

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-359

CHEMISTRY REVIEW(S)

NDA 21-359

Rectiv (nitroglycerine ointment USP) 0.4%

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: ProStraken, Inc.
1430 US Highway 206, Suite 110
Bedminster, NJ 07921

Indication: For the treatment of moderate to severe pain associated with chronic anal fissure

Presentation: Available in 30 g (NDC 42747-235-30) aluminum tubes with polyethylene screw caps.

EER Status:	Recommendations:	Acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	Consult requested
	Methods Validation -	Not recommended
	DMETS-	Acceptable
	Biopharm-	acceptable
	Microbiology -	Satisfactory
	Pharm/toxicology -	Satisfactory

Original Submission: 26-Jun-2001
Resubmission: 21-Dec-2010

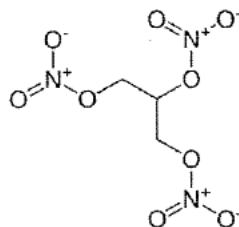
Post-Approval CMC Agreements: None

Background:

This is a standard NDA resubmission with a 6 month clock. Theis NDA was originally submitted to the Division of CardioRenal products and later submitted to the current Division of Anesthesia, Analgesia, and Addiction Products. The NDA is electronic format with electronic labeling provided in SPL format. The original submission was given a Complete Response due to several CMC and Clinical issues.

Drug Substance:

Nitroglycerin is 1,2,3,-propanetriol trinitrate, an organic nitrate whose structural formula is as follows and whose molecular weight is 227.09.



The drug substance is obtained as a (b) (4) % colorless solution of nitroglycerin in (b) (4). The CMC information for the drug substance is referenced in a DMF (b) (4) which was found adequate. Compliance status of the drug substance manufacturing facility was found acceptable as of Oct. 2009.

The drug substance is controlled by testing for appearance, identification (TLC and HPLC methods), assay, purity and related substances.

Conclusion: The drug substance is satisfactory.

Drug Product:

RECTIV (nitroglycerin) Ointment 0.4% contains 0.4% nitroglycerin w/w (4 mg nitroglycerin/1 g ointment), propylene glycol, lanolin, sorbitan sesquioleate, paraffin wax, and white petrolatum. It is available in tubes with a one-inch dosing line on the carton allowing the measurement of approximately 375 mg of nitroglycerin ointment 0.4% (1.5 mg nitroglycerin) for application. The composition is provided below.

Ingredient	Quantity w/w%	Function	Compendial
(b) (4) Nitroglycerin in (b) (4)	4.0	Active	USP
White Petrolatum*	(b) (4)		USP
Lanolin			USP
Paraffin			NF
Sorbitan Sesquioleate			NF

*White Petrolatum is also known as White Soft Paraffin.

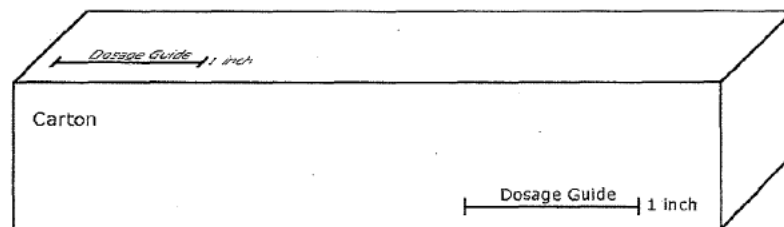
The drug product has seen many changes in scale and site. The clinical batches were made in (b) (4). In the current submission, the applicant proposed a new manufacturing site in Germany (Pharbill Waltrop GmbH, Waltrop, Germany-NextPharma) and has also increase the scale to (b) (4) kg. The applicant also proposes to increase the scale to (b) (4) Kg in the future with a prior approval supplement.

Compliance status of the drug product manufacturing facility was found acceptable as of Oct. 2009

The comparability of the drug product attribute *in vitro* drug release was used to bridge the scale and site transfers proposed by the applicant. The ONDQA biopharm reviewer found the drug products to be comparable.

The drug product is controlled by testing for the following attributes: appearance, viscosity, identity, homogeneity of nitroglycerin, assay, related substances, minimum fill, microbial limits, and packaging integrity.

The drug product is packaged in an unlined printed 30 gm aluminum tube and a white low density polyethylene cap. Although the applicant has provided a 5 gm presentation, it is not proposed for marketing.



The current stability data supports a proposed shelf life of 18 months.

Conclusion: The drug product is satisfactory.

CMC issues that are still pending: None.

Overall Conclusion: The NDA is recommended for approval from CMC standpoint.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

RECTIV

(nitroglycerin)
Ointment 0.4%



(01)103 42747 235305

For Intra-anal Use Only.

Read Patient Information before use.

Each 375 mg dose of ointment (1 inch) contains 1.5 mg of nitroglycerin.

Keep out of the reach of children.

Usual Dose: Apply 1 inch of ointment intra-anally approximately every 12 hours.
Treatment should continue for up to three weeks or as instructed by your physician.

Active Ingredient: nitroglycerin. **Inactive Ingredients:** propylene glycol, lanolin, sorbitan sesquilester, paraffin wax, and white petrolatum.

Store at 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F).
[see USP Controlled Room Temperature]

Keep the tube tightly closed. Use within 8 weeks of first opening.

