CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208400Orig1s000
208400Orig2s000

PRODUCT QUALITY REVIEW(S)

Overall Manufacturing Inspection Recommendation

As of Apr 26, 2017 4:37 pm GMT

Inspection Management Form

NDA-208400-ORIG-1-RESUB-17

(b) (4)

(b) (4) Approve Facility

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold
- No Evaluation Necessary

Save Cancel

Submission Manufacturing Facilities

Loading...

Assigned To

Ebern Dobbin

Edit Assignment

This was done on
Apr 20, 2017
(6 days ago)

Status
Complete

Requested by

Rabiya Laiq

This task is waiting on
Facilities

Tasks waiting on this
Upload Final Decision

Last Update	Submitted On
Apr 20, 2017	Oct 27, 2016

Reference Number
10984555

NDA-208400-ORIG-1 » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

The option needed is associated with one or more facilities found unacceptable. (b) (4)

Edit Task | Task Actions

Task Summary | Task Details | Documents | Approvals | Updates | Application Life Cycle

Inspection Management Form

As of Nov 22, 2016 9:35 am GMT

Inspection Management Form

NDA-208400-ORIG-1

(b) (4)

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Cancel

Submission Manufacturing Facilities

Loading...

Assigned To

Ebern Dobbin

IM - OPF Reviewer

Edit Assignment

This was done on

Jun 17, 2016

(158 days ago)

Status

Complete

Requested by

Kristine Leahy

Regulatory Businesss and Project Manager

This task is waiting on

Facilities

Last Update	Submitted On
Jun 17, 2016	Sep 1, 2015

Reference Number

5539423

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

/s/

JONATHAN T DOW
05/05/2017

Inspection View

Updated Inspection View for OPQ Layout Template

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (2)								
7	Enter Application Specific Inspection Criteria	If you are finished with this task, change the Task Status to Complete.	Rabiya Laiq, Team: IM - Filing PM/Coordinator	10/29/16	10/27/16	Complete	Go to Form	
18	Overall Manufacturing Inspection Recommendation		Ebern Dobbin	4/13/17	4/20/17	Complete	Go to Form	Recommendation: Approve
Parent: Facility: (b) (4) FACILITY STATUS: (1)								
10	Enter Profile Codes		Ebern Dobbin, Team: IM - Facility Profile Reviewer, Job Role: Facility Profile Reviewer	11/3/16	3/1/17	Complete	Go to Form Go to Program	
Parent: Profile Evaluation for DUNS: (b) (4) | FACILITY STATUS: (5) (b) (4)								
12	(b) (4)		Ebern Dobbin, Team: IM - OPF Reviewer	11/8/16	3/1/17	Complete	Go to Form	
13			Ebern Dobbin, Team: IM - OPF Reviewer	11/13/16	3/1/17	Complete	Go to Form	
14	(b) (4)			11/23/16	4/18/17	Complete	Go to Form	

Reference ID: 4094184

Inspection View (cont'd)

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
16	(b) (4)			4/2/17	4/18/17	Complete	Go to Form	Recommendation: Approve Facility Reason: Inspection
17	(b) (4)		Ebern Dobbin	4/12/17	4/20/17	Complete	Go to Form	Recommendation: Approve Facility Reason: District Recommendation

Reference ID: 4094184

NDA-208400-ORIG-1 » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

The option needed is associated with one or more facilities found unacceptable. (b) (4)

Edit Task | Task Actions

Task Summary | Task Details | Documents | Approvals | Updates | Application Life Cycle

Inspection Management Form

As of Jun 28, 2016 5:03 pm GMT

Inspection Management Form

NDA-208400-ORIG-1

(b) (4)

[redacted]

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Cancel

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Global ID	Facility Name	Profile
Withhold Approval	6/17/2016	NDA-208400-ORIG-	(b) (4)				
Cancelled	1/12/2016	NDA-208400-ORIG-					
Cancelled	1/12/2016	NDA-208400-ORIG-					
Approve Facility	10/28/2015	NDA-208400-ORIG-					
Approve Facility	10/28/2015	NDA-208400-ORIG-					

Assigned To

Ebem Dobbin

IM - OPF Reviewer

Edit Assignment

This was done on
Jun 17, 2016
(11 days ago)

