowable as part of the clin pharm review – realizing that the future labeling may take care of relative bioavailability concerns. The division should know how close the proposed product is to the listed drug with respect to BE. Can the division confirm that this has been documented?

Yes, we confirm that this has been documented in the reviews.

- With respect to the bridge to the published literature, the committee requested that the description be revised to include SPECIFIC information that is described in the literature that is relevant to the proposed product (for example, does the literature describe dosing, drug exposure, etc., etc.) and HOW is the specific literature information relevant to the proposed drug product. Can the division please provide a specific description of the bridge? – it does not need to be lengthy, but as explained earlier, it just needs to connect the dots.

The applicant provided a bioavailability study establishing bioequivalence of the proposed methotrexate oral solution to the listed drug, methotrexate tablets. The safety/efficacy of methotrexate has already been established in both populations and is reflected in the listed drug's label. The published literature was utilized to provide scientific information relevant to the application and labeling, such as for the proposed indications, dosing, and safety sections of the labeling. For JIA, the literature provides support for the safety and efficacy of methotrexate. It is reasonable to rely on the published literature because the listed drug, methotrexate tablets (NDA 008085), was initially approved in 1953 and the published literature provides additional up-to-date information relevant to methotrexate. The data described in the submitted literature is scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient as contained in the sponsor's drug product.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

From: Nabavian, Sadaf
Sent: Wednesday, June 22, 2016 3:14 PM
To: Holovac, Mary Ann
Cc: Boehmer, Jessica; Kim, Tamy; Goldstein, Beth A (Duvall)
Subject: RE: NDA 208400 (MTX oral solution) - additional clarity needed

Hello Mary Ann,

This is to acknowledge your email (was on leave yesterday). Thank you for your feedback, Jessica and I will follow-up with the team and provide you with the additional information requested as soon as possible.

Thanks so much again,

Sadaf

From: Holovac, Mary Ann
Sent: Tuesday, June 21, 2016 9:17 AM
To: Nabavian, Sadaf
Cc: Boehmer, Jessica; Kim, Tamy; Goldstein, Beth A (Duvall); Holovac, Mary Ann
Subject: NDA 208400 (MTX oral solution) - additional clarity needed

Sadaf,
The 505(b)(2) committee discussed the subject application at yesterday's clearance meeting and had a couple of issues with the description of the bridge as follows:

- The committee noted the food effect delay in tmax and 50% decrease in cmax as part of the bridge description. The committee does not opine on scientific decisions but would like the division to assure that it is documented WHY the 50% difference is acceptable/allowable as part of the clin pharm review – realizing that the future labeling may take care of relative bioavailability concerns. The division should know how close the proposed product is to the listed drug with respect to BE. Can the division confirm that this has been documented?
- With respect to the bridge to the published literature, the committee requested that the description be revised to include SPECIFIC information that is described in the literature that is relevant to the proposed product (for example, does the literature describe dosing, drug exposure, etc., etc.) and HOW is the specific literature information relevant to the proposed drug product. Can the division please provide a specific description of the bridge? – it does not need to be lengthy, but as explained earlier, it just needs to connect the dots.

Additionally fyi:

- It was also noted that labeling for this product is still under discussion and there may be additional 505(b)(2) questions for the next cycle.

Thank you again for your patience as we work through this application. Once this information has been provided, I will be able to clear the application for CR for your division. Please let me know if you have any questions.
(FYI I am working from home today only until 2:30 and on leave tomorrow. I can call you if needed.) I will be back in the office on Thursday.

Also, I have attached below a document that contains some bridge examples that the division may find useful as this quest is considered, in particular, see the first example in the document that describes a literature bridge that passed committee review no questions asked.

Mary Ann << File: Bridge examples.doc >>

From: Nabavian, Sadaf
Sent: Thursday, June 16, 2016 3:20 PM
To: Holovac, Mary Ann
Cc: Boehmer, Jessica
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Hi Mary Ann,

Let's give this another try as clinical has provided further input and hopefully this will connect the dots for you. If not, let me know!

Thanks again! Sadaf

<< File: NDA 208400 505(b)(2) Assessment (REV-RPM-07)_updated_21April2016.doc >>

From: Holovac, Mary Ann
nt: Thursday, June 16, 2016 1:11 PM
: Nabavian, Sadaf

Cc: Boehmer, Jessica
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Hi Sadaf,

As you know, the bridge is the most painful thing on these applications.

Please note that I will be asking you to remove the reliance on the IND 117387 as this is the applicant's own information - so this does not constitute reliance in the 505(b)(2) sense.

Secondly, The additional hi-lited information provided with respect to reliance on the published literature should be provided as part of the question 3 (bridge question) response.... But the additional information still does not connect the dots. The committee will need to know WHY it is reasonable to utilize the published literature. The WHY is the scientific rationale that is needed.

The thought needs to be completed..... It is reasonable to utilize the published literature...etc. etc.... BECAUSE ???

Can we try again?

Feel free to call if this does not make sense.

Mary Ann

From: Nabavian, Sadaf
Sent: Thursday, June 16, 2016 12:35 PM
To: Holovac, Mary Ann
Cc: Boehmer, Jessica
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Hi Mary Ann,

know WHY it is reasonable to utilize the published literature. The WHY is the
Please find the attached updated template with the additional information (highlighted in yellow) and let me know if this information is what you are looking for. Thanks again for all your help! Sadaf

<< File: NDA 208400 505(b)(2) Assessment (REV-RPM-07)_updated_21April2016.doc >>

From: Holovac, Mary Ann
Sent: Wednesday, June 15, 2016 9:32 AM
To: Nabavian, Sadaf
Cc: Boehmer, Jessica
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Hi Sadaf,
Per our conversation yesterday, the only thing I see missing in the 505(b)(2) assessment for the MTX NDA is a scientific rationale for reliance on the published literature. Can the division provide this information – usually a sentence or two is adequate to explain WHY it makes sense to rely upon the published literature. I plan to present to the committee on Monday.

