CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208424Orig1s000

CHEMISTRY REVIEW(S)

NDA 208424 (Nitroglycerin Sublingual Powder)

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Nitroglycerin sublingual powder dosage
Strength	400 mcg per packet (" (b) (4)
Route of Administration	Sublingual
Rx/OTC Dispensed	Rx
Applicant	G. Pohl-Boskamp GmbH & Co. KG
US agent, if applicable	

Submissions (s) Reviewed	eCTD Sequence Number	Document Date
NDA 208424	0000	8/10/2015
Amendment/IR Response	0005	11/09/2015
Amendment/IR Response	0008	11/27/2015
Amendment/IR Response	0012	01/28/2016
Amendment/Response	0014	2/28/2016
Amendment/Response	0015	03/04/2016
Amendment/Response	0018	03/11/2016
Amendment/Response	0019	03/29/2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sithamalli Chandramouli	ONDP/DNDPI/NDPBI
Drug Product	Mariappan Chelliah	ONDP/DNDPI/NDPBI
Process	Xuhong Li	OPQ/OPF/DPAI/PABI
Microbiology	Xuhong Li	OPQ/OPF/DPAI/PABI
Facility	Steven Hertz	OPF/DIA/IABI
Biopharmaceutics	Jing Li	ONDP/DB/BBI
Regulatory Business Process Manager	Maryam Changi	OPRO DRBPMI/RBPMBI
Environmental Assessment (EA)	Mariappan Chelliah	ONDP/DNDPI/NDPBI
Laboratory (OTR)	N/A	
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Acceptable	March 14, 2016	Acceptable. Stability data received as amendments for batches made from 2012 – 2015.
	Type II			Adequate	Jul. 21, 1992 (DMF review). May 18, 2005 review of amendment.	Based on review from Jul. 21, 1992, the DMF was found adequate (Archived in Volume 1.1 of DMF No. (b) (4)). The amendment to the DMF was reviewed in May 18, 2005 and no deficiencies were cited for the drug substance. The annual reports / Letters of Authorizations received through Dec. 08, 2015 state that the DMF remains current.
	Type II					This is the (b) (4) DMF was not reviewed (b) (4)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
pIND	116,608	
NDA	18705	Nitrolingual Pumpspray

2. CONSULTS: N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, NDA 208424 (nitroglycerin sublingual powder) is recommended for approval. The Agency has approved a shelf-life of 18 months for the product when stored in the approved commercial container closure system at 20°C - 25°C (68°F-77°F); with excursions permitted between 5°C – 40°C (41°F – 104°F).

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

N/A

II. Summary of Quality Assessments

The applicant, G. Pohl-Boskamp GmbH & Co. KG., has sought U.S. marketing approval for Nitroglycerin Sublingual Powder under the provisions of Section 505(b)(1) of the Federal Food and Cosmetic Act and 21 CFR §314.54. G. Pohl-Boskamp GmbH & Co. KG is the owner of the approved NDA 018705 for Nitrolingual Pumpspray and has now developed a new formulation of nitroglycerin i.e., nitroglycerin powder for sublingual administration. Nitroglycerin exerts its therapeutic action by means of cGMP-mediated venous and arteriolar vasodilatation, resulting in reduced cardiac pre-and afterload, myocardial wall tension and oxygen demand.

A. Drug Substance (Nitroglycerin) Quality Summary

The drug substance nitroglycerin (glyceryl trinitrate; GTN; $C_3H_5N_3O_9$; CAS-Registry No. 55-63-0) is a well-known nitric oxide (NO)-donator and the sublingual administration in particular is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

Drug substance-related CMC Details: For description of drug substance, including structural characterization, impurity profile, manufacturing process, process controls, control of materials, controls of critical steps /intermediates, process validation, manufacturing process development, container closure system, and stability data, the applicant has cross-referenced DMF No.: [redacted] (b) (4) DMF No.: [redacted] (b) (4), and subsequent annual reports have been previously reviewed and found adequate. The drug substance has also been reviewed in detail for previously approved NDA 018705 for Nitrolingual Pumpspray. The drug product manufacturer (who is also the applicant) will perform quality control testing of the

drug substance per specifications, which are acceptable. The analytical methods used have been validated for critical analytical parameters such as linearity, specificity, precision, accuracy, and robustness, and are suitable for intended applications.