Status
Complete

Requested by

Kristine Leahy
Regulatory Businesss and Project Manager

This task is waiting on
Facilities

Last Update	Submitted On
Jun 17, 2016	Sep 1, 2015

Reference Number
5539423

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

/s/

JONATHAN T DOW
05/05/2017

Recommendation:
NDA: Approval

NDA 208400
Review #1

Drug Name/Dosage Form	XATMEP™ (Methotrexate) Oral Solution
Strength	2 (b)(4)mg/mL
Route of Administration	O 1
Rx/OTC Dispensed	Rx
Applicant	Silvergate Pharmaceuticals, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	25-OCT-2016	Facility, Labeling
Amendment	06-DEC-2016	Proprietary Name
Amendment	06-FEB-2017	Labeling
Amendment	17-MAR-2017	Labeling
Amendment	07-APR-2017	Labeling
Amendment	18-APR-2017	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	OPQ/ONDP/NDAPI/II
Drug Product	Sam Bain	OPQ/ONDP/NDAPI/II
Process	Yetao Jin	OPQ/OPF/DPAIII/BIX
Microbiology	Wendy Tan	OPQ/OPF/DMA/BII
Facility	Ebern Dobbin	OPQ/OPF/DIA/IABII
Biopharmaceutics	Banu Zolnik	OPQ/ONDP/DB/ B1
Regulatory Business Process Manager	Rabiya Laiq	OPQ/OPRO/B1
Application Technical Lead	Anamitro Banerjee	OPQ/ONDP/DNDPI/NDPBII
Laboratory (OTR)	Lucinda Buhse	
ORA Lead	Paul Perdue Jr.	
Environmental Assessment (EA)	Sam Bain	OPQ/ONDP/NDAPI/II

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	REVIEW DATE
(b) (4)	II		(b) (4)	Adequate	09-FEB-2016

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117387	Methotrexate Pediatric Oral Solution
NDA	008085	Methotrexate Sodium Tablets, USP

2. CONSULTS:

None

Executive Summary

I. Recommendations

This NDA is recommended for APPROVAL from the CMC perspective.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues
   During the evaluation of the original NDA, the (b) (4) *facility was found to be inadequate. A Withhold recommendation was provided by the facility reviewer. The* (b) (4) *facility was recently inspected in support of this resubmission and was found to be acceptable. The No pending deficiencies are identified at this time. This NDA is recommended for approval from the CMC perspective.*

2. Action letter language, related to critical issues such as expiration date
   Expiration dating period of 24 months is granted for the drug product when stored at 5 ± 3 ℃

3. Benefit/Risk Considerations
   None

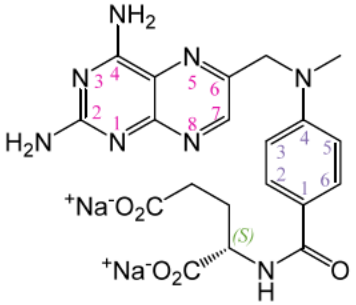
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance [Methotrexate Sodium] Quality Summary

1. Chemical Name or IUPAC Name/Structure
   N-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methyl-amino]benzoyl]-L-(+)-glutamic acid, Disodium Salt



sodium (4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino)benzoyl)-*L*-glutamate
Chemical Formula: $C_{20}H_{20}N_8Na_2O_5$
Molecular Weight: 498.41

2. Properties/CQAs Relevant to Drug Product Quality

Methotrexate Sodium is a yellow to orange crystalline powder. It is freely soluble in water, slightly soluble in ethanol, and practically insoluble in chloroform. The pH of an aqueous solution (1%w/v) is 7.0 to 9.0. It is hygroscopic and shows no polymorphism. The structure of Methotrexate Sodium contains one asymmetric carbon atom, located in the glutamicacid side chain. (b) (4)

3. Manufacture
The applicant has referred to the DMF (b) (4) for the manufacture of the drug substance. The DMF was reviewed on February 09, 2016 and was found to be adequate. No quality amendment has since been submitted to this DMF (as of April 19, 2017).

4. Control of Drug Substance
The drug substance specifications proposed by the applicant is the same as that found adequate in the DMF (b) (4).

5. Container Closure
The drug substance is packaged in (b) (4).
(b) (4)

6. Retest Period & Storage Conditions
The applicant is proposing a retest period of (b) (4) when stored at room temperature in the proposed container closure.

B. Drug Product [Methotrexate Oral Solution] Quality Summary

1. Strength
2.5 mg/mL of methotrexate (120 mL total volume)

2. Description/Commercial Image
The product is a clear, yellow to orange colored, ready to use oral solution. It is filled in a 150 cc (b) (4) round, white, opaque HDPE bottles with white, (b) (4) CRCs (b) (4) heat induction layered inner seals.

3. Summary of Product Design
The formulation was developed to provide a pleasant tasting, chemically and physically stable, aqueous oral solution. (b) (4)
(b) (4)
(b) (4) The HDPE bottles were chosen (b) (4).
(b) (4). The product contains 2.74 mg/mL of methotrexate sodium, equivalent to 2.5 mg/mL of the free acid.

4. List of Excipients:
Citric acid (b) (4) USP, sodium citrate (b) (4) USP, methylparaben sodium USP, propylparaben sodium USP, sucralose NF, sodium hydroxide (b) (4) NF, hydrochloric acid (b) (4) NF, and purified water. All excipients are compendial. No excipient is of human or animal origin. No novel excipients are used.

5. Process Selection (Unit Operations Summary)
The manufacturing process consists of (b) (4)
(b) (4)

6. Container Closure
150 cc (b) (4) round, white HDPE bottle capped with (b) (4) white cap (b) (4) and (b) (4) induction seal.

7. Expiration Date & Storage Conditions
The applicant has proposed a 24 months expiration dating period when stored at 5±3°C.