Thank you.
Mary Ann

From: Nabavian, Sadaf
Sent: Thursday, June 02, 2016 4:12 PM
To: Holovac, Mary Ann
Cc: Boehmer, Jessica
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Hi Mary Ann,

Just a heads up that due to facility issues/deficiencies both Divisions (DPH and DPARP) are gearing towards taking a CR action. I wanted to make you aware of this new update and please let me know if you have any questions.

Also, cc'ing, Jessica Boehmer, the RPM from DHP.

Thanks so much,
Sadaf

From: Nabavian, Sadaf
Sent: Tuesday, May 03, 2016 9:06 AM
To: Holovac, Mary Ann
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

You bet and thanks again!
Sadaf

From: Holovac, Mary Ann
Sent: Tuesday, May 03, 2016 9:05 AM
To: Nabavian, Sadaf
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Thanks Sadaf. I have it in the queue.
Mary Ann

From: Nabavian, Sadaf
Sent: Tuesday, May 03, 2016 9:01 AM
To: Holovac, Mary Ann
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Hi Mary Ann,
We are planning to take an approval action.
Thanks so much, Sadaf

From: Holovac, Mary Ann
Sent: Tuesday, May 03, 2016 8:37 AM

To: Nabavian, Sadaf
Subject: RE: NDA 208400 (MTX oral solution)-505(b)(2) template

Hi Sadaf,
What is the planned action for each application?
Thank you.
Mary Ann

From: Nabavian, Sadaf
Sent: Monday, May 02, 2016 4:26 PM
To: CDER OND IO (Mailbox)
Cc: Holovac, Mary Ann
Subject: NDA 208400 (MTX oral solution)-505(b)(2) template

Dear IO Staff,

Please find the attached 505(b)(2) template for methotrexate oral solution and note that the NDA is administratively split between DPARP And DHP (due to two different proposed indications). Also, cc'ing CAPT May Ann Holovac to keep her in the loop. The PDUFA due date is June 30th, 2016.
Please let me know if you have any questions.

<< File: NDA_208400_505b2_Assessment_updated_21April2016.doc >>
Very Respectfully,

~Sadaf

Sadaf Nabavian, Pharm.D.
CDR, U.S Public Health Service
Senior Regulatory Project Manager
FDA/CDERII/OND/DPARP

10903 New Hampshire Ave
Bldg. 22, Rm. 3306
Silver Spring, MD 20993-0002
Phone: (301) 796-2777
Fax: (301) 796-9718/9715
Email: sadaf.nabavian@fda.hhs.gov

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 31, 2016

To: Michael C. Beckloff Chief Development Officer	**From:** CDR Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager
Company: Silvergate Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: NA	**Fax number:** 301-796-9728
Phone number: (b) (6) **Email Address:** michael.beckloff@silvergatepharma.com	**Phone number:** 301-796-2777

Subject: NDA 208400; FDA Labeling Comments

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES xNO

NDA 208400, Original-1
NDA 208400, Original-2
Methotrexate Oral Solution
Silvergate Pharmaceuticals, Inc.

Dear Mr. Beckloff:

Your NDA submission dated August 31, 2015, for methotrexate oral solution is currently under review. We have the following comments and requests for information.

We acknowledge your response to our information request (IR) communicated on February 25, 2016, requesting for an integrated review of published literature relevant to methotrexate use during pregnancy, lactation, and in females and males of reproductive potential. While we agreed that the literature review could be limited to 2009 to 2016, you were to provide an adequate rationale to support the date range of the literature review you performed. In addition, the limited literature review would be determined whether it was sufficient upon our review. Upon review of your response to the IR, we found that you provided an interval review of publications without an integrated summary. You did not capture the key historical human data on MTX exposure during pregnancy to support the new required Data heading under Section 8.1 Pregnancy of the full prescribing information. A PLLR conversion requires an integrated review of the published literature sufficient to document the basis for the warnings related to MTX exposure during the periconceptional and prenatal periods, risk to the mother and infant from MTX exposure during lactation and risk of infertility following exposure.

1. Provide an integrated review of the published literature to support the Warnings and Precautions related to:
    - Embryo-fetal toxicity
    - Fetal death
    - Congenital anomalies
    - Infertility
    - Data to support the presence of MTX in breast milk and the risk that drug exposure poses to the breastfeeding infant.

2. Propose labeling language for the Data heading under Section 8.1 Pregnancy of the full prescribing information. Refer to the PLLR guidance for additional information.

Submit revised labeling incorporating the recommendations listed above via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on Thursday, June 2, 2016, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/5.31.2016

Cleared by: LJafari/5.31.2016

Finalized by: SNabavian/5.31.2016

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/s/

SADAF NABAVIAN
05/31/2016

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, May 26, 2016 12:55 PM
To: Susan Prather
Cc: Michael Beckloff; Nabavian, Sadaf; Boehmer, Jessica
Subject: Response required: NDA 208400 - Methotrexate Oral Solution IR due June 1st

Importance: High

Dear Susan,

Please refer to your NDA for Methotrexate Oral Solution, NDA 208400. Please respond to the following information request to Sadaf Nabavian and me via email by 2:00 PM ET, June 1, 2016. Please also formally submit your response to the NDA. Please confirm receipt and contact me if you have any questions.

Information Request:

In order to complete the review of your proposed Prescribing Information, we are requesting that you provide additional data to fulfill the requirements of the Pregnancy and Lactation Labeling Rule.

Please refer to the PLLR guidance for information on what is needed for Section 8 of labeling.