Rx Only

30 g

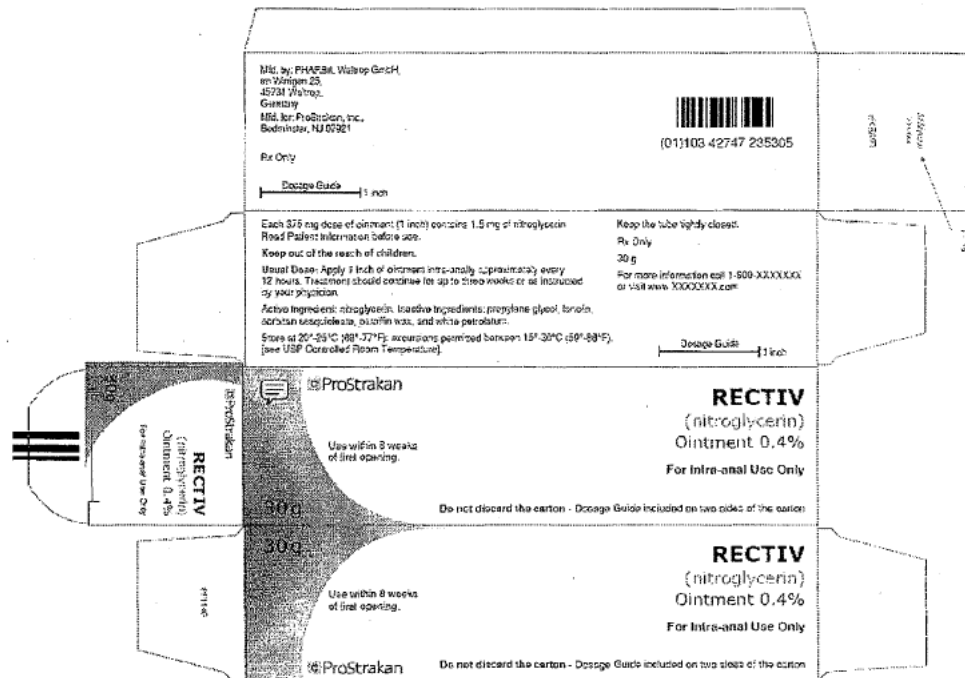
Mfd. by: PHARBI, Waltryp GmbH, Im Wirtigen 25, 46731 Waltryp, Germany
Mfd. for: ProStrakan, Inc., Bedminster, NJ 07921

PRO136

ProStrakan

LOT/EXP:

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/s/

PRASAD PERI
06/21/2011
Recommend Approval

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

Application:	NDA 21359/000	Action Goal:	
Submission Date:	26-JUN-2001	District Goal:	29-JAN-2010
Regulatory:	21-JUN-2011		
Applicant:	PROSTRAKAN INC 1430 STATE HWY 206 STE 110 BEDMINSTER, NJ 07921	Brand Name:	CELLEGESIC NITROGLYCERIN OINTMENT 0.4%
		Estab. Name:	
		Generic Name:	NITROGLYCERIN OINTMENT
Priority:	3S	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	170		001; OINTMENT; NITROGLYCERIN; .2% 002; OINTMENT; NITROGLYCERIN; .4%
Application Comment:	THIS IS A RE-SUBMISSION FOLLOWING A COMPLETE RESPONSE (on 16-OCT-2009 by (b) (4))		
	CONTACT PERSON FOR THE APPLICATION IS MARY NORVITCH, PHONE: 908-375-7903; FAX: 908-234-9068 (on 16-OCT-2009 by (b) (4))		
FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	O. STEPHENS	Review Chemist (HFD-170)	301-796-3901
	D. CHRISTODOULOU	Team Leader	301-796-1342
Overall Recommendation:	ACCEPTABLE	on 05-NOV-2009	by FERGUSONS
	ACCEPTABLE	on 09-DEC-2004	by ADAMSS

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: THE STREET ADDRESS FOR THE FACILITY IS

(b) (4)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-AUG-2001				(b) (4)
OC RECOMMENDATION	06-AUG-2001			ACCEPTABLE BASED ON PROFILE	(b) (4)
REQUEST CANCELLED	25-APR-2002				EES_PROD
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	19-JUL-2004				(b) (4)
OC RECOMMENDATION	19-JUL-2004			ACCEPTABLE BASED ON PROFILE	(b) (4)
SUBMITTED TO OC	16-OCT-2009				(b) (4)
SUBMITTED TO DO	16-OCT-2009	10-Day Letter			(b) (4)
DO RECOMMENDATION	26-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	(b) (4)
LAST GMP EI OF 9/22-23/09 IS CLASSIFIED NAI. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.					
OC RECOMMENDATION	26-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	(b) (4)

**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) (on 16-OCT-2009 by (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	16-OCT-2009				(b) (4)
SUBMITTED TO DO	19-OCT-2009	10-Day Letter			
DO RECOMMENDATION	22-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	
OC RECOMMENDATION	23-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	(b) (4)

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

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

PHARBIL WALTROP GMBH
IM WIRRIGEN 25
WALTROP, , GERMANY 45731

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

(b) (4)

Estab. Comment: MANUFACTURE, (b) (4) (on 16-OCT-2009 by (b) (4))

Profile: OINTMENT, NONSTERILE (INCLUDES (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	16-OCT-2009				(b) (4)
SUBMITTED TO DO	19-OCT-2009	Product Specific			
DO RECOMMENDATION	22-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	
OC RECOMMENDATION	23-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	(b) (4)

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

Application: NDA 21359/000 Date: 26-JUN-2001 Regulatory: 30-MAR-2010 Applicant: PROSTRAKAN INC 1430 STATE HWY 206 STE 110 BEDMINSTER, NJ 07921 Priority: S Org. Code: 170	Action Goal: District Goal: 29-JAN-2010 Brand Name: CELLEGESIC NITROGLYCERIN OINTMENT 0.4% Estab. Name: Generic Name: NITROGLYCERIN OINTMENT Product Number; Dosage Form; Ingredient; Strengths 001; OINTMENT; NITROGLYCERIN; .2% 002; OINTMENT; NITROGLYCERIN; .4%
--	---