8. List of co-packaged components
None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	XATMEP™ (Methotrexate) Oral Solution
Non Proprietary Name of the Drug Product	Methotrexate Oral Solution
Non Proprietary Name of the Drug Substance	Methotrexate Sodium
Proposed Indication(s) including Intended Patient Population	Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a

	combination regimen Management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy
Duration of Treatment	NA
Maximum Daily Dose	(b) (4) mg/m^2 given (b) (4) weekly
Alternative Methods of Administration	NA

D. Biopharmaceutics Considerations

The proposed drug product is an oral solution; therefore, the Application does not contain any biopharmaceutics data or information for review. The Division of Biopharmaceutics defers the approvability decision on this NDA to the other disciplines.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Life Cycle Knowledge Information (see Attachment A)

None

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Anamitro Banerjee, Ph.D.
CDER/OPQ/ONDP/DNDPI/Branch 2

April 21, 2017

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2017.04.21 20:01:20 -04'00'

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

No new information submitted in the resubmission. The NDA remains acceptable for drug substance.

ASSESSMENT OF THE DRUG PRODUCT

No new information submitted in the resubmission. The NDA remains acceptable for drug product.

ASSESSMENT OF THE PROCESS

No new information submitted in the resubmission. The NDA remains acceptable for drug product process.

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)				VAI	Acceptable

Reviewer's Assessment: Adequate; See Review #1. No changes proposed for the drug substance facilities from the previous review.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)				VAI	Acceptable

			(b) (4)		
(b) (4)					Acceptable based on insecption results.

Reviewer's Assessment: Adequate

(b) (4)

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Recommend Approval

Ebern Dobbin 4/20/2017
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Secondary Review Comments and Concurrence:

I concur with the Approval recommendation.

Christina Capacci-Daniel, PhD
Acting QAL, OPQ/OPF/DIA/IABII

ASSESSMENT OF THE BIOPHARMACEUTICS

No new information submitted in the resubmission. The NDA remains acceptable for biopharmaceutics.

ASSESSMENT OF MICROBIOLOGY

No new information submitted in the resubmission. The NDA remains acceptable for Drug Substance.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

No new information submitted in the resubmission.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

Minor editorial changes were recommended by the FDA in Section 16 of the PI. These recommendations were accepted by the applicant. The PI is acceptable.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

> Prior to dispensing to the patient, keep XATMEP refrigerated (2°C to 8°C/36°F to 46°F), (b) (4) (b) (4) Avoid freezing and excessive heat. After dispensing, (b) (4) patients may store XATMEP at room temperature (20°C to 25°C/~~(~~68°F to 77°F~~)~~) for up to 60 days (b) (4) ~~,~~ excursions permitted to 15°C to 30°C (59°F to 86°F) ~~[~~see USP Controlled Room Temperature].

Reviewer's Assessment:

Conclusion: The CMC section of the PI is adequate.

II. List of Deficiencies To Be Communicated

None

III. Attachments

Refer to the Review of the original NDA

Recommendation:
NDA: Complete Response

NDA 208400
Review #1 Addendum

Drug Name/Dosage Form	Methotrexate Oral Solution
Strength	2.(b)(4) mg/mL
Route of Administration	Or l
Rx/OTC Dispensed	Rx
Applicant	Silvergate Pharmaceuticals, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	31-AUG-2015	DS, DP
Amendment*	02-OCT-2015	DP
Amendment	08-FEB-2016	DP
Amendment	10-MAR-2016	DP
Amendment	29-APR-2016	DP

* Trade name request

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	OPQ/ONDP/NDAPI/II
Drug Product	Sam Bain	OPQ/ONDP/NDAPI/II
Process	Yetao Jin	OPQ/OPF/DPAIII/BIX
Microbiology	Wendy Tan	OPQ/OPF/DMA/BII
Facility	Ebern Dobbin	OPQ/OPF/DIA/IABII
Biopharmaceutics	Banu Zolnik	OPQ/ONDP/DB/ B1
Regulatory Business Process Manager	Rabiya Laiq	OPQ/OPRO/B1
Application Technical Lead	Anamitro Banerjee	OPQ/ONDP/DNDPI/NDPBII
Laboratory (OTR)	Lucinda Buhse	
ORA Lead	Paul Perdue Jr.	
Environmental Assessment (EA)	Sam Bain	OPQ/ONDP/NDAPI/II

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1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	REVIEW DATE
(b) (4)	II		(b) (4)	Adequate	09-FEB-2016
	III				
	IV				
	Other				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117387	Methotrexate Pediatric Oral Solution
NDA	008085	Methotrexate Sodium Tablets, USP

2. CONSULTS:

None

Executive Summary

I. Recommendations

COMPLETE RESPONSE is recommended for this NDA from the CMC perspective.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

   The following deficiency should be conveyed to the applicant:

   During a recent inspection of the [redacted] (b) (4) [redacted] (b) (4) manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. Action letter language, related to critical issues such as expiration date