Please conduct literature searches (primary and tertiary) for data to support the following sections of labeling:

8.1 Pregnancy
Risk Summary: What are the animal data that inform the risks in pregnancy?
What are the human data that inform the risks in pregnancy?

8.2 Lactation
What human and animal data is available to provide guidance on lactation (safety of) and how long to avoid?

8.3 Females and Males of Reproductive Potential
What human/animal data is available to advise for how long males and females should use contraception?
Infertility: What human/animal data is available to describe the occurrence of infertility and duration?

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

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/s/

JESSICA L BOEHMER
05/26/2016

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, April 15, 2016 3:49 PM
To: Susan Prather (susan.prather@silvergatepharma.com)
Cc: Nabavian, Sadaf; Michael Beckloff (michael.beckloff@silvergatepharma.com); Boehmer, Jessica
Subject: Response Needed: Information Request: NDA 208400 - response due April 29th

Importance: High

Dear Susan,

Please refer to NDA 208400 for Methotrexate Oral Solution, and to your March 22, 2016 amendment. Kindly respond to the following information request by the date indicated.

DMEPA Information Request:

The "Ready-to-Use" statement, as depicted on the revised container label submitted 22 March 2016, is displayed with similar prominence as the name of the product, given the bold (b) (4) font and capital letters. If the firm is intent to retain this "Ready-to-Use" statement, we recommend the following changes to the revised container label to improve the safe use of this product.

1. Move the "Ready-to-Use" statement to follow the "For Oral Use Only" statement, thus increasing the white space on the principal display panel which improves the readability of important prescribing information such as product name, strength, and route of administration.
2. Decrease the prominence of the "Ready-to-Use" statement, so as to not draw attention away from important product information (such as product name, strength, and route of administration) by the following means:
    a) Remove bold;
    b) Change font color (b) (4)

Please respond to Sadaf Nabavian and me via email by close-of-business, **April 29, 2016**. You will also need to officially submit your response to the NDA.

Please confirm receipt.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

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/s/

JESSICA L BOEHMER
04/15/2016

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2016

To: Michael C. Beckloff Chief Development Officer	**From:** CDR Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager
Company: Silvergate Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: NA	**Fax number:** 301-796-9728
Phone number: (b) (6) **Email Address:** michael.beckloff@silvergatepharma.com	**Phone number:** 301-796-2777

Subject: NDA 208400; FDA Labeling Comments

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES xNO

NDA 208400, Original-1
NDA 208400, Original-2
Methotrexate Oral Solution
Silvergate Pharmaceuticals, Inc.

Dear Mr. Beckloff:

Your NDA submission dated August 31, 2015, for methotrexate oral solution is currently under review. We are providing our labeling comments noted below for your consideration. Be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Container Label

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.[1] Example: ***Xatmep***

2. Harmonize the font size for the words "Oral" and "Solution" on the principal display panel, so that are in equal font size and appear at the same prominence.

3. Remove the text, "READY-TO-USE" as this statement does not provide any useful information and does not contribute to safe use of the product.

4. Provide the route of administration on the principal display panel because there are other routes of administration of methotrexate. Example: ***For Oral Use Only***

5. Revise usual dosage statement in accordance with 21 CFR 201.55. Example: ***Usual Dose: See prescribing information***

6. Relocate "KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN" from the principal display panel to side panel. Only the most important information (e.g., proprietary and established names of the product, route of administration, strength,) should be retained on the principal display panel.

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

7. Decrease the overall size of the manufacturer trademark or move the trademark to the side panel to prevent taking the readers' attention away from important information such as proprietary names and strength.[2]

8. Revise and bold the statement refrigeration statement to increase the prominence of this important information and minimize the risk of this storage information being overlooked. Example: ***Must be refrigerated, store at 2°- 8°C (36°- 46°F).***

9. The after dispensing statement does not have a 60 day storage limitation stated on the container as the prescribing information suggests. Add the 60 day storage limitation to container labeling to ensure consistency between the prescribing information and the container labeling. Example: ***After dispensing, may be stored at room temperature 15°-30° (59°-86°F) for 60 days.***

10. The storage temperature presented on the container labeling and the storage temperature listed in the prescribing information are inconsistent. The prescribing information states patients may store this product at room temperature and notes an acceptable range of (b) (4) while the prescribing information states that patients may store this product at room temperature (25°C (77°F)) and states excursions permitted to 15°-30° (59°-**86°**F). Revise the storage temperature to provide accurate and consistent storage temperature requirements between the prescribing information and the container labeling.

11. Remove ancillary dosing information from container label and place in prescribing information as appropriate. Remove the following:

    a. (b) (4)
    b.

12. The concentration statement describing methotrexate sodium salt on the container label should be consistent with the concentration statement listed in the prescribing information. The prescribing information states, "2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL" and the container label states "Each mL contains methotrexate sodium equivalent to 2.5 mg of methotrexate." The statement is confusing and could be misinterpreted. Revise to ensure consistency between container label and prescribing information.

Submit revised labeling incorporating the recommendations listed above via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on Tuesday, March 22, 2016, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

[2] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

Drafted by: SNabavian/3.14.2016

Cleared by: LJafari/3.14.2016

Finalized by: SNabavian/3.14.2016

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/s/

SADAF NABAVIAN
03/15/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208400

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Silvergate Pharmaceuticals, Inc.
7300 W 110th Street
Suite 950
Overland Park, KS 66210

ATTENTION: Michael C. Beckloff,
Chief Development Officer

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated and received August 31, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Oral Solution, 2.5 mg per mL.

We also refer to your correspondence, dated and received December 23, 2015, requesting review of your proposed proprietary name, Xatmep.

