CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

December 18, 2009

NDA: **21-201 amendment 056**

Drug Product Name
Proprietary: (b) (4)
Non-proprietary: polidocanol

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
December 9, 2009	December 10, 2009	December 18, 2009	December 18, 2009

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
July 10, 2009	1	November 30, 2009
July 21, 2008	Non-Fileable submisson	August 19, 2008

Applicant/Sponsor
Name: Chemische Fabrik Kreussler
Address: 4700 Falls of Neuse Road, Raleigh, NC 27609
Representative: Howard M. Smith, US Agent for Kreussler
Telephone: 804-556-6357, Cell: 804-248-2645

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: The application is recommended for approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Amended response concerning qualification of (b) (4).

2. SUBMISSION PROVIDES FOR: New Drug Application.

3. MANUFACTURING SITE: (b) (4), (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Intravenous solution, in 0.5%, 1%, (b) (4) presentations.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Vericose Vein Treatment

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: The original NDA 21-201 was submitted by Kreussler in 1999 with (b) (4) as the contract manufacturer and re-submitted in 2003 with (b) (4) as the designated manufacturer. In response to the Agency's approvable letter dated August 2, 2004, the NDA was once again resubmitted on June 21, 2008 with (b) (4) as the new contract manufacturer. At the time of the June 2008 submission, (b) (4) was in a process of constructing a new extension containing new and old transferred equipment for manufacturing this product. The incomplete submission was deficient in the product sterility information and therefore received a non-fileable status (FDA's letter dated August 18, 2008). The sponsor responded by submitting an amendment dated July 10, 2009. This amendment received an approvable status pending resolution of a deficiency regarding (b) (4) (b) (4) The sponsor has responded to this deficiency in an amendment (#056) dated December 9, 2009. This review pertains to amendment #056. The original IQA was filed by Kasturi Srinivasachar on August 8, 2008.

filename: **C:\my documents\review\NDA\NO21201R2**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is recommended for approval.

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 bulk Aethoxysklerol solution (b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D.

B. Endorsement Block _____
Stephen E. Langille, Ph.D.

C. CC Block
N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1%(b) (4)

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/s/

VINAYAK B PAWAR
12/18/2009

STEPHEN E LANGILLE
12/21/2009

Product Quality Microbiology Review

November 20, 2009

NDA: **21-201**

Drug Product Name
Proprietary: (b) (4)
Non-proprietary: polidocanol

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
July 10, 2009	July 12	July 15, 2009	July 17, 2009

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
July 21, 2008	Non-Fileable submisson	August 19, 2008

Applicant/Sponsor
Name: Chemische Fabrik Kreussler
Address: 4700 Falls of Neuse Road, Raleigh, NC 27609
Representative: Howard M. Smith, US Agent for Kreussler
Telephone: 804-556-6357, Cell: 804-248-2645

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: The application is approvable pending resolution of the deficiency cited in Section H of this review.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Resubmitted NDA for priority review in response to a non-fileable status.

2. SUBMISSION PROVIDES FOR: New Drug Application.

3. MANUFACTURING SITE: (b) (4), Germany.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Intravenous solution, in 0.5%, 1%, (b) (4) presentations.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Vericose Vein Treatment

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: The original NDA 21-201 was submitted by Kreussler in 1999 with (b) (4) as the contract manufacturer and re-submitted in 2003 with (b) (4) as the designated manufacturer. In response to the Agency's approvable letter dated August 2, 2004, the NDA was once again resubmitted on June 21, 2008 with (b) (4) as the new contract manufacturer. At the time of the June 2008 submission, (b) (4) was in a process of constructing a new extension containing new and old transferred equipment for manufacturing this product. This incomplete submission was deficient in the product sterility information and therefore received a non-fileable status (FDA's letter dated August 18, 2008). The sponsor has since responded by submitting the subject amendment dated July 10, 2009. The original IQA was filed by Kasturi Srinivasachar on August 8, 2008.

filename: **C:\my documents\review\NDA\NO21201R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is approvable pending resolution of the deficiency cited in Section H of this review.