   None

3. Benefit/Risk Considerations

   None

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

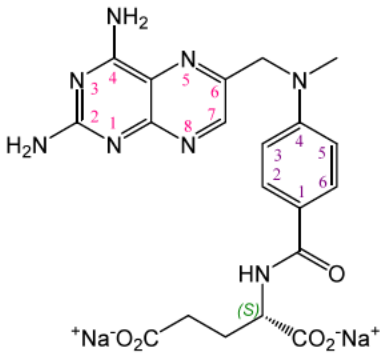
None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure

   N-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methyl-amino]benzoyl]-L-(+)-glutamic acid, Disodium Salt



sodium (4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino)benzoyl)-*L*-glutamate
Chemical Formula: $C_{20}H_{20}N_8Na_2O_5$
Molecular Weight: 498.41

2. Properties/CQAs Relevant to Drug Product Quality
Methotrexate Sodium is a yellow to orange crystalline powder. It is freely soluble in water, slightly soluble in ethanol, and practically insoluble in chloroform. The pH of an aqueous solution (1%w/v) is 7.0 to 9.0. It is hygroscopic and shows no polymorphism. The structure of Methotrexate Sodium contains one asymmetric carbon atom, located in the glutamic acid side chain. (b) (4)

3. Manufacture
The applicant has referred to the DMF (b) (4) for the manufacture of the drug substance. The DMF was reviewed on February 09, 2016 and was found to be adequate.

4. Control of Drug Substance
The drug substance specifications proposed by the applicant is the same as that found adequate in the DMF (b) (4)

5. Container Closure
The drug substance is packaged in (b) (4)
(b) (4)

6. Retest Period & Storage Conditions
The applicant is proposing a retest period of (b) (4) when stored at room temperature in the proposed container closure.

B. Drug Product [Established Name] Quality Summary

1. Strength
2.5 mg/mL of methotrexate (120 mL total volume).

2. Description/Commercial Image

The product is a clear, yellow to orange colored, ready to use oral solution. It is filled in a 150 cc (b) (4) round, white, opaque HDPE bottles with white, (b) (4) CRCs (b) (4) and heat induction layered inner seals.

3. Summary of Product Design
The formulation was developed to provide a pleasant tasting, chemically and physically stable, aqueous oral solution. (b) (4) (b) (4) (b) (4) The HDPE bottles were chosen (b) (4). (b) (4) The product contains 2.74 mg/mL of methotrexate sodium, equivalent to 2.5 mg/mL of the free acid.

4. List of Excipients:
Citric acid (b) (4) USP, sodium citrate (b) (4) USP, methylparaben sodium USP, propylparaben sodium USP, sucralose NF, sodium hydroxide (b) (4) NF, hydrochloric acid (b) (4) NF, and purified water.
All excipients are compendial. No excipient is of human or animal origin. No novel excipients are used.

5. Process Selection (Unit Operations Summary)
The manufacturing process consists of (b) (4) (b) (4)

6. Container Closure
150 cc (b) (4) round, white HDPE bottle capped with a (b) (4) white cap with a (b) (4) induction seal.

7. Expiration Date & Storage Conditions

The applicant has proposed a 24 months expiration dating period when stored at 5±3°C.

8. List of co-packaged components
None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xatmep
Non Proprietary Name of the Drug Product	Methotrexate Oral Solution
Non Proprietary Name of the Drug Substance	Methotrexate Sodium
Proposed Indication(s) including Intended Patient Population	Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination regimen Management of (b) (4) with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy
Duration of Treatment	NA
Maximum Daily Dose	(b) (4) mg/m2 given (b) (4) weekly
Alternative Methods of Administration	NA

D. Biopharmaceutics Considerations

The proposed drug product is an oral solution; therefore, the Application does not contain any biopharmaceutics data or information for review. The Division of Biopharmaceutics defers the approvability decision on this NDA to the other disciplines.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2016.06.15 11:52:52 -04'00'

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

I. List of Deficiencies To Be Communicated

Facility

During a recent inspection of the [redacted] (b) (4) [redacted] (b) (4) manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

II. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Not needed for low risk	Acceptable	None
Physical stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Not needed for low risk	Acceptable	None
Dosing accuracy	• Dosing device • Formulation • Process Parameters • Scale/equipment • Site	M	[redacted] (b) (4)	Acceptable	No dosing device is included. Dosing accuracy remains a medium risk.

			(b) (4)		
Palatability	• Formulation • Excipient change • Process parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L L	Not needed for low risk	Acceptable	
Leachables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M	The risk related to the potential leachables from the drug product manufacturing process is low.	Acceptable	Extractable/ leachable studies are found satisfactory.

Recommendation:
NDA: Pending for Facility recommendation

NDA 208400
Review #1

Drug Name/Dosage Form	Methotrexate Oral Solution
Strength	2 (b) (4) mg/mL
Route of Administration	O 1
Rx/OTC Dispensed	Rx
Applicant	Silvergate Pharmaceuticals, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	31-AUG-2015	DS, DP
Amendment*	02-OCT-2015	DP
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Amendment	29-APR-2016	DP

* Trade name request

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	IV				
	Other				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117387	Methotrexate Pediatric Oral Solution
NDA	008085	Methotrexate Sodium Tablets, USP

2. CONSULTS:

None

Executive Summary

I. Recommendations

Pending

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues
   Pending. A recommendation cannot be made at this time as the facility review is pending for this submission.