We have completed our review of the proposed proprietary name, Xatmep, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 23, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Jessica Boehmer, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
02/29/2016

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 25, 2016

To: Michael C. Beckloff Chief Development Officer	**From:** CDR Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager
Company: Silvergate Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: NA	**Fax number:** 301-796-9728
Phone number: (b) (6) **Email Address:** michael.beckloff@silvergatepharma.com	**Phone number:** 301-796-2777

Subject: NDA 208400; FDA Labeling Comments

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES xNO

NDA 208400, Original-1
NDA 208400, Original-2
Methotrexate Oral Solution
Silvergate Pharmaceuticals, Inc.

Dear Mr. Beckloff:

Your NDA submission dated, August 31, 2015, for methotrexate oral solution is currently under review and we have the following labeling comments noted below. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.

We acknowledge that the proposed labeling is in the requested format and structure of the Pregnancy and Lactation Labeling Rule (PLLR) (79 FR 72064); however, during our review of your submitted labeling, we found that you have not provided adequate information to support the labeling content for subsections 8.1, 8.2 or 8.3. We also acknowledge your clinical program and your worldwide marketing experience with injectable methotrexate, the Integrated Safety Summary, summaries in Module 1.11.2, 2.5, 2.7.3 and 2.7.4; however, this document does not provide an integrated review of the published human data on methotrexate exposure during pregnancy, lactation or the effects on females and males of reproductive potential. We note that a PubMed search yields numerous publications in English which are related to methotrexate and pregnancy, and a smaller amount related to methotrexate use and lactation.

Therefore, to further support your proposed labeling, we request that you provide:

1. An integrated review of relevant publications on the effects of methotrexate exposure during pregnancy, lactation and reproductive potential in females and males. Copies of the references cited should accompany the integrated review.
2. Labeling revised to reflect your integrated review of the published literature.

Submit the requested information via email to Sadaf.Nabavian@fda.hhs.gov by COB March 10, 2016, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/2.25.2016

Cleared by: LJafari/2.25.2016

Finalized by: SNabavian/2.25.2016

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/s/

SADAF NABAVIAN
02/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400

INFORMATION REQUEST

Silvergate Pharmaceuticals, Inc.
Attention: Michael C. Beckloff
Chief Development Officer
7300 W 110th St. Ste. 950
Overland Park, KS 66210

Dear Mr. Beckloff:

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

We also refer to your August 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product:

1. You have not submitted any studies on extractables/leachables from the cap (b) (4) into the drug product. Demonstrate that the extractables/leachables from the (b) (4) into the drug product are at a safe level.

2. Your extractable studies on the bottle with printed label involved deionized water at pHs 2.5 and 8. As stated in the meeting held on April 7, 2015, conduct these studies with the drug product to demonstrate that extractables/leachables from the bottles with printed labels into the drug product are at a safe level.

3. As per your agreement with the Agency in the meeting dated April 7, 2015, submit updated stability data on the drug product within four months of the submission of the NDA.

Microbiology:

1. It is noted that Antimicrobial Effectiveness Test (AET) report VR 4423 (Appendix 2) is provided in Section P.5.3 of the submission. However, it appears that the AET described in VR 4423 (06/17/2014) was performed using [redacted] (b) (4). Please provide data from AET studies using the drug product formulated with the [redacted] (b) (4) content (i.e. [redacted] (b) (4) %) established in the release or stability specifications.

2. Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech 2011; 65(5): 535-43*. In order to control for the presence of BCC in your product you should consider the following:

    a. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

    b. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g.,temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to ensure that the proposed recovery methods are adequate to recover organisms potentially present in the environment. For more information, we refer you to *Envir. Microbiol. 2011; 13(1):1-12* and *J. Appl. Microbiol. 1997; 83(3):322-6.*

Provide test methods and acceptance criteria to demonstrate that the product is free of the objectionable microorganism Burkholderia cepacia. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided.

If you have any questions, please contact me, at (240) 402-6153. Please respond by COB January 29, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.01.22 01:55:07 -05'00'

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, January 14, 2016 2:16 PM
To: Susan Prather (susan.prather@silvergatepharma.com)
Cc: Boehmer, Jessica; Nabavian, Sadaf; Michael Beckloff (michael.beckloff@silvergatepharma.com)
Subject: Response Needed: Information Request: NDA 208400 - responses requested 1/14/2016 and 1/19/2016

Importance: High

Dear Susan,

Please refer to NDA 208400 for Methotrexate Oral Solution. Kindly respond to the following information request by the dates indicated.

Information Request:

At this time, we have received your proposed container label but have not received proposed carton labeling. Are you planning to utilize carton packaging for this product? If so, you will need to submit proposed labeling for Agency review.

Also, please indicate which previously submitted container label is your active proposed container label for Agency review. We note there are currently 2 different versions that have been submitted.

Please respond via email to let us know if you are planning to use a carton for packaging purposes by today, **January 14, 2016**. If you plan to use a carton, please submit proposed labeling by 4:00 PM ET, **January 19, 2016**.

Please confirm receipt.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

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/s/

JESSICA L BOEHMER
01/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

METHODS VERIFICATION
MATERIALS RECEIVED

NDA 208400 January 8, 2016

Silvergate Pharmaceuticals, Inc.
Attention: Michael Beckloff
6251 Greenwood Plaza Blvd, Ste 101
Greenwood Village, CO 80111

Dear Michael Beckloff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Methotrexate oral solution, 2.5 mg/mL and to our November 16, 2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on January 7, 2016, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
01/08/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208400

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Silvergate Pharmaceuticals, Inc.
7300 West 110th Street
Suite 950
Overland Park, KS 66210

ATTENTION: Michael Beckloff
Chief Development Officer

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated and received August 31, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Oral Solution, 2.5 mg per mL.

We also refer to your correspondence, dated and received October 2, 2015, requesting review of your proposed proprietary name, (b) (4).