Application Comment: THIS IS A RE-SUBMISSION FOLLOWING A COMPLETE RESPONSE (on 16-OCT-2009 by (b) (4))

CONTACT PERSON FOR THE APPLICATION IS MARY NORVITCH, PHONE: 908-375-7903; FAX: 908-234-9068 (on 16-OCT-2009 by (b) (4))

FDA Contacts:	(b) (4) Project Manager Review Chemist (HFD-170) Team Leader	(b) (4)
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Overall Recommendation:	ACCEPTABLE	on 05-NOV-2009	by	(b) (4)	
	ACCEPTABLE	on 09-DEC-2004	by	(b) (4)	(b) (4)

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

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

(b) (4)

DMF No: AADA: (b) (4)

Responsibilities: (b) (4)

Estab. Comment: (b) (4)

(on 16-OCT-2009 by (b) (4)) (b) (4)

(b) (4) (on 16-OCT-2009 by (b) (4))

ADDITIONAL CONTACT PERSON IS DAWN CLARKE, PHONE: 905-814-1696 X102; FAX: 905-814-9025 (on 16-OCT-2009 by (b) (4))

Profile: NON-STERILE (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	06-AUG-2001				(b) (4)
OC RECOMMENDATION	06-AUG-2001			ACCEPTABLE BASED ON PROFILE	(b) (4)
REQUEST CANCELLED	25-APR-2002				EES_PROD APPLICATION WITHDRAWN
SUBMITTED TO OC	19-JUL-2004				(b) (4)
OC RECOMMENDATION	19-JUL-2004			ACCEPTABLE BASED ON PROFILE	(b) (4)
SUBMITTED TO OC	16-OCT-2009				(b) (4)
SUBMITTED TO DO	16-OCT-2009	10-Day Letter			(b) (4)
DO RECOMMENDATION	26-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	(b) (4)
LAST GMP EI OF 9/22-23/09 IS CLASSIFIED NAI. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.					
OC RECOMMENDATION	26-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	(b) (4)

**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: (on 16-OCT-2009 by (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	16-OCT-2009				(b) (4)
SUBMITTED TO DO	19-OCT-2009	10-Day Letter			
DO RECOMMENDATION	22-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	
OC RECOMMENDATION	23-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	(b) (4)

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

Establishment: CFN: FEI: 3004620586

PHARBIL WALTROP GMBH

IM WIRRIGEN 25
WALTROP, , GERMANY 45731

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

(b) (4)

Estab. Comment: MANUFACTURE, (b) (4) (on 16-OCT-2009 by (b) (4))

Profile: OINTMENT,NONSTERILE (INCLUDES (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	16-OCT-2009				(b) (4)
SUBMITTED TO DO	19-OCT-2009	Product Specific			
DO RECOMMENDATION	22-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	
OC RECOMMENDATION	23-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	(b) (4)

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/s/

NIKOO N MANOCHEHRI-KALANTARI
07/05/2011

**CMC Memo to File**

To:	NDA
Date	8 Jun 2011
Sponsor:	Prostrakan Inc.
Drug:	Rectiv Nitroglycerin Ointment 0.4%
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall "acceptable" recommendation given on 8-Jun-2011 from the biopharmaceutics reviewer and overall "acceptable recommendation for the manufacturing facilities by the Office of Compliance (5-Nov-2009), CMC recommends that NDA application 21-359 be approved. All labeling changes have been communicated to the applicant through the clinical project manager. There are no pending CMC review deficiencies.

HFD-/Division File
HFD-170
HFD-170/C. Hilfiger

Olen Stephens, Ph.D.
Chemistry Reviewer

Prasad Peri, Ph.D.
Branch VII Chief, ONDQA

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/s/

OLEN M STEPHENS

06/08/2011

CMC final recommendation: approval

PRASAD PERI

06/09/2011

I concur



NDA 21-359

**TRADENAME NOT YET SUBMITTED
(nitroglycerine ointment USP) 0.4%**

ProStrakan, Inc.

Olen M. Stephens

**Division of Pre-Marketing Assessment I, Branch II, ONDQA
for the
Division of Anesthesia and Analgesia Products,
HFD-170**



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Chemistry Review Data Sheet

1. NDA: 21-359
2. REVIEW #: 5
3. REVIEW DATE: 18-MAY-2011
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 45,326
Original
N(000)NC
N(000)RS
N(000)BZ

Document Date

01-Jun-1994
26-Jun-2001
04-Dec-2001
07-Jul-2004
22-Nov-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Resubmission Amendment 0064
Amendment 0068

Document Date

21-Dec-2011
09-May-2011

7. NAME & ADDRESS OF APPLICANT:

Name:

ProStrakan, Inc.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Address: 1430 US Highway 206, Suite 110
Bedminster, NJ
07921-2652

Representative: Mary E. Norvitch, Ph.D.
Vice President, US Regulatory Affairs

Telephone: 908-375-7903

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Not yet approved
- b) Non-Proprietary Name (USAN): Nitroglycerin Ointment
- c) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 505(b)(2)

10. PHARMACOL. CATEGORY: Vasodilator

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 0.4% w/w

13. ROUTE OF ADMINISTRATION: Intra-anal

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☒ SPOTS product – Form Completed

☐ Not a SPOTS product

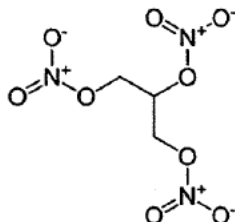


CHEMISTRY REVIEW



Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Names Nitroglycerin; 1,2,3-propanetriol, trinitrate; 1,3-dinitrooxypropan-2-yl nitrate; Propane-1,2,3-triyl trinitrate
Molecular Formula: $C_3H_5N_3O_9$
Molecular Weight: 227.1 g/mol
CAS Number: CAS No.: 55-63-0