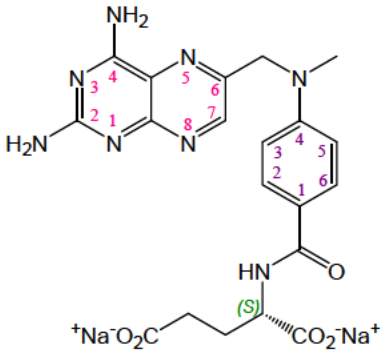
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure
   N-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methyl-amino]benzoyl]-L-(+)-glutamic acid, Disodium Salt



sodium (4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino)benzoyl)-*L*-glutamate
Chemical Formula: $C_{20}H_{20}N_8Na_2O_5$
Molecular Weight: 498.41

2. Properties/CQAs Relevant to Drug Product Quality
   Methotrexate Sodium is a yellow to orange crystalline powder. It is freely soluble in water, slightly soluble in ethanol, and practically insoluble in chloroform. The pH of an aqueous solution (1%w/v) is 7.0 to 9.0. It is hygroscopic and shows no polymorphism. The structure of Methotrexate Sodium contains one asymmetric carbon atom, located in the glutamic acid side chain. (b) (4)

3. Manufacture

The applicant has referred to the DMF (b) (4) for the manufacture of the drug substance. The DMF was reviewed on February 09, 2016 and was found to be adequate.

4. Control of Drug Substance
The drug substance specifications proposed by the applicant is the same as that found adequate in the DMF (b) (4).

5. Container Closure
The drug substance is packaged in (b) (4), (b) (4)

6. Retest Period & Storage Conditions
The applicant is proposing a retest period of (b) (4) when stored at room temperature in the proposed container closure.

B. Drug Product [Established Name] Quality Summary

1. Strength
2.5 mg/mL of methotrexate (120 mL total volume).

2. Description/Commercial Image
The product is a clear, yellow to orange colored, ready to use oral solution. It is filled in a 150 cc (b) (4) round, white, opaque HDPE bottles with white, (b) (4) CRCs with (b) (4) heat induction layered inner seals.

3. Summary of Product Design
The formulation was developed to provide a pleasant tasting, chemically and physically stable, aqueous oral solution. (b) (4) (b) (4) (b) (4) The HDPE bottles were chosen (b) (4). (b) (4) The product contains 2.74 mg/mL of methotrexate sodium, equivalent to 2.5 mg/mL of the free acid.

4. List of Excipients:
Citric acid (b) (4) USP, sodium citrate (b) (4) USP, methylparaben sodium USP, propylparaben sodium USP, sucralose NF, sodium hydroxide (b) (4) NF, hydrochloric acid (b) (4) NF, and purified water.
All excipients are compendial. No excipient is of human or animal origin. No novel excipients are used.

5. Process Selection (Unit Operations Summary)

The manufacturing process consists of [redacted]

6. Container Closure
   150 cc [redacted] round, white HDPE bottle capped with a [redacted] white cap with a [redacted] induction seal.

7. Expiration Date & Storage Conditions
   The applicant has proposed a 24 months expiration dating period when stored at 5±3°C.

8. List of co-packaged components
   None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xatmep
Non Proprietary Name of the Drug Product	Methotrexate Oral Solution
Non Proprietary Name of the Drug Substance	Methotrexate Sodium
Proposed Indication(s) including Intended Patient Population	Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination regimen Management of [redacted] with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy
Duration of Treatment	NA
Maximum Daily Dose	[redacted] mg/m2 given [redacted] weekly
Alternative Methods of Administration	NA

D. Biopharmaceutics Considerations

The proposed drug product is an oral solution; therefore, the Application does not contain any biopharmaceutics data or information for review. The Division of Biopharmaceutics defers the approvability decision on this NDA to the other disciplines.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2016.06.03 11:51:01 -04'00'

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2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

PENDING

37. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

PENDING

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence:

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Biopharmaceutics

This 505(b)(2) application is submitted for methotrexate oral solution, 2.5 mg/mL. The proposed indications for methotrexate oral solution are 1) The treatment of pediatric patients with acute lymphoblastic leukemia as part of a combination regimen, 2) The management of children with active polyarticular juvenile idiopathic arthritis 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.

The proposed drug product is an oral solution.

The Applicant conducted two BA studies (SG02-03 and SG02-04); the results of the two studies constitute the clinical basis for approval of the NDA. **Study SG02-03**: A single dose, two-period, two-treatment, two-way cross-over BA study of the proposed

methotreaxate oral solution versus methotrexate tablet, USP under fasting. **Study SG02-04:** A single-dose, open-label, randomized, 2-period, 2-treatment, food-effect study of the the proposed methotrexate oral solution.

These BA/BE studies will be evaluated by the Office of Clinical Pharmacology.