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name (b) (4) is similar in pronunciation to the root name, (b) (4), of the currently marketed product, (b) (4) Both names have beginning and ending syllables that sound similar when spoken: the names begin with similar sounding vowels (b) (4) and end with identical syllables (b) (4). Although the second syllable (b) (4) have some differences, they both contain a consonant followed by a vowel. This minor difference in the second syllable can be missed given the overall phonetic similarities of the names. The similarity in pronunciation of this name pair is further supported by the FDA's Phonetic and Orthographic Computer Analysis (POCA) system which calculates a combined orthographic and phonetic score of 70% (77% phonetic only score) for this name pair.

In addition to the similarity in pronunciation of this name pair, the name pair also shares orthographic similarities and overlapping product characteristics that may also contribute to potential confusion between the names. Both names begin with similar letters (b) (4) and end with identical letter strings (b) (4). Additionally, the infixes (b) (4) both contain a consonant, which can be scripted as a downstroke, followed by a vowel giving the two names identical shape. The two products also share the same route of administration (oral) and can be administered once daily. Additionally, the dose of (b) (4) can have a numerical

similarity to the strength/dose of [redacted] (e.g., if [redacted] is dosed at [redacted] then the dose of [redacted] could be misinterpreted as a dose of [redacted] and vice versa). Although [redacted] is available as a capsule and the proposed formulation for [redacted] is an oral solution, these product characteristics may be omitted on the prescription (e.g., [redacted]). Additionally, the dosage form may be overlooked due to confirmation bias (tendency to interpret information in a way that confirms one's preconceptions).

We note that [redacted] is an over-the-counter product, however, our post marketing experience with other drug products suggests that name confusion can occur between similarly named prescription drug products and over-the-counter drug products.[1]

Based on the similarity in pronunciation to [redacted] we find the proposed proprietary name [redacted] unacceptable based on 21 CFR 201.10(c)(5), which states "The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient."

We note that you have proposed an alternate proprietary name in your submission dated October 2, 2015. In order to initiate the review of the alternate proprietary name, [redacted], submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

[1] Institute for Safe Medication Practices summary of article citations

Rx product	OTC product	Institute for Safe Medication Practices article citation
sertraline	cetirizine	Institute for Safe Medication Practices. Safety briefs: Sound-alike names. ISMP Med Saf Alert Community/Ambulatory Care. 2009; 8(9): 1-7.
benazepril	Benadryl	Institute for Safe Medication Practices. Safety briefs: Benazepril confused with Benadryl. ISMP Med Saf Alert Community/Ambulatory Care. 2008; 7(12): 1-6.
sotalol	Sudafed	Institute for Safe Medication Practices. Safety briefs: Sudafed-Sotalol mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2006; 5(5): 1-5.
Mucomyst	Mucinex	Institute for Safe Medication Practices. Safety briefs: Mucinex-Mucomyst: Too close for comfort. ISMP Med Saf Alert Community/Ambulatory Care. 2005; 4(1): 1-4.
Mirapex	Miralax	Institute for Safe Medication Practices. Safety briefs: Mirapex and Miralax confusion. ISMP Med Saf Alert Acute Care. 2002;7(20):1-3.
Cozaar	Colace	Institute for Safe Medication Practices. Safety briefs: More on confirmation bias. ISMP Med Saf Alert Acute Care. 1996;1(23):1-2.

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3621. For any other information regarding this application, contact Jessica Boehmer, Regulatory Project Manager in the Office of New Drugs, at 301-796-5957.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
11/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

REQUEST FOR METHODS VALIDATION MATERIALS

NDA 208400 November 16, 2015

Silvergate Pharmaceuticals, Inc.
Attention: Michael Beckloff
6251 Greenwood Plaza Blvd, Ste 101
Greenwood Village, CO 80111

Dear Michael Beckloff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Methotrexate oral solution, 2.5 mg/mL.

We will be performing methods validation studies on Methotrexate oral solution, 2.5 mg/mL, as described in NDA 208400.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

HPLC Method for the Identification, Assay, (b) (4) and Related Substances of Methotrexate Oral Solution (b) (4) 14-0050.01)

Samples and Reference Standards

2 bottles	Methotrexate, USP RS Standard
2 bottles	Methotrexate Related Compound B, USP RS Standard
2 bottles	Methotrexate Related Compound C, USP RS Standard
2 bottles	Methotrexate Related Compound E, USP RS Standard
2 bottles	Methylparaben, USP RS
2 bottles	Propylparaben, USP, RS
2 bottles	(b) (4)
25 bottles	Methotrexate drug product

Equipment

(b) (4)

Please include the SDSs and the Certificates of Analysis for the sample and reference materials as well as any health/safety hazards related to the materials requested (i.e. teratogenicity, mutagenicity, etc.).

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
11/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400, Original-1
NDA 208400, Original-2

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Silvergate Pharmaceuticals, Inc.
Attention: Michael C. Beckloff
Chief Development Officer
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated August 31, 2015, received August 31, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Methotrexate Oral Solution, 2.5 mg/mL.

We have administratively split your application into Original 1 and Original 2 which provides for the following indications:

Original 1: Treatment of pediatric patients with acute lymphoblastic leukemia (ALL), as part of a combination regimen.

Original 2: Management of children with active polyarticular juvenile idiopathic arthritis (pJIA), who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 30, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If

major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 2, 2016.

During our filing review of your application, we identified the following potential review issues:

Clinical Pharmacology, Original-1:

1. Provided that methotrexate has non-linear PK, specifically saturable absorption at the higher doses intended for the ALL indication, we are concerned that the BA/BE findings obtained at lower dose (2.5 mg) maybe not be extrapolated to BA/BE scenarios at higher (20 to 30 mg) doses. Provide data or rationale in order to determine whether the BA/BE findings using methotrexate doses of 2.5 mg can be used to extrapolate to BA/BE scenarios at higher clinical doses (20 – 30 mg).