Retest period and storage conditions: The drug substance is stable at (b) (4) months. However, the DMF holder has set a retest period of (b) (4) months for the drug substance.

B. Drug Product [Nitroglycerin Sublingual Powder] Quality Summary

The nitroglycerin sublingual powder is the first sublingual powder drug product to be approved. Nitroglycerin powder, containing 0.4 mg glyceryl trinitrate (GTN) per (b) (4) (packet), is a vasodilator indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease. In adults, nitroglycerin powder is recommended to be used in acute doses of one to three (b) (4) i.e., 0.4 to 1.2 mg GTN applied sublingually under the tongue, which may be repeated if not resulting in prompt relief. The applicant is currently marketing a nitroglycerin drug product, Nitrolingual Pumpspray - a metered sublingual spray, approved by the FDA on 31-Oct-1985 under NDA 018705.

Product Design: The drug product contains the active substance nitroglycerin (glyceryl trinitrate; GTN) in a powder dosage form for the sublingual route of administration. Specifically, it is (b) (4)

(b) (4)

Drug Product Manufacturing: The manufacturing process involves (b) (4)

(b) (4)

[redacted]

Microbiological Aspects: The risk of microbial proliferation or contamination for this product is minimal. Nevertheless, as part of the drug product release specification, the microbiological quality will be suitably tested on every batch (b) (4) [redacted]

Biopharmaceutics Aspects: The applicant has not included an *in vitro* dissolution test in the drug product release specification. This is acceptable due to the nature of the dosage form and the fast drug release exhibited by the drug product. The solubility studies conducted indicate that the drug substance is distributed in (b) (4) [redacted] excipients, and the equilibrium is driven by the partitioning coefficient of the drug substance (b) (4) [redacted]. The solubility of the drug product does not increase as a function of time (b) (4) [redacted] To ensure the consistent quality of the drug product, for post-approval changes in formulation or manufacturing process, the Biopharmaceutics review team has recommended that the applicant perform a comparative solubility study, using a validated method, to support post-approval changes in formulation or drug product manufacturing process. Specifically, it is recommended that for the pre-change and post-change drug product batches, not less than (b) (4) % of the drug product should be dissolved (b) (4) [redacted] This has been communicated to the applicant via General Advice Letter, dated 3/28/2016.

Control Strategies: The product control strategies mainly consist of (b) (4) [redacted] Given that the drug product has a low active load, (b) (4) [redacted]

(b) (4)

(b) (4)

Via a General Advice Letter, dated 3/28/2016, the applicant has been notified that: a) the firm's proposed sampling plan and acceptance criteria (b) (4) during validation are deemed currently acceptable, b) subsequent acceptability of the validation studies will be based on the review of the data during the future inspections, and c) it is recommended that the firm refer to FDA's *Process Validation Guidance: General Principles and Practices (2011)* for more information on continuous process verification.

Container Closure System: The nitroglycerin sublingual powder is provided in (b) (4) Each packet will be filled with 200 mg of nitroglycerin sublingual powder, which contains 400 micrograms of the active ingredient. It will be packaged into cartons containing 3, 12, 36 and 96 packets.

Expiration Date & Storage Conditions: Although the applicant provided stability data for drug product batches that were manufactured (b) (4) our approach was to determine the product shelf-life solely based on the data from the batches (b) (4) A total of 9 months of long-term and 6 months of

accelerated stability data and statistical evaluation of the stability data per ICH Q1E support product shelf-life of 18 months when stored at 25°C (77°F); with provision for excursions between 5- 40 °C (41-104 °F).

Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended overall approval for the manufacturing facilities concerning this NDA.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	(b) (4)
Non Proprietary Name of the Drug Product	Nitroglycerin sublingual powder
Non Proprietary Name of the Drug Substance	Nitroglycerin (glyceryl trinitrate)
Proposed Indication(s) including Intended Patient Population	A vasodilator indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease
Methods of Administration	Sublingual powder
Maximum Daily Dose/ Duration of Treatment	• At the onset of an attack, to be administered under the tongue every 5 minutes (b) (4) • May use up to three packets (400 mcg/packet) within a 15-minute period • May be used prophylactically 5 to 10 minutes prior to engaging in activities that might precipitate an acute attack
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation:

   - Drug Substance: Nitroglycerin was reported to be BCS class 1. However, the FDA BCS committee has not classified the drug substance, nitroglycerin, as BCS class I drug substance.

- Drug Product: Not established.

2. Biowaivers/Biostudies

   - Biowaiver Requests: N/A.
   - PK studies: The NDA submission contains a bioequivalence study comparing the bioavailability of the proposed sublingual powder and the pumpspray formulation, which has been reviewed by the Office of Clinical Pharmacology.
   - IVIVC: N/A.

E. Novel Approaches

The nitroglycerin ("glyceryl trinitrate") powder for sublingual administration is the first sublingual powder drug product (b) (4) to be approved. The product i.e., 400 mcg of nitroglycerin as a (b) (4) powder will be filled into single dose packet ("(b) (4) which represents an innovative pharmaceutical configuration for individual doses.

F. Any Special Product Quality Labeling Recommendations

In the original filing, the sponsor referred to the product package as "(b) (4) The applicant was notified that for the purpose of labeling, "(b) (4) is not an accepted regulatory term for describing a package type (*refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071748.htm*).

The applicant agreed to replace the word "(b) (4) with the standard term 'packet' in the labeling. Furthermore, the applicant proposed (b) (4) as the proprietary name for the product. The CMC recommendation to DMEPA was against approval of this proposed proprietary name. The applicant has now agreed to eliminate the term "(b) (4) from the proprietary name for the product. The revised proprietary name for the product is (b) (4)

G. Life Cycle Knowledge Information

(See Attachment A on the next page)

Attachment A

Final Risk Assessment- NDA 208424 (Nitroglycerin Sublingual Powder)

Attribute/ CQA	Factors that can Impact the CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay, Stability	• Formulation • Container closure • Impurity exceeding specification • Process parameters • Scale/ equipment/ site	Low (L)	The product CQAs such as identification, assay, impurity levels are controlled by appropriate release specification using validated analytical methods. The proposed acceptance limits for the assay, nitrite and nitrate content (b) (4) the USP monograph limits. •The acceptance limit for the related substances at release was (b) (4) from NMT (b) (4) %.	Acceptable	Changes to formulation, manufacturing process/ site, or proposal to change release specification should be evaluated for possible impact on approved control strategy and product CQAs, including impurity levels.
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Moderate (M)	Product stability has been demonstrated. (b) (4)	Acceptable	Formulation changes, including proposals to change stabilizing excipients or in-process controls will need to be evaluated for (b) (4) stability.

Attribute/ CQA	Factors that can Impact the CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Content uniformity	• Formulation • Particle size • Segregation • Raw materials • Process parameters • Scale/ equipment/ site	Moderate (M)	The proposed product is (b) (4)	Acceptable	Changes to manufacturing process or control strategies, (b) (4) For the pre-change and post-change drug product batches, not less than (b) (4) % of the drug product should be dissolved in 30 mL of the phosphate buffer (pH 6.8) in 5 minutes.
Microbial limits	• Moisture • Process parameters • Scale/ equipment/ site	Low (L)	As part of the drug product release specification, the microbiological quality will be tested on every batch (b) (4).	Acceptable	Changes to raw materials, formulation, manufacturing process/ site, or proposal to delete microbial testing on release should be evaluated for possible impact on microbial contamination.
Dosing accuracy	• Formulation • Dosing Device • Process parameters • Scale/ equipment/ site	Moderate (M)	(b) (4) there are no major concerns regarding dosing accuracy for nitroglycerin powder for sublingual administration.	Acceptable	

Attribute/ CQA	Factors that can Impact the CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Palatability	• Formulation • Failure to mask unpleasant taste/smell • Excipient change	Moderate (M)	Formulated with (b) (4)	Acceptable	(b) (4) DMEPA and the clinical division did not deem it as an issue of concern.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

From the chemistry, manufacturing and controls