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)					Adequate	8-Jul-2008	
				3	Adequate	9-Dec-2009	LoA is supp doc #338

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	45,326	Nitroglycerin (b) (4) Topical Ointment



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	05-Nov-2009	
Biopharmaceutics	Pending		Dr. Tapash Ghosh



The Chemistry Review for NDA 21-359

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In the previous review cycle, the applicant changed drug product manufacturers, but had *not* submitted sufficient stability data to bridge the drug product registration batches to batches from the previous drug product manufacturer. The current resubmission provides that bridging stability data, but proposes an increased commercial manufacturing scale that would require different manufacturing equipment and process parameters. In order to bridge this larger manufacturing scale to the clinical and registration processes, the applicant has submitted complete process comparisons, in vitro release rate comparisons, and stability data. The biopharmaceutics reviewer is awaiting additional data from the applicant concerning the in vitro release rate method development and computation method, and is not able to render a recommendation at this time. The Office of Compliance rendered an "acceptable" recommendation for all manufacturing facilities within the past two years. The CMC recommendation is for approval pending the recommendation of the biopharmaceutics reviewer.

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

None.

II. Summary of Chemistry Assessments

This NDA has a long regulatory history. Refer to the clinical review and previous CMC reviews for background.

In the previous review cycle, the applicant submitted new clinical data and changed the drug product manufacturer. This change in drug product manufacturer was accompanied by technology transfer reports, validation data, and 3 batch analyses for registration batches at the (b) (4) kg scale manufactured at the new site (b) (4). The technology transfer data and validation reports demonstrated a successful transfer of the analytical methods. The applicant used SUPAC-SS as a guide for changing the drug



CHEMISTRY REVIEW



Executive Summary Section

product manufacturer; SUPAC-SS requires a comparison of the process parameters, equipment, in vitro release rates, and stability data to support the manufacturing change. The registration batches demonstrated equivalent *in vitro* release profiles to comparative batches from the previous drug product manufacturer. However, the bridging stability data was not available at that time.

CMC Review #4 also noted that 2 of the 3 supporting stability batches exceed the viscosity specification limit at all time points after release. These out-of-specification measurements for viscosity were caused by (b) (4). The applicant had explored the dependence of viscosity on the drug product components and (b) (4). However, the applicant had not implemented acceptance criteria for (b) (4) to control for viscosity.

In the current review cycle, the firm has implemented adequate (b) (4) acceptance criteria and viscosity release specifications. The resubmission also proposes a new commercial batch size (b) (4) kg. Because the new commercial scale necessitates equipments changes and process parameter changes, the firm must now bridge the commercial scale process to the registration process. The applicant has provided an adequate comparison of the (b) (4) kg, (b) (4) kg, and (b) (4) kg manufacturing processes and sufficient stability data to support a 18-month shelf-life. Though batches from the proposed commercial and registration processes failed stage 1 testing for in vitro release rate comparisons, stage 2 testing demonstrated comparability. Dr. Tapash Ghosh (biopharmaceutics reviewer) has requested information regarding the in vitro release rate method development and clarification of how the data was treated for the comparison. The NDA is recommended for approval pending evaluation of the in vitro release rate data by the biopharmaceutics reviewer.

Note that the OC evaluation for the manufacturing sites is that they are adequate. There are no other CMC deficiencies.

- A. Description of the Drug Product(s) and Drug Substance(s)
- B. Description of How the Drug Product is Intended to be Used

A and B: Previously discussed; refer to CMC Review #2; C: N/A.

- C. Basis for Approvability or Not-Approval Recommendation



CHEMISTRY REVIEW



Executive Summary Section

The firm has bridged the registration batches to the previous drug product manufacturer. Sufficient stability data is provided to allow an 18 month shelf life. The Office of Compliance recommendation is "acceptable" for all manufacturing facilities and there are no outstanding CMC deficiencies to be resolved.

The biopharmaceutics reviewer is evaluating in vitro release rate data used to support an increased commercial scale.

From CMC perspective, this application is for approval with an 18 month shelf-life pending review of the in vitro release rate data by the biopharmaceutics reviewer.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

25 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

OLEN M STEPHENS

05/18/2011

CMC Recommendation: approval pending recommendation of the biopharmaceutics reviewer

PRASAD PERI

05/19/2011

I concur



NDA 21-359

CELLEGESICTM
(nitroglycerine ointment USP) 0.4%

ProStrakan, Inc.

Olen M. Stephens

Division of Pre-Marketing Assessment I, Branch II, ONDQA
for the
Division of Anesthesia, Analgesia and Rheumatology
Products,
HFD-170

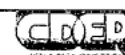


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Chemistry Review Data Sheet

1. NDA: 21-359
2. REVIEW #: 4
3. REVIEW DATE: 27-JAN-2010
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 45,326

Original

N(000)NC

N(000)RS

N(000)BZ

Document Date

01-Jun-1994

26-Jun-2001

04-Dec-2001

07-Jul-2004

22-Nov-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

N(000)RS

Document Date

30-Sep-2009

7. NAME & ADDRESS OF APPLICANT:

Name: ProStrakan, Inc.
Address: 1430 US Highway 206, Suite 110
Bedminster, NJ
07921-2652



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Mary E. Norvitch, Ph.D.
Vice President, US Regulatory Affairs
Telephone: 908-375-7903

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cellegesic
- b) Non-Proprietary Name (USAN): Nitroglycerin Ointment
- c) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 505(b)(2)

10. PHARMACOL. CATEGORY: Vasodilator

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 0.4% w/w

13. ROUTE OF ADMINISTRATION: Intra-anal

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☒ SPOTS product – Form Completed

