

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-468

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

09-SEP-2009

NDA 22-468/N-000 and NDA 22-468/Amendment 0007

Drug Product Name

Proprietary: Folotyn™
Non-proprietary: Pralatrexate Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
23-MAR-2009	24-MAR-2009	N/A	17-AUG-2009
03-JUN-2009/0007	03-JUN-2009	N/A	17-AUG-2009

Applicant/Sponsor

Name: Allos Therapeutics, Inc.
Address: 11080 Circlepoint Road, Suite 100
Westminster, CO 80020
Representative: Todd Marshall
Director, CMC regulatory affairs
Telephone: 720-540-5256

Name of Reviewer: Steven E. Fong, Ph.D.

Conclusion: Recommended for approval from a microbiology quality standpoint.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA
2. **SUBMISSION PROVIDES FOR:** New drug product.
3. **MANUFACTURING SITES:**
- **Drug product manufacturing, labeling, and packaging:** Will take place at two sites:

(b) (4)



- **Drug product QC release and stability testing:** Will take place at two sites:

(b) (4)



- **Container-closure integrity testing**  (b) (4)

(b) (4)



4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile solution for intravenous injection
- 30 mg/m² administered twice weekly for 6 to 7 weeks
- 20 mg presentation: supplied as a 20 mg/1 mL solution
- 40 mg presentation: supplied as a 40 mg/2 mL solution

5. METHOD(S) OF STERILIZATION: (b) (4)**6. PHARMACOLOGICAL CATEGORY:** Cancer therapeutic.**B. SUPPORTING/RELATED DOCUMENTS:** None.**C. REMARKS:**

- 1) The original NDA application contained duplicate quality manufacturing information for product produced at the (b) (4) facilities. On 03-JUN-2009, in response to an Agency request to provide merged drug product sections, the sponsor submitted an amendment, NDA 22-468/0007, that merged the following sections: 2.3.P.2, 2.3.P.3, 3.2.P.2.3, 3.2.P.2.5, 3.2.P.3.1, 3.2.P.3., 3.2.P.3.5, 3.2.P.4.4, and 3.2.P.7.
- 2) The following e-mail information requests were sent to sponsor representative Todd Marshall:
 - 28-AUG-2009: Request for: (1) validation protocol and data for (b) (4) (2) data or submission location regarding (b) (4)
 - 31-AUG-2009: Request for (b) (4) report for (b) (4)
 - 02-SEP-2009: Request for: (1) product hold period specification; (2) validation protocol and data for (b) (4) used to assess container-closure integrity.
 - 04-SEP-2009: Request for (1) location of endotoxin testing validation assay; (2) justification of (b) (4) specification for container-closure integrity testing.
- 3) The sponsor provided e-mail responses to the 28-AUG-2009, 31-AUG-2009, 02-SEP-2009 and 04-SEP-2009 information requests on 28-AUG-2009, 02-SEP-2009, 03-SEP-2009, and 04-SEP-2009/08-SEP-2009, respectively. These responses were formalized as an amendment and submitted to the Agency on 08-SEP-2009.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – Recommended for approval from a microbiology quality standpoint.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

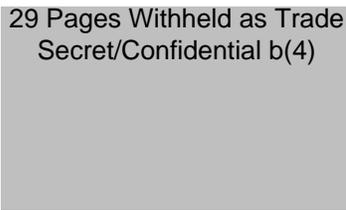
II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is to be sterilized by [REDACTED] (b) (4)
- B. Brief Description of Microbiology Deficiencies** – None.
- D. Assessment of Risk Due to Microbiology Deficiencies** – Acceptable risk.

III. Administrative

- A. Reviewer's Signature:** _____
Steven E. Fong, Ph.D.
Microbiology Reviewer
- B. Endorsement Block:** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

29 Pages Withheld as Trade Secret/Confidential b(4)



Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

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

/s/

STEVEN E FONG

09/09/2009

Recommended for approval from a microbiology quality standpoint.

STEPHEN E LANGILLE

09/10/2009

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 22468/000
Submit Date: 24-MAR-2009
Regulatory: 24-SEP-2009

Action Goal:
District Goal: 25-NOV-2009

Applicant: ALLOS
 11080 CIRCLE POINT RD STE 200
 WESTMINSTER, CO 80020

Brand Name: FOLOTYN
Estab. Name:
Generic Name: PRALATREXATE INJECTION
 20MG/1ML40MG/2ML

Priority:
Org. Code: 150

Product Number; Dosage Form; Ingredient; Potency
 001; INJECTION; PRALATREXATE; 20MG/1ML
 002; INJECTION; PRALATREXATE; 40MG/2ML

Application Comment: THIS IS A PRIORITY NDA. (on 22-APR-2009 by D. MESMER (HFD-800) 301-796-4023)

FDA Contacts:	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	S. LIN	Review Chemist		301-796-1403
	T. OCHELTREE	Team Leader	(HFD-800)	301-796-1988

Overall Recommendation: ACCEPTABLE on 18-SEP-2009 by C. CRUZ (HFD-323) 301-796-3254

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: (b) (4)
 Estab. Comment: (b) (4)
 Profile: OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-APR-2009				MESMERD
OC RECOMMENDATION	23-APR-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)

Estab. Comment: (b) (4)

(b) (4)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-APR-2009				MESMERD
OC RECOMMENDATION	23-APR-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)
(b) (4)