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 bulk Aethoxysklerol solution (b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D.

B. Endorsement Block _____
Stephen E. Langille, Ph.D.

C. CC Block
N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1%/ (b) (4)

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/s/

VINAYAK B PAWAR
11/30/2009

STEPHEN E LANGILLE
11/30/2009

Product Quality Microbiology Review

19 August 2008

NDA: 21-201

Drug Product Name
Proprietary: (b) (4)
Non-proprietary: polidocanol
Drug Product Priority Classification: S1

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
July 21, 2008	July 22, 2008	August 6, 2008	August 7, 2008

Submission History (for amendments only) - N/A

Applicant/Sponsor

Name:	Chemische Fabrik Kreussler
Address:	4700 Falls of Neuse Road, Raleigh, NC 27609
Representative:	Howard M. Smith, US Agent for Kreussler
Telephone:	804-556-6357, Cell: 804-248-2645

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: The data provided for review is not fileable from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Resubmitted NDA for Priority Review. PDUFA Goal Date Jan-21, 2009.

2. SUBMISSION PROVIDES FOR: NDA resubmission as a complete response to the approvable letter date August 2, 2004.

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Intravenous solution, in 0.5%, 1%, (b) (4) presentations.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Vericose Vein Treatment

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This NDA 21-201 was submitted as an amendment and a response to the Agency's approvable letter dated August 2, 2004. The original NDA was submitted in 1999 with (b) (4) as the manufacturer and re-submitted in 2003 with (b) (4) as the designated manufacturer. The sponsor has resubmitted the NDA with (b) (4) as the new manufacturer which will utilize new equipment as well as the transfer of the original equipment. All equipment will/are being located to the new facility. The IQA was filed by Kasturi Srinivasachar on August 8, 2008.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is not fileable from microbiology product 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 – N/A

B. Brief Description of Microbiology Deficiencies – See Product Quality Microbiology Assessment.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Vinayak. B. Pawar, Ph.D.
CDER/OPS/NDMS

B. Endorsement Block _____

James McVey, Team Leader
Team Leader, CDER/OPS/NDMS

C. CC Block

N/A

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/s/

Vinayak Pawar
8/21/2008 02:11:00 PM
MICROBIOLOGIST

The NDA 21-201 N000 BZ is not fileable in its presented form

James McVey
8/21/2008 02:17:10 PM
MICROBIOLOGIST
I concur.

Product Quality Microbiology Review
Review for HFD 540
18-October-2004

NDA:	21-201 (MP)
Drug Product Name:	Aethoxysklerol
Non-proprietary	Polidocanol
Drug Product Classification:	
Review Number:	2
Subject of this Review	
Submission Date:	September 20, 2004
Receipt Date:	Not provided
Consult Date:	Not provided
Date Assigned for Review:	October 4, 2004
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	September 19, 2003
Date(s) of Previous Micro Review(s):	June 17, 2004
Applicant/Sponsor	
Name:	Chemische Fabrik Kreussler & Co., GmbH
Address:	Rheingaustrasse 87-93 D-65203 Weisbaden Germany
Representative:	Howard M. Smith INC Research, Inc. 675 Peter Jefferson Parkway, Suite 120 Charlottesville, VA 22911
Telephone:	434-244-5165

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Approvable pending revision

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Meeting package submitted in response to the non-approvable letter provided to the Applicant following the first review of NDA 21-201.