☐ Not a SPOTS product

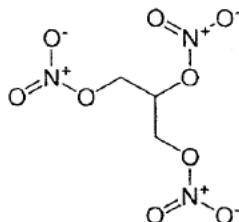


CHEMISTRY REVIEW



Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Names Nitroglycerin; 1,2,3-propanetriol, trinitrate; 1,3-dinitrooxypropan-2-yl nitrate; Propane-1,2,3-triyl trinitrate
Molecular Formula: $C_3H_5N_3O_9$
Molecular Weight: 227.1 g/mol
CAS Number: CAS No.: 55-63-0

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)					Adequate	8-Jul-2008	
				3	Adequate	9-Dec-2009	LoA is supp doc #338

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	45,326	Nitroglycerin (b) (4) Topical Ointment



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	05-Nov-2009	



The Chemistry Review for NDA 21-359

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has changed drug product manufacturers since the last review cycle and has *not* bridged the current drug product registration batches to batches from the previous drug product manufacturer. Therefore, the submitted stability data does not support the registration batches. The Office of Compliance recommendation is "acceptable" for all manufacturing facilities. The CMC recommendation is approvable pending the submission of adequate registration and stability data for the drug product.

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

None.

II. Summary of Chemistry Assessments

This NDA was originally submitted on 26-JUL-2001 and withdrawn (by the applicant) on 25-APR-2002. Subsequent to withdrawal, the sponsor was notified, via teleconference on 5-APR-2002, that the NDA was not approvable (NA) due to clinical efficacy issues. At the time of withdrawal, there were no CMC *approvability issues*. However, there were several CMC questions that remained unanswered. These questions were submitted to the NDA sponsor and have since been reviewed and clarified in CMC Review 2 and 3. Again, there were no CMC *approvability issues* at the end of the second review cycle – the CMC recommendation was for *APPROVAL*. However, the application was issued a complete response due to clinical deficiencies.

In the current review cycle, the applicant has submitted new clinical study data and changed the drug product manufacturer. This change in drug product manufacturer is accompanied by technology transfer reports, validation data, and 3 batch analyses for registration batches manufactured at the new site (b) (4). The technology transfer data and validation reports demonstrate a successful transfer of the analytical methods.



CHEMISTRY REVIEW



Executive Summary Section

Though this application is not subject to SUPAC-SS, the applicant is using SUPAC-SS as a template for changing the drug product manufacturer. The registration batches demonstrated equivalent *in vitro* release profiles to comparative batches from the previous drug product manufacturer as per SUPAC-SS. SUPAC-SS requires a comparison of stability data from three registration batches with 3 months of accelerated stability data at a minimum. This accelerated stability data was not provided.

Additionally, 2 of the 3 supporting stability batches exceed the viscosity specification limit (as agreed upon in the previous review cycle) at all time points after release. These out-of-specification measurements for viscosity are likely caused (b) (4)

The applicant has explored the dependence of viscosity on the drug product components and (b) (4)

However, the applicant has not implemented acceptance criteria for (b) (4) to control for viscosity.

- A. Description of the Drug Product(s) and Drug Substance(s)
- B. Description of How the Drug Product is Intended to be Used

A and B: Previously discussed; refer to CMC Review #2; C: N/A.

C. Basis for Approvability or Not-Approval Recommendation

The inability to bridge the registration batches to the previous drug product manufacturer and the lack of supportive stability data are approvability issues. A deficiency letter is attached to this review, outlining steps the applicant must take to address the CMC deficiencies.

From CMC perspective, this application is approvable pending resolution of the two deficiencies identified above.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

26 Pages have been Withheld as b4 (CCI/TS) immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21359

ORIG-1

PROSTRAKAN INC

CELLEGESIC NITROGLYCERIN
OINTMENT 0.4%

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

/s/

OLEN M STEPHENS

01/27/2010

CMC Recommendation: Approvable
Draft Deficiency letter attached

PRASAD PERI

01/27/2010

I concur. Let us discuss the letter.



CHEMISTRY REVIEW



NDA 21-359

-- *Resubmission* --

Cellegesic (nitroglycerin ointment USP), 0.4%

Cellegy Pharmaceuticals Inc.

**William C. Timmer, Ph.D.
Division of Cardio-Renal Drug Products
HFD-110**



Chemistry Review Data Sheet

1. NDA 21-359
2. REVIEW #3
3. REVIEW DATE: 12/8/04
4. REVIEWER: William C. Timmer, Ph.D.
5. PREVIOUS DOCUMENTS:

Document	Date
IND 45,326	01-JUN-94
NDA 21-359	26-JUN-01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N (000) BZ	22-NOV-04

7. NAME & ADDRESS OF APPLICANT:

Name: Cellegy Pharmaceuticals
349 Oyster Point Pharamceuticals
Address: Suite 200
South San Francisco, CA 94080-1913
Representative: Daniel L. Azarnoff, M.D.
Telephone: 650-616-2200



CHEMISTRY REVIEW



8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Cellegesic
Non-Proprietary Name (USAN): Nitroglycerin Ointment
Chem. Type 3
Submission Priority P

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 505(b)(2)

10. PHARMACOL. CATEGORY: Vasodilator

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 0.4%

13. ROUTE OF ADMINISTRATION: Intra-anal

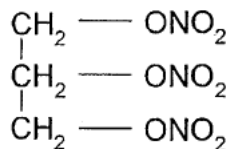
14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

 X Not a SPOTS product

16. CHEMICAL INFORMATION:



Nitroglycerin; 1,2,3-propanetriol, trinitrate

Molecular Formula: $\text{C}_3\text{H}_5\text{N}_3\text{O}_9$

Molecular Weight: 227.1

CAS Number: CAS No.: 55-63-0



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	45, 326	Nitroglycerin (b) (4) Topical Ointment

B. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	27-MAY-04	Review #9
				3	Adequate	03-JUL-00	Review #3
				1	Adequate	08-JAN-02	Review #1
				1	Adequate	20-MAR-02	Review #1

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	09-DEC-04	S. Adams
Methods Validation	To be initiated	07-SEP-04	W.C. Timmer, Ph.D.
ODS DMETS	'Cellegesic' approved	08-JAN-02	H.J. Kim, Pharm.D.
EA	CE granted	05-APR-02	W.C. Timmer, Ph.D.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

The Chemistry Review for NDA 21-359

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval. All CMC issues have been satisfactorily resolved at this time. The Office of Compliance has issued an ACCEPTABLE recommendation to all manufacturing facilities.