This NDA submission does not require further assessment from the Division of Biopharmaceutics

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

N/A

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

N/A

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics defers the approvability decision on this NDA to the other review disciplines.

1/14/2015
Banu Sizanli Zolnik, Ph. D
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Zolnik's assessment of NDA 208400.

1/14/2016
Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics

Office of New Drug Products

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:
Product Quality Microbiology Assessment

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – A clear, yellow to orange colored solution.
- Drug product composition – The drug product composition is provided on Table 3.2.P.1-1 duplicated here:

Component	Function	Mg/mL
Methotrexate Sodium, DMF (b) (4)	API	2.74
Citric acid, (b) (4), USP	(b) (4)	
Sodium citrate, (b) (4), USP		
Methylparaben sodium, NF		
Propylparaben sodium, NF		
Sucralose, NF		
Sodium Hydroxide (b) (4)	pH adjustment	(b) (4)
Hydrochloric acid (b) (4)	pH adjustment	
Purified water, USP	(b) (4	

- Description of container closure system – 150 cc round, white, opaque high-density polyethylene (HDPE) bottles with (b) (4) white (b) (4) cap, with a (b) (4) induction seal.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – N/A (non-sterile drug product)
- (b) (4)

Protocol # VR4423 dated 05/11/2012
The test was performed on 06/17/2014. Results are provided and summarized in the Table below:

Test microorganisms	Initial count (cfu)	Day 7	Day 14	Day 28
S. aureus	3.45×10^5	10	10	10

P.aeruginosa	1.95×10^5	10	10	10
E. coli	2.4×10^5	10	10	10
C. albicans	7.3×10^5	50	15	10
A. niger	2.7×10^5	5.0×10^2	5	10

Test microorganisms	Log Reduction		
	Day 7	Day 14	Day 28
S. aureus	4.5966	4.5966	4.5966
P.aeruginosa	4.2900	4.2900	4.2900
E. coli	4.3802	4.3802	4.3802
C. albicans	4.1643	4.6872	4.8633
A. niger	2.7324	4.4314	4.4314

Note to reviewer: It appears that the AET was conducted using (b) (4) (b) (4) This this information will be requested from the applicant.

- Microbial Limits – According to USP <1111>, a limit of total aerobic microbial counts (TAMC) and total yeast & mold (TYMC) is set at NMT (b) (4) cfu/mL and NMT (b) (4) cfu/mL respectively.

Note to reviewer: The data provided by the applicant is inadequate to support the AET test validations. The set microbial limit is acceptable.

The following IR was communicated to the applicant on 01/31/2016 and the response was received on 02/08/2016:

IR:

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 (b) (4) (b) (4) *Please provide data from AET studies using drug product formulated with the* (b) (4) *content (i.e.* (b) (4) *%) established in the release or stability specifications.*

Applicant's Response:

(b) (4)

ADEQUATE

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(b) (4)

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to place the first three commercial lots on stability, and thereafter one lot annually will be placed on long-term stability.

- Microbial Limits and Antimicrobial effectiveness testing are conducted at initial, 6, 12, 18, 24 and 36 months on long-term samples and initial and 6 months for accelerated samples
- AET testing is only performed on registration stability batches and not for release

P.8.3 Stability Data

Data are provided for Long term and accelerated storage from initial to 6M:
Long Term 5°C ± 3°C and accelerated 25°C ± 2°C/60% 5% RH
Microbial Limits: TAMC - < 10 cfu/mL (specifications NMT (b) (4) cfu/mL)
TYMC- <10 cfu/mL (specifications NMT (b) (4) cfu/mL)
Escherichia coli- absent (specifications (b) (4) /mL)
Antimicrobial Effectiveness Test: conforms to USP <51> (specifications Meets current USP <51>)
Exhibit Batches 23101.004A, 23101.005A, and 23101.006A were tested.

In addition, the applicant has performed and provided data for in-use stability of the drug product. The data provided showed that the drug product remains within specification after 3 months under long-term storage condition followed by 2 months at accelerated conditions.

Note to reviewer: The 6 months stability data submitted is adequate. However, the applicant has committed to update the Agency within 4 months of filing and a regression analysis to support the proposed shelf-life of 24 months. Updated information has not been received by the Agency.

ADEQUATE

Reviewer's Assessment: Acceptable

Based on the information provided in the application, there were no product quality

microbiology deficiencies identified.

2.3.P.7 Container/Closure System

41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:
Please refer to question #40 above

Reviewer's Assessment: Acceptable

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:
Not Applicable.

Reviewer's Assessment: N/A

Please refer to Question #40 above for product quality microbiology

43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:
There are no components of biological origin in the submission.

Reviewer's Assessment: N/A

Please refer to question #40 for product quality microbiology

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The drug product is a non-sterile oral solution. There are no microbiology deficiencies identified based on the information submitted. The application is recommended for approval.

Reviewer's Signature:
Wendy Tan, Ph.D., May 05, 2016
Microbiologist
OPQ/OPF/DMA/Branch II

Secondary Review Comments and Concurrence:
I concur with Dr. Tan's Microbiology assessment and approval recommendation.