2. SUPPLEMENT PROVIDES FOR: Not applicable

3. MANUFACTURING SITE: (b) (4)

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

- Solution
- Intravenous injection
- 0.5%, 1%, (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Varicose vein treatment

B. SUPPORTING/RELATED DOCUMENTS: none

C. REMARKS: INC research has submitted a briefing package for the Type A meeting held on October 13, 2004. In this briefing package, the Applicant has responded to the microbiology deficiencies provided in the June 16, 2004 review. The Applicant was advised to submit the responses to these deficiencies in writing as part of the response to the non-approvable letter.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 21-201 is approvable pending the resolution of microbiological deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The drug product will (b) (4)

B. Brief Description of Microbiology Deficiencies –

The applicant failed to provide adequate information regarding:

- (b) (4) of production and validation cycles
- A re-validation schedule for the (b) (4)
- Diagrams of (b) (4) and biological indicator placement in validation loads
- D-value estimations for the biological indicators in the drug product.

C. Assessment of Risk Due to Microbiology Deficiencies -

Failure to address the microbiological deficiencies could result in an increased risk of microorganisms surviving the sterilization cycles.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Stephen E. Langille, Ph.D.
David Hussong, Ph.D.

C. CC Block

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/s/

Stephen Langille
10/20/04 01:47:22 PM
MICROBIOLOGIST

David Hussong
10/20/04 02:54:33 PM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD 540
17-June-2004

NDA:	21-201
Drug Product Name:	Aethoxysklerol
Non-proprietary	Polidocanol
Drug Product Classification:	
Review Number:	1
Subject of this Review	
Submission Date:	September 29, 2003
Receipt Date:	October 2, 2003
Consult Date:	October 28, 2003
Date Assigned for Review:	April 28, 2004
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	
Date(s) of Previous Micro Review(s):	
Applicant/Sponsor	
Name:	Chemische Fabrik Kreussler & Co., GmbH
Address:	Rheingaustrasse 87-93 D-65203 Weisbaden Germany
Representative:	Howard M. Smith INC Research, Inc. 675 Peter Jefferson Parkway, Suite 120 Charlottesville, VA 22911
Telephone:	434 244-5165

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Approvable pending revision

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Original Submission

2. SUPPLEMENT PROVIDES FOR: Not applicable

3. MANUFACTURING SITE: (b) (4)

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

- Solution
- Intravenous injection
- 0.5%, 1%, (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Varicose vein treatment

B. SUPPORTING/RELATED DOCUMENTS: none

C. REMARKS:

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Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 21-201 is approvable pending the resolution of microbiological deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The drug product will be (b) (4)

B. Brief Description of Microbiology Deficiencies –

The applicant failed to provide adequate information regarding:

- (b) (4) of production and validation cycles
- A re-validation schedule for the (b) (4)
- Diagrams of (b) (4) and biological indicator placement in validation loads
- D-value estimations for the biological indicators in the drug product.

C. Assessment of Risk Due to Microbiology Deficiencies -

Failure to address the microbiological deficiencies could result in an increased risk of microorganisms surviving the sterilization cycles.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Stephen E. Langille, Ph.D.
Peter Cooney, Ph.D.

C. CC Block

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/s/

Stephen Langille
6/21/04 10:46:47 AM
MICROBIOLOGIST

Peter Cooney
6/21/04 01:06:25 PM
MICROBIOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Peter H. Cooney, PhD., Associate Director for New Drug Microbiology
HFD-805, Office of Pharmaceutical Science

FROM: Lea Carrington, Regulatory Project Manager
HFD-540, Derm and Dental

DATE:	IND NO.	NDA NO.:	TYPE OF DOCUMENT	DATE OF DOCUMENT:
October 28, 2003		21-201		September 29, 2003

NAME OF DRUG:	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Aethoxysklerol (polidocanol) injectable		Sclerosing agent	Filing meeting on 11/10/03; review completion date TBD.

NAME OF FIRM: Chemische Fabrik Kreussler & Co., GmbH

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Please provide microbiological consultation for preservative effectiveness and sterility. Review information is located in volumes 5.1, 5.2, and 5.29.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Lea Carrington	x☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Peter Cooney

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