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

None.

II. Summary of Chemistry Assessments

This NDA was originally submitted on 26-JUL-01 and withdrawn (by the sponsor) on 25-APR-02. Subsequent to withdrawal, the sponsor was notified, via teleconference on 5-APR-02, that the NDA was not approvable (NA) due to clinical issues. At the time of withdrawal, there were no CMC *approvability issues*. However, there were several CMC questions that remained unanswered. These questions were submitted to the NDA sponsor in the current review cycle. An evaluation of the sponsor's responses to the questions are addressed below. Note that this is Review #2 of the Re-Submission.

- A. Description of the Drug Product(s) and Drug Substance(s)
- B. Description of How the Drug Product is Intended to be Used
- C. Basis for Approvability or Not-Approval Recommendation

A and B: Previously discussed; refer to Review #1 of the Re-Submission; C: N/A.

III. Administrative

A. Reviewer's Signature

/s/ William C. Timmer, Ph.D.
Review Chemist, HFD-150

/s/ Kasturi Srinivasacharr, Ph.D.
Chemistry Team Leader, HFD-110

File Name: nda21359_org_grp_resub_final_2.doc

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

/s/

William Timmer
12/10/04 04:09:05 PM
CHEMIST

Kasturi Srinivasachar
12/13/04 09:17:00 AM
CHEMIST



CHEMISTRY REVIEW



NDA 21-359

-- *Resubmission* --

Cellegesic (nitroglycerin ointment USP), 0.4%

Cellegy Pharmaceuticals Inc.

**William C. Timmer, Ph.D.
Division of Cardio-Renal Drug Products
HFD-110**



Chemistry Review Data Sheet

1. NDA 21-359
2. REVIEW #2
3. REVIEW DATE: 12/2/04
4. REVIEWER: William C. Timmer, Ph.D.
5. PREVIOUS DOCUMENTS:

Document	Date
IND 45,326	01-JUN-94
NDA 21-359	26-JUN-01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N (000) RS	07-JUL-04

7. NAME & ADDRESS OF APPLICANT:

Name: Cellegy Pharmaceuticals
349 Oyster Point Pharamceuticals
Address: Suite 200
South San Francisco, CA 94080-1913
Representative: Daniel L. Azarnoff, M.D.
Telephone: 650-616-2200



CHEMISTRY REVIEW



8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Cellegesic
Non-Proprietary Name (USAN): Nitroglycerin Ointment
Chem. Type 3
Submission Priority S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 505(b)(2)

10. PHARMACOL. CATEGORY: Vasodilator

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 0.4%

13. ROUTE OF ADMINISTRATION: Intra-anal

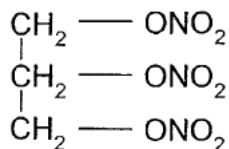
14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

16. CHEMICAL INFORMATION:



Nitroglycerin; 1,2,3-propanetriol, trinitrate

Molecular Formula: $\text{C}_3\text{H}_5\text{N}_3\text{O}_9$

Molecular Weight: 227.1

CAS Number: CAS No.: 55-63-0



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	45, 326	Nitroglycerin (b) (4) Topical Ointment

B. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	27-MAY-04	Review #9
				3	Adequate	03-JUL-00	Review #3
				1	Adequate	08-JAN-02	Review #1
				1	Adequate	20-MAR-02	Review #1

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		-----
Methods Validation	To be initiated	07-SEP-04	W.C. Timmer, Ph.D.
ODS DMETS	'Cellegesic' approved	08-JAN-02	H.J. Kim, Pharm.D.
EA	CE granted	05-APR-02	W.C. Timmer, Ph.D.



The Chemistry Review for NDA 21-359

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

None. The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections. All other CMC approvability issues have been satisfactorily resolved at this time.

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

None.

II. Summary of Chemistry Assessments

This NDA was originally submitted on 26-JUL-01 and withdrawn (by the sponsor) on 25-APR-02. Subsequent to withdrawal, the sponsor was notified, via teleconference on 5-APR-02, that the NDA was not approvable (NA) due to clinical issues. At the time of withdrawal, there were no CMC *approvability issues*. However, there were several CMC questions that remained unanswered. These questions were submitted in this, the current, review cycle and are addressed in Review #2 of the Re-Submission.

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is nitroglycerin (NG). NG is a high explosive that is so unstable that the slightest jolt, impact or friction can cause it to spontaneously detonate. Unlike burning, which can only travel as fast as the flame front can move through a material, high explosives are decomposed almost instantaneously by a supersonic shock wave passing through the material. This instantaneous destruction of all the molecules in the sample is called a detonation, and the rapid expansion of hot gases that results is what causes the destructive blast.

In vivo, NG dilates blood vessels by relaxing the smooth muscles surrounding them, resulting in increased blood flow. NG is commonly used to treat or prevent chest pain in people with angina or angina pectoris, which results from reduced



CHEMISTRY REVIEW



Executive Summary Section

blood flow to the heart. Hardening of the coronary arteries (atherosclerosis) that feed the heart is usually the underlying factor in angina.