Product Quality, Original-1 and Original-2:

2. DMF (b) (4) for the drug Methotrexate Sodium is inadequate. Please be advised that the NDA cannot be approved until the drug substance DMF deficiencies are addressed satisfactorily.

3. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the Burkholderia cepacia complex (Bcc). We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for these species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of Bcc and cells that are acclimated to the product and the environments (e.g., warm or cold water) that may be tested.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. A horizontal line must separate the Table of Content from the Full Prescribing Information (FPI).

2. White space should be present before each major heading in the highlights (HL) section. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval.

3. The Boxed Warning (BW) must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE.**" If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by December 6, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please contact the regulatory project managers listed below.

NDA 208400/Original-1	Jessica Boehmer, Division of Hematology Products, 301 796-5357
NDA 208400/Original-2	Sadaf Nabavian, Division of Pulmonary, Allergy, and Rheumatology Products, 301-796-2777

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
11/13/2015

SARAH K YIM
11/13/2015
Signing for Badrul Chowdhury, M.D., Ph.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400

NDA ACKNOWLEDGMENT

Silvergate Pharmaceuticals, Inc.
Attention: Michael C. Beckloff
Chief Development Officer
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Dear Mr. Beckloff:

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: Methotrexate Oral Solution, 2.5 mg/mL

Date of Application: August 31, 2015

Date of Receipt: August 31, 2015

Our Reference Number: NDA 208400

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 October 30, 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 Hematology 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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JESSICA L BOEHMER
09/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117387

MEETING MINUTES

Silvergate Pharmaceuticals, Inc.
Attention: Michael C. Beckloff
Chief Development Officer
7300 W 110th St, Ste 950
Overland Park, KS 66210

Dear Mr. Beckloff:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Pediatric Oral Solution.

We also refer to the teleconference between representatives of your firm and the FDA on April 7, 2015. The purpose of the meeting was to discuss and obtain FDA's agreement on certain Chemistry, Manufacturing, and Controls requirements for a methotrexate pediatric oral solution regarding the active pharmaceutical ingredient and drug product specifications, as well as the stability requirements for submission of the 505(b)(2) NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rabiya Laiq, Pharm.D., Regulatory Project Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: CMC Meeting

Meeting Date and Time: Tuesday, April 7, 2015 from 11:00AM- 12:00PM
Meeting Location: Teleconference

Application Number: 117387
Product Name: Methotrexate Pediatric Oral Solution
Indication: Maintence therapy of acute lymphatic leukemia
Sponsor/Applicant Name: Silvergate Pharmaceuticals, Inc.

Meeting Chair: Janice Brown, M.S.
Meeting Recorder: Rabiya Laiq, Pharm.D.

FDA ATTENDEES
Office of Pharmaceutical Quality
Office of New Drug Product
Janice Brown, M.S., Quality Assessment Lead
Raymond Frankewich, Ph.D., CMC Reviewer

Office of Program and Regulatory Operations
Rebecca McKnight, Regulatory Business Process Manager
Rabiya Laiq, Pharm.D., Regulatory Business Process Manager

Office of Surveillance and Epidemiology
Kevin Wright, Pharm.D., Project Manager

Office of Medication Error Prevention and Risk Management
Yelena Maslov, PharmD., Team Leader, DMEPA
Michelle Rutledge, PharmD., Safety Evaluator, DMEPA

SPONSOR ATTENDEES
Michael C. Beckloff Chief Development Officer; Silvergate Pharmaceuticals, Inc.
Susan J. Prather Director, Regulatory Affairs; Silvergate Pharmaceuticals, Inc.
Gerold L. Mosher, PhD Vice President, Drug Development; Silvergate Pharmaceuticals, Inc.

1.0 BACKGROUND

The purpose of the meeting was to discuss and obtain FDA's agreement on certain Chemistry, Manufacturing, and Controls requirements for a methotrexate pediatric oral solution regarding the active pharmaceutical ingredient and drug product specifications, as well as the stability requirements for submission of the 505(b)(2) NDA.

2. DISCUSSION

Question 1:
Does the Agency agree that the specifications are appropriate for the proposed active pharmaceutical ingredient and drug product?

FDA Response:
The proposed drug substance and product specification appear reasonable provided the following are addressed:

Drug Substance:
It is recommended that the following be added to the drug substance specification:

- A qualitative test for Description.
- Tests and appropriate acceptance criteria for USP impurities H and I.
- Compendial (USP) tests for Residue on Ignition and Heavy Metals
- Appropriate tests for microbiological purity (or justification for why these tests are not necessary).

Drug Product:

- The proposed analytical method for identity which uses HPLC retention time is not sufficiently specific (b) (4) (b) (4) Propose a sufficiently specific test method or use a combination of two complementary methods to confirm the identity of the drug substance.

A final determination of adequacy for the proposed release specifications for the drug substance and drug product will be made when complete CMC information has been evaluated in the NDA submission.

Meeting Discussion: *The sponsor agreed to the proposed revisions to the drug substance specification except for heavy metals and microbiological testing. The sponsor stated that they would provide a justification for* (b) (4) *heavy metals and microbiological testing in the NDA submission. Regarding microbiological testing, the sponsor indicated that the drug substance supplier's specification contains microbiological controls, and that they (the sponsor) include microbiological controls on their drug product specification. The agency reminded the sponsor that their product should comply with Q3D requirements for elemental impurities.*

The sponsor agreed to include an additional complementary identification test in the drug product specification.

Question 2:

Does the Agency agree that 6-months of refrigerated stability is acceptable for NDA submission, given the (b) (4) system?