Neal J. Sweeney, Ph.D. May 5, 2016
Microbiology Quality Assessment Lead (Acting)
OPQ/OPF/DMA/Branch II

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant states the following:

1.12.14 Environmental Analysis

Silvergate Pharmaceuticals, Inc. (Silvergate), hereby claims a categorical exclusion from the requirement to submit an environmental assessment under 21 CFR 25.31(a) for Methotrexate Oral Solution as action on this NDA does not increase the use of the active moiety.

Furthermore, to the best of Silvergate's knowledge, no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment [21 CFR 25.15(d)].

Reviewer's Assessment: As the Categorical Exclusion is a 'no increased use' claim (21CFR25.31(a)), it is acceptable based on all available dosage forms for Methotrexate, as per the Agency's Environmental Assessment Team (R. A. Bloom). The applicant's Environmental Assessment is adequate for the approval of the NDA.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The applicant's Environmental Assessment and Categorical Exclusion Claim are acceptable for the approval of the NDA.

Sukhamaya (Sam) Bain, Ph.D., 31-MAY-2016

Secondary Review Comments and Concurrence:

I concur with Dr. Bain's assessment that the information is adequate to support approval of the NDA.

Donna F. Christner, Ph.D
Branch Chief (Acting)
31-May-2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADENAME safely and effectively. See full prescribing information for TRADENAME.

TRADENAME (methotrexate) oral solution
Initial U.S. Approval: 1953

----------DOSAGE AND ADMINISTRATION----------

- Use another formulation of methotrexate for patients requiring (b) (4) (b) (4) (2.1).
- Measure with an accurate measuring device (2.1)
- ALL: 20 mg/m^2 weekly (2.2)
- pJIA: 10 mg/m^2 once weekly (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Oral solution: 2.5 mg/mL (3).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	TRADENAME (methotrexate) oral solution	Proprietary name has not yet been accepted by the Agency. However, the presentation of the proprietary and established names is appropriate.
Dosage form, route of administration	Oral Solution, 2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL)	Supported by CMC information in the NDA
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Oral solution: 2.5 mg/mL	Supported by CMC information in the NDA and in conformance with Labeling Tool.

Conclusion: The information in the label is supported by that in the CMC section, and is adequate.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

TRADENAME is a clear yellow to orange oral solution that contains 2.5 mg of methotrexate per milliliter.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Oral solution	Supported by CMC information in the NDA
Strengths: in metric system	2.5 mg/mL	Supported by CMC information in the NDA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear solution, yellow to orange in color	Supported by CMC information in the NDA

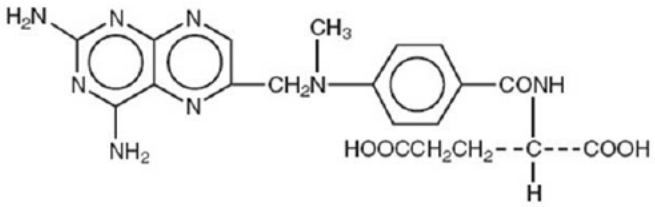
Conclusion: The information in the label is supported by that in the CMC section, and is adequate.

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

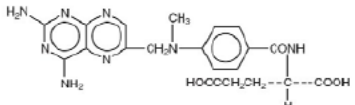
TRADENAME contains methotrexate, a folate analog metabolic inhibitor.

Chemically methotrexate is N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid. The structural formula is:



Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$

TRADENAME is a clear yellow to orange oral solution that contains 2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL). Inactive ingredients include purified water, sodium citrate, citric acid, methylparaben sodium, propylparaben sodium, and sucralose. It may also contain sodium hydroxide or hydrochloric acid for pH adjustment.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRADENAME (methotrexate) oral solution	Supported by CMC information in the NDA
Dosage form and route of administration	Oral solution and oral	Supported by CMC information in the NDA
Active moiety expression of strength with equivalence statement for salt (if applicable)	2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL)	Supported by CMC information in the NDA and provided in the appropriate format
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Purified water, sodium citrate, citric acid, methylparaben sodium, propylparaben sodium, and sucralose	Supported by CMC information in the NDA and provided in the appropriate format
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Folate analog metabolic inhibitor	Adequate
Chemical name, structural formula, molecular weight	Chemically methotrexate is N-[4-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-L-glutamic acid. The structural formula is:  Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$	Supported by CMC information in the NDA and in the appropriate format
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	N/A

Conclusion: The information in the label is supported by that in the CMC section, and is adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADENAME is an oral solution that contains 2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL). It is packaged in a high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal. Each bottle contains 120 mL.