The drug substance is commercially known as (b) (4), which is (b) (4) Nitroglycerin in (b) (4). The mixture, where (b) (4) complies with the current USP monograph.

The manufacturing and control of (b) (4) are described in DMF (b) (4). Review #9 was completed, by M.P. Delvan on 27-May-04, and the DMF was found to be **ADEQUATE**.

2. Drug Product

The drug product is an ointment containing 0.4% nitroglycerin.

Ointments are semisolid preparations intended for external application to the skin or mucous membranes. Cellegesic®(nitroglycerin) Ointment is a water-removable ointment that is formulated using a white petrolatum and lanolin base that is both non-irritating and pharmacologically inactive.

The excipients are all compendial and the concentrations used in the formulation were based on general appearance, syneresis, viscosity, and ease of manufacture. The detailed procedure for the manufacture of Cellegesic®Ointment is presented in Review #1, Section II.4.A.

The acceptance criteria are appropriate ensure the identity, strength, quality, potency and purity of the finished drug product. The acceptance criteria are presented in Review #1, Section II.5.B.

Two unique container-container closure systems will be used for this drug product:

- A (b) (4) 30 g collapsible aluminum tube (plus the 3.5 g physician's sample) with a white low density polyethylene, non-piercing cap.
- A 30 g metered-dose pump consisting of a lined aluminum canister with a pumping mechanism.

Packaging is discussed in Review #1, Section II.6.

The sponsor has requested, and is granted, a (b) (4) month shelf-life for the nitroglycerin ointment packaged into both collapsible aluminum tubes as well as metered-dose cannisters. The recommended storage temperature is 25°C (77°F).



CHEMISTRY REVIEW



Executive Summary Section

Analysis of the stability data are presented in Review #1, Section II.8 and Review #2 (*i.e.*, this review), Section II.8.

B. Description of How the Drug Product is Intended to be Used

Cellegesic® Ointment has been developed for the topical treatment of anal fissures. An anal fissure is a linear laceration in the thin epithelial layer (anoderm) lining the most distal portion of the anal canal. It is a common benign disorder that affects both men and women.

The presence of an anal fissure is associated with elevated intra-anal pressure generated by hypertonicity of the internal anal sphincter (IAS) muscle and subsequent decrease of blood flow to the anoderm. It has been well established that application of nitroglycerin results in the generation of nitric oxide (NO), which has been associated with relaxation of vascular smooth muscle. Hence the rationale for the use of nitroglycerin ointment.

Cellegesic ointment is to be applied ~ every 12 hours intra-anally. Treatment is indicated until the pain abates or up to 8 weeks.

The recommended dose of Cellegesic is ~375 mg of ointment. One actuation of the metered-dose canister delivers ~ 375 gm of ointment each time the piston is fully depressed. The ointment is also available in a tube. To obtain ~ 375 mg of ointment, the finger cot (included in the packaging) is laid alongside the dosing line on the carton. The tube is squeezed until a ribbon of ointment the length of the line is expressed onto the covered finger.

The sponsor performed two studies to determine the accuracy and reproducibility of squeezing out 375 mg of ointment. The first study found that 12 individuals could, at least 10 times each, reproducibly extrude 375 mg of ointment. A second study found that 6 individuals could, at least 10 times each, extrude 375 mg of ointment onto the finger cot before application. These studies are detailed in the submission.

C. Basis for No Recommendation

The cGMP inspections are not completed at this time.



CHEMISTRY REVIEW



Executive Summary Section

III. Administrative

A. Reviewer's Signature

/s/ William C. Timmer, Ph.D.
Review Chemist, HFD-150

/s/ Kasturi Srinivasacharr, Ph.D.
Chemistry Team Leader, HFD-110

File Name: nda21359_org_grp_resub_final.doc

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

/s/

William Timmer
12/7/04 03:19:56 PM
CHEMIST

Kasturi Srinivasachar
12/7/04 03:55:56 PM
CHEMIST



NDA 21-359

Cellegesic (nitroglycerin ointment USP) 0.2%, 0.4%

Cellegy Pharmaceuticals Inc.

**William C. Timmer, Ph.D.
Division of Cardio-Renal Drug Products
HFD-110**



Chemistry Review Data Sheet

1. NDA 21-359
2. REVIEW #1
3. REVIEW DATE: 4/5/02
4. REVIEWER: William C. Timmer, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 45,326

Document Date

01-JUN-94

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

N(000)NC

Document Date

26-JUN-01

04-DEC-01

7. NAME & ADDRESS OF APPLICANT:

Name:	Cellegy Pharmaceuticals
	349 Oyster Point Pharamceuticals
	Suite 200
Address:	South San Francisco, CA 94080-1913
Representative:	Daniel L. Azarnoff, M.D.
Telephone:	650-616-2200



CHEMISTRY REVIEW



8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Cellegesic
Non-Proprietary Name (USAN): Nitroglycerin Ointment
Code Name/# (ONDC only): N/A
Chem. Type/Submission Priority (ONDC only):
Chem. Type: 3
Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2) Application

10. PHARMACOL. CATEGORY: Relief of pain associated with anal fissure.

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 0.2% and 0.4%

13. ROUTE OF ADMINISTRATION: Intra-anal

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

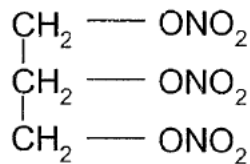
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nitroglycerin; 1,2,3-propanetriol, trinitrate



Molecular Formula: $\text{C}_3\text{H}_5\text{N}_3\text{O}_9$
Molecular Weight: 227.1
CAS Number: CAS No.: 55-63-0