FDA Response:
No. However, we would accept 6 month long term and 6 months accelerated stability data for a limited number of batches of drug product in the initial submission with a commitment to provide additional stability data during the review of your NDA submission. The determination of the shelf life is a review issue and is based on the complete stability data submitted in your NDA.

Meeting Discussion: *The sponsor agreed to submit the 6 months long term and 6 months stability data in the NDA with additional stability update within 4 months of submitting the NDA submission.*

Additional CMC Comments:

1. The regulatory acceptance criteria are the same from release throughout the shelf-life of your product. Therefore, combine the drug product release and stability specification into a single drug product specification.

2. Conduct packaging materials extractables/leachables studies using the intended commercial formulation to determine the level of the extractables in the container closure and any leachables in the drug product. Provide a justification for the safety of potential leachables that are present at release and expiry. Where data show that leachables are present, add tests and acceptance criteria for leachables to the drug product specification. Where development and stability data show evidence that extractables from the container/closure systems are consistently below levels that are demonstrated to be acceptable and safe, elimination of this test can be considered.

Additional Meeting Discussion:

The Agency requested the following clarification of the container closure system:

Your containing closure system description states that "The oral solution is packaged in a 150-cc, round, white opaque high-density polyethylene bottle with a (b) (4) white (b) (4) closure (b) (4) induction seal."
Please explain what " (b) (4) induction seal are. Also, please clarify whether the bottle contain (b) (4).

The Sponsor explained that (b) (4) are trademarked seals for the bottle. The Sponsor further explained that the bottle (b) (4)


(b) (4)

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/s/

RABIYA LAIQ
04/14/2015

JANICE T BROWN
04/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 117387

MEETING MINUTES

Silvergate Pharmaceuticals, Inc.
Attention: Wayne F. Vallee, R.Ph., R.A.C.
Director, Managing Consultant
Beckloff Associates, Inc.
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Dear Mr. Vallee:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Sodium Methotrexate (b) (4) Oral Solution.

We also refer to the telecon between representatives of your firm and the FDA on May 21, 2013. The purpose of the meeting was to the clinical development plan for a sodium methotrexate (b) (4) oral solution formulation leading up to the submission and review of a 505(b)(2) NDA referencing (b) (4) .

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, M.D., Ph.D.,
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-IND
Meeting Date and Time:	May 21, 2013, 10:00 AM ET
Meeting Location:	Teleconference
Application Number:	PIND 117387
Product Name:	Sodium Methotrexate (b) (4) Oral Solution
Indication:	For maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen in children.
Sponsor/Applicant Name:	Silvergate Pharmaceuticals, Inc.
Meeting Chair:	Albert Deisseroth
Meeting Recorder:	Jessica Boehmer

FDA ATTENDEES

Division of Hematology Products (DHP)
Albert Deisseroth, M.D., Ph.D., Clinical Team Leader
Pat Dinndorf, M.D., Medical Officer
Jessica Boehmer, M.B.A., Regulatory Project Manager

Division of Hematology Oncology Toxicology
Haleh Saber, Ph.D., Supervisory Pharmacologist
Shwu-Luan Lee, Ph.D., Pharmacologist

Office of New Drug Quality Assessment (ONDQA)
Janice Brown, M.S., Chemistry, Manufacturing & Controls Lead
William M. Adams, Chemist

Office of Clinical Pharmacology (OCP)
Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacologist

Office of Hematology and Oncology Products (OHOP)
Gregory Reaman, M.D., Associate Director for Oncology Sciences

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA)
James Schlick, R.Ph., M.B.A., Acting Team Leader
Kevin Wright, Pharm.D., Safety Evaluator

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Risk Management (DRISK)
Cynthia LaCivita, Pharm.D., Risk Management Analyst Team Leader

SPONSOR ATTENDEES

Silvergate Pharmaceuticals, Inc.
Frank Segrave, Chief Executive Officer
Michael C. Beckloff, Chief Development Officer
Peter Colabuono, Director of Business Development and Finance
Jerry Mosher, Ph.D., Vice President, Product Development
Susan Prather, Director, Regulatory Affairs

Consultants
(b) (4)
Wayne F. Vallee, R.Ph., R.A.C.; Consultant; Director, Beckloff Associates, Inc.

1.0 BACKGROUND

The purpose of this meeting is to discuss the clinical development plan for a sodium methotrexate (b) (4) oral solution formulation leading up to the submission and review of a 505(b)(2) NDA referencing DAVA's 2.5-mg Methotrexate Tablet as the RLD, and to discuss the proposed CMC development plan.

Methotrexate Tablets, USP (formerly Amethopterin), is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course JRA.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis.

A commercial methotrexate pediatric formulation does not exist. To fill this void, Silvergate is developing a (b) (4) formulation for methotrexate. (b) (4)

Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present-day chemotherapy. The intended indication for Methotrexate Sodium (b) (4) Oral Solution is treatment of childhood ALL as part of a combination regimen. Silvergate's development plan is to conduct a randomized, parallel, single-dose pivotal comparative bioavailability study of their methotrexate product to the RLD methotrexate tablet in healthy adult male subjects. Silvergate is requesting guidance from the Agency regarding any concerns that may exist for the development plans or formulation regarding safety; efficacy; or drug chemistry, manufacturing, and controls (CMC) for treatment of pediatric ALL.

2. DISCUSSION

2.1. Nonclinical

Question 1:

Silvergate plans to make reference to the nonclinical section of the DAVA's Methotrexate Tablets, USP to fulfill the nonclinical requirements for the 505(b)(2) NDA. In addition, a literature search will be conducted to identify new clinical pediatric information. Any significant findings will be included in the NDA.

Does the Agency agree that the nonclinical plan is acceptable and will meet the nonclinical requirements for a 505(b)(2) NDA?

FDA Response to Question 1:

Your approach is generally acceptable. Also see our comments below.