NDC 52652-2001-1

Prior to dispensing to the patient, keep TRADENAME refrigerated (2 to 8°C/36 to 46°F) (b) (4) avoid freezing and excessive heat. Patients may store TRADENAME at room temperature (25°C (77°F)) for up to 60 days; excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	2.5 mg/mL and oral solution	Supported by CMC information in the NDA
Available units (e.g., bottles of 100 tablets)	HDPE bottles containing 120 mL	Supported by CMC information in the NDA
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Oral solution NDC 52652-2001-1	Color of oral solution should be added. NDC number is provided and is the same as that provided on the primary container.
Special handling (e.g., protect from light, do not freeze)	The drug product is stored refrigerated prior to dispensing. Freezing and excessive heat should be avoided.	Supported by CMC information in the NDA
Storage conditions	Prior to dispensing to the patient, keep TRADENAME refrigerated (2-8 °C/36-46 °F) and avoid freezing and excessive heat. Patients may store TRADENAME at room temperature (25°C (77°F)) for up to 60 days; excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].	Storage condition is supported by stability data in CMC Module 3.2.P.8.3.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Silvergate Pharmaceuticals, Inc.	Supported by CMC information in the NDA

Conclusion: No physical description of the drug product is provided in "How Supplied" section. The color of the solution will be added to the PI. This is adequate pending the recommended change.

2. Container and Carton Labeling

1) Immediate Container Label (Updated 06-MAY-2016)

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name and established name are provided in clearly readable and prominent fonts.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided prominently	Adequate
Route of administration 21.CFR 201.100(b)(3))	Provided prominently	Adequate
Net contents* (21 CFR 201.51(a))	(120 ml) Provided prominently	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not required for oral dosage forms	Adequate
Lot number per 21 CFR 201.18	Provided prominently	Adequate
Expiration date per 21 CFR 201.17	Provided prominently	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided prominently	Adequate
Storage (not required)	Provided prominently	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided prominently, and is identical to that in the PI.	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided prominently	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided prominently	Adequate
Others	Keep out of the reach of children	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: The information in the label is supported by that in the CMC section, and is adequate.

2) Carton Labeling

Not provided. No secondary packaging.

Conclusion: N/A

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The color of the solution will be added to the PI that will be conveyed with other labeling comments. Once this issue is addressed, the labeling will be adequate per CMC.

Sukhamaya (Sam) Bain, Ph.D., 13-APR-2016

Secondary Review Comments and Concurrence:

I concur with Dr. Bain's assessment that the information is adequate to support approval of the NDA.

Donna F. Christner, Ph.D
Branch Chief (Acting)

28-May-2016

II. List of Deficiencies To Be Communicated

Facility Review Pending

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Not needed for low risk	Acceptable	None
Physical stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Not needed for low risk	Acceptable	None
Dosing accuracy	• Dosing device • Formulation • Process Parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	No dosing device is included. Dosing accuracy remains a medium risk.
Palatability	• Formulation • Excipient change • Process parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Oral solution	Acceptable	
Leachables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M	The risk related to the potential leachables from the drug product manufacturing process is low.	Acceptable	Extractable/ leachable studies are found satisfactory.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VERIFICATION REPORT SUMMARY

TO: Sam Bain, CMC Reviewer
Janice Brown, Quality Assessment Lead (QAL)
Rabiya Laiq
Office Name: OPQ/ONDP
E-mail Address: sam.bain@fda.hhs.gov
Phone: 240-402-8890

FROM: FDA
Division of Pharmaceutical Analysis
Laura C. Pogue, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-2155

Through: Michael Trehy, Ph.D., Lab Chief, Branch II
Phone: (314) 539-3815

SUBJECT: Methods Verification Report Summary

Application Number: NDA 208400

Name of Product: (methotrexate) oral solution, 2.5 mg/mL

Applicant: Silvergate Pharmaceuticals, Inc.

Applicant's Contact Person: Michael Beckloff

Address: 6251 Greenwood Plaza Blvd, Ste 101, Greenwood Village, CO 80111

Telephone: 913.871.1247 Email: michael.beckloff@silvergatepharma.com

Date Methods Verification Consult Request Form Received by DPA: 11/11/2005

Date Methods Verification Package Received by DPA: 1/6/2016

Date Samples Received by DPA: 1/6/2016

Date Analytical Completed by DPA: 3/7/2016

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached summary for analyst comments and results.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, Missouri 63110
Telephone (314) 539-3863
FAX (314) 539-2113

Date: March 4, 2016

To: Sam Bain, CMC Reviewer
Janice Brown, Quality Assessment Lead (QAL)
Rabiya Laiq, Method Verification Requestor

From: Kimberly D. Story, Chemist, CDER/OPQ/OTR/DPA

Through: Michael Trehy, Ph.D., Lab Chief, Branch II, CDER/OPQ/OTR/DPA

Subject: Method Verification of NDA 208400: Methotrexate Oral Solution, 2.5mg/mL

The following method has been verified and found acceptable for quality control and regulatory purposes:

1) (b) (4) Number: (b) (4) 14-0050.01 HPLC Method for the Identification, Assay, (b) (4) and Related Substance of Methotrexate Oral Solution, Effective Date: APR 28, 2015

Link to supporting data: http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c9bd15

Summary of Analysis:

(b) (4)

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/s/

LAURA POGUE
03/07/2016

MICHAEL L TREHY
03/07/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

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Division of Pharmaceutical Analysis
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