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	45, 326	Nitroglycerin (b) (4) % Topical Ointment

B. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate	01-APR-02	Review #8
				3	Adequate	03-JUL-00	Review #3
				1	Adequate	08-JAN-02	Review #1
				1	Adequate	20-MAR-02	Review #1

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Waiting	05-APR-02	-----
Pharm/Tox	Approvable	10-APR-02	A. Proakis, Ph.D.
Biopharm	Acceptable	12-MAR-02	B. Nhi Nguyen, Pharm.D.
LNC	N/A	N/A	N/A
Methods Validation	To be initiated	05-APR-02	W.C. Timmer, Ph.D.
ODS DMETS	'Cellegesic' approved	08-JAN-02	H.J. Kim, Pharm.D.
EA	Categorical exclusion granted	05-APR-02	W.C. Timmer, Ph.D.
Microbiology	N/A	N/A	N/A



The Chemistry Review for NDA 21-359

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A final recommendation cannot be given at this time. The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections.

The sponsor should however respond to the deficiencies presented in Section VIII.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is nitroglycerin ($C_3H_5N_3O_9$; hereafter referred to NG). It is produced by the nitration of glycerin. Nitroglycerin is a compendial substance (*i.e.*, listed in the USP). NG is also a high explosive that is so unstable that the slightest jolt, impact or friction can cause it to spontaneously detonate. It is the speed of the decomposition reaction that makes NG such a violent explosive. Unlike burning, which can only travel as fast as the flame front can move through a material, high explosives are decomposed almost instantaneously by a supersonic shock wave passing through the material. This instantaneous destruction of all the molecules in the sample is called a detonation, and the rapid expansion of hot gases that results is what causes the destructive blast. Four moles of NG detonate to produce 35 moles of gas.

In vivo, NG dilates blood vessels by relaxing the smooth muscles surrounding them, resulting in increased blood flow. NG is commonly used to treat or prevent chest pain in people with angina or angina pectoris, which results from reduced blood flow to the heart. Hardening of the coronary arteries (atherosclerosis) that feed the heart is usually the underlying factor in angina.



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The drug substance is commercially known as (b) (4), which is (b) (4) Nitroglycerin in (b) (4). The mixture, where (b) (4) refers to (b) (4), complies with the current USP monograph. (b) (4) CMC information is included in DMF # (b) (4).

2. Drug Product

Cellegesic® Ointment is designed to release therapeutic levels of nitroglycerin intra-anally to relieve the pain of anal fissure. The ointment is formulated using a white petrolatum and lanolin base that is non-irritating and pharmacologically inactive.

Ointments are semisolid preparations intended for external application to the skin or mucous membranes. Ointments, which soften or melt at body temperature may be classified into three types: water-removable, emulsifiable, and water-repellant; however, the distinction between the three types is not always obvious or definitive. (b) (4)

The excipients (all components are either NF or USP) and concentrations used in the formulation were based on general appearance, syneresis, viscosity, and ease of manufacture. Ointments are manufactured by (b) (4)

(b) (4). The detailed procedure for the manufacture of Cellegesic® Ointment is presented in Section II.4.A.

The sponsor has developed two concentrations (0.2% and 0.4%) of the ointment. Of interest, the two formulations are *not* identical: the 0.2% formulation contains (b) (4) w/w (b) (4) while the 0.4% formulation does not.

The acceptance criteria are appropriate ensure the identity, strength, quality, potency and purity of the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. The acceptance criteria are presented in Section II.5.B.

Two unique container-container closure systems will be used for this drug product. The first configuration (for (b) (4) 0.4% concentrations) in a collapsible aluminum tube in 30 g, (b) (4) sizes. A measuring device, consisting of a polyethylene dispenser and calibrated to deliver ~374 mg of ointment, will be included in the packaging.



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The second packaging configuration consists of a metered-dose pump. Metered-dose pumps are designed to dispense high viscosity semi-solids; they are the pump of choice when it comes to dispensing facial creams, body lotions and skin gels. The metered dose pump package size is 30 g, for both the 0.2% and 0.4% concentrations. Packaging is discussed in Section II.6.

Based on analysis of the stability data, the approved shelf-life for both 0.2% and 0.4%, for nitroglycerin ointment packaged into aluminum tubes is (b) (4) months; for both 0.2% and 0.4%, for nitroglycerin ointment packaged into a metered-dose pump it is (b) (4) months. The storage temperature is 25°C (77°F). Analysis of the stability data are presented in Section II.8.

B. Description of How the Drug Product is Intended to be Used

Cellegesic® Ointment has been developed for the topical treatment of anal fissures. An anal fissure is a linear laceration in the thin epithelial layer (anoderm) lining the most distal portion of the anal canal. It is a common benign disorder that affects both men and women.

The presence of an anal fissure is associated with elevated intra-anal pressure generated by hypertonicity of the internal anal sphincter (IAS) muscle and subsequent decrease of blood flow to the anoderm. It has been well established that application of nitroglycerin results in the generation of nitric oxide (NO), which has been associated with relaxation of vascular smooth muscle. Hence the rationale for the use of nitroglycerin ointment.

C. Basis for No Recommendation

The cGMP inspections are not completed at this time.

III. Administrative

A. Reviewer's Signature

William C. Timmer, Ph.D.
Review Chemist, HFD-150



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Kasturi Srinivasacharr, Ph.D.
Chemistry Team Leader, HFD-110

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B. Endorsement Block

HFD-110/Chem/WCTimmer
HFD-110/ChemTL/KSrinivascher

C. CC Block

Original NDA 21-359

HFD-110/Division File

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/s/

William Timmer
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Kasturi Srinivasachar
4/19/02 02:51:55 PM
CHEMIST