- **We note that your meeting briefing package included FDA Summary Basis of Approvals for (b) (4) approvals. Please note if you are proposing to reference information from the Summary Basis of Approval or FDA reviewers' public summaries for support of safety and/or efficacy, this is not acceptable. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug. Please see our additional comments regarding the 505(b)(2) below.**

- **Address and justify the level of impurities present in your drug if they are above the thresholds described in the guidance documents, e.g. ICH Q3A(R2) and ICH Q3B(R2).**

Discussion:

No discussion occurred.

2.2. Clinical

Question 2:

Silvergate plans to conduct a randomized, parallel, single-dose pivotal comparative bioavailability study of its methotrexate product to DAVA's Methotrexate Sodium 2.5-mg Tablet in 60 healthy adult male subjects

(30 subjects per treatment arm) under fasted conditions. The primary endpoint of the study is to assess bioequivalence (comparable bioavailability) between the formulations.

Does the Agency agree that this type of study should provide suitable bioavailability information for review for approval and that no additional studies would be required if the bioavailability results are bioequivalent (have comparable bioavailability)?

FDA Response to Question 2:

Your general approach is reasonable; however, you should address the following concerns:

- **Based on the protocol provided, we find your PK sampling approach inadequate. In general, your sampling scheme should characterize 90% or more (3.5 half-lives or more) of the AUC of the drug being measured and include an equal number of samples at each phase of the concentration versus time curve spaced based on the anticipated rate of absorption and elimination. We note the half life reported in the approved label for the NDA 008085 LD was as high as 15 hours and Tmax as high as 2 hours in adults.**
- **The approved label for the NDA 008085 LD approved label states "Food has been shown to delay absorption and reduce peak concentration." Therefore, the sponsor should assess relative BA of their MTX formulation under both fed and fasted conditions. Please refer to the guidances titled Food-Effect Bioavailability and Fed Bioequivalence Studies and Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations for additional information.**
- **The equivalence range of your proposed BA study was not specified. You must justify the safety and/or efficacy of your proposed formulation if the equivalence range falls outside the Agency accepted 80-125% bounds for the bioavailability study.**
- **Validate the analytical methods used to determine the concentrations of methotrexate. Refer to the Guidance for Industry Bioanalytical Method Validation.**

Discussion:

The sponsor provided examples from other ANDA applications to justify their sampling scheme up to 24 hours post dose.

The sponsor provided examples of instances where methotrexate was stated to not have a food effect. The Agency still requires an assessment of food for formulation change such as the sponsor is proposing.

The sponsor plans to use the 80-125% bounds for the bioavailability study.

2.3. Chemistry, Manufacturing, and Controls

Question 3:

Silvergate will be using the sodium salt of methotrexate as the active pharmaceutical ingredient (API) and will utilize the USP monographs for Methotrexate, USP and Methotrexate Tablets, USP to assist in the development of test methods and specifications for Methotrexate Sodium (b) (4) Oral Solution.

Does the Agency have any concerns with this approach?

FDA Response to Question 3:

Using the current USP monographs as a starting point for the development of specifications for drug substance and drug product is acceptable. Both specifications should address identity, assay, purity and appropriate physical attributes based on the proposed dosage form and route of administration.

Discussion:

No discussion occurred.

Question 4:

Does the Agency have any comments or suggestions regarding the overall CMC development plan?

FDA Response to Question 4:

Your IND should include the following information:

- **The identity and compatibility of the possible dosage administration devices which may be used with the varying adolescent patient population.**
- **A profile of impurities and degradants observed at or above the analytical limit of quantitation in bulk drug substance, in the drug product (b) (4) (b) (4) solution at release, on stability, or in the in-use studies. The safety of the observed level of each impurity or degradant should be justified.**
- **Your proposed strength(s) for the investigational drug product Methotrexate Sodium (b) (4) Oral Solution is based on the amount of the drug substance salt form present in the proposed drug product. The USP recommends that the labeled strength be expressed in terms of the parent acid or base for drug products formulated with a salt unless justified otherwise as described in USP <1121>. In consideration of this USP policy, which became effective May 1, 2013, we suggest**

that you consider adjusting the investigational drug product strength(s) such that, once approved, the label provides the desired strength(s) when expressed in the drug product established name as the parent acid/base.

Discussion:

The sponsor stated that a single dose will be administered to healthy adults using a glass syringe at the clinical site. This is acceptable to the Agency. No compatibility studies will be needed.

Sponsor's Follow-up Questions for the FDA:

1. **Please confirm the acceptability of using one lot of API for the three registration batches.**

Discussion:

There is not enough information in the meeting package to make a determination of the acceptability of a single API batch to produce the 3 registration batches. The sponsor will provide a written justification for their proposal and FDA will provide a written response.

2. **The Sodium Methotrexate (b) (4) Oral Solution is intended for the pediatric population. Please confirm the acceptability of pediatric only indications and dosing in the labeling.**

Discussion:

The FDA has no objection to the sponsor restricting the label indication to the pediatric population.

Additional Comments:

The Agency has not completed a risk assessment on the design of the container and closure system. However, a cursory examination indicates some of the following issues. Please note these are preliminary comments that should be considered during your product design and/or your risk assessment.

1. (b) (4)

Discussion:

(b) (4)

The Agency further clarified that the sponsor should submit the packaging, when available, for review.

2. (b) (4)

Discussion:

(b) (4)

3. Are you planning to supply the patient with education on the proper storage, handling, and disposal of methotrexate? Post-marketing cases and medication-error articles in the literature demonstrate handling, storage, and disposal issues with oral chemotherapy.

Discussion:

The sponsor confirmed their intent to comply with the proper disposal practices for chemotherapy drugs.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below).In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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/s/

ALBERT B DEISSEROTH
05/23/2013