Estab. Comment: (b) (4)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					<u>Reason</u>
SUBMITTED TO OC	23-APR-2009				MESMERD
SUBMITTED TO DO	23-APR-2009	10-Day Letter			FERGUSONS
EIR RECEIVED BY OC	14-SEP-2009				CRUZC
DO RECOMMENDATION	18-SEP-2009			WITHHOLD	DEMERSON
BASED ON THE LACK OF INFORMATION IN THE CURRENT INSPECTION REPORT, WE CANNOT BE ASSURED THAT ALL PREVIOUS DEFICIENCIES HAVE BEEN CORRECTED BY THIS FIRM. THE FIRM'S PREVIOUS INSPECTION WAS OAI WHICH RESULTED IN A REGULATORY MEETING.				PREVIOUS DEVIATIONS PERSIST	
			(b) (4)		
OC RECOMMENDATION	18-SEP-2009			ACCEPTABLE	CRUZC
CDER OC REVIEWED THE FIRM RESPONSE AND FOUND IT TO BE ADEQUATE			(b) (4)	FIRM RESPONSE TO DEFIC. ADEQUA	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)
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(b) (4)
(b) (4)

Estab. Comment: (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

Profile: OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-APR-2009				MESMERD
OC RECOMMENDATION	23-APR-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)

Estab. Comment: (b) (4)

Proc: (b) (4)

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					<u>Reason</u>

SUBMITTED TO OC	23-APR-2009				MESMERD
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SUBMITTED TO DO	23-APR-2009	Product Specific			FERGUSONS
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DO RECOMMENDATION	30-APR-2009			WITHHOLD	SBERRYMA
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THE PREVIOUS INSPECTION OF (b) (4) FOUND SEVERAL SIGNIFICATION DEFICIENCIES UNDER PROCEDURES DESIGNED TO PREVENT MICROBIOLOGICAL CONTAMINATION OF DRUG PRODUCTS INCLUDING NO CLEANING VALIDATION, NO PROTOCOL/Written PROCEDURES FOR HEPA FILTER LEAK TESTING, FILTER VELOCITIES & VELOCITY VARIATION, NO PROTOCOL FOR SMOKE TEST PROCEDURE OR ACCEPTANCE OF SMOKE STUDY, AND DIFICIENCIES WITH MEDIA FILLS. IN ADDITION, THERE WERE ALSO ISSUES WITH TRAINING, INADEQUATE INVESTIGATIONS, AND INTEGRITY OF MICRO SAMPLES DUING SHIPMENT. (b) (4)

EQUIPMENT CLEANING VALIDATION
INADEQUATE ENVIRONMENT CONTROL
(b) (4)

BASED ON FILE REVIEW, (b) (4) RECOMMENDS WITHHOLD AT THIS TIME FOR THIS APPLICATION.

OC RECOMMENDATION	18-MAY-2009			WITHHOLD	TGOEN
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BASED ON REVIEW OF FDA-483 AND DISTRICT RECOMMENDATION. RECENT INSPECTION FOUND THE FOLLOWING DEFICIENCIES:
INADEQUATE/LACK OF PROCEDURES DESIGNED TO PREVENT MICROBIOLOGICAL CONTAMINATION OF DRUG PRODUCTS INCLUDING NO CLEANING VALIDATION, NO PROTOCOL/Written PROCEDURES FOR HEPA FILTER LEAK TESTING, FILTER VELOCITIES & VELOCITY VARIATION, NO PROTOCOL FOR SMOKE TEST PROCEDURE OR ACCEPTANCE OF SMOKE STUDY, AND DEFICIENCIES WITH MEDIA FILLS. IN ADDITION, THERE WERE ISSUES WITH TRAINING, INADEQUATE INVESTIGATIONS, AND INTEGRITY OF MICRO PLES DURING SHIPMENT.

DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

SUBMITTED TO DO 09-SEP-2009 10-Day Letter (b) (4)

DO RECOMMENDATION 10-SEP-2009 ACCEPTABLE SBERRYMA

AN INSPECTION WAS CONDUCTED (b) (4) TO COVER 483 OBSERVATIONS FROM THE PREVIOUS INSPECTION OF (b) (4) PRALATREXATE WAS ALSO COVERED DURING THE (b) (4) INSPECTION. A TWO ITEM FDA 483 WAS ISSUED AND INCLUDED INADEQUATE GOWNING. EMPLOYEES DON SHOE COVERS, CROSS OVER TO THE CLEAN SIDE, THEN DON THE REST OF THEIR STERILE GOWN. DURING CLEANING OF THE CLEAN ROOMS EMPLOYEES WERE OBSERVED PLACING USED WIPES IN A PLASTIC BAG IN THE SAME BUCKET WITH STERILE WIPES. THE WIPES ARE USED TO DISINFECT EQUIPMENT IN THE 100 AREA. SEVERAL VERBAL ITEMS WERE ALSO DISCUSSED AND SOME CORRECTED PRIOR TO THE CONCLUSION OF THE INSPECTION. PROCESS VALIDATION WAS COVERED DURING THE INSPECTION. BASED ON FILE REVIEW, (b) (4) RECOMMENDS APPROVABLE FOR THIS APPLICATION. BASED ON FILE REVIEW

OC RECOMMENDATION 11-SEP-2009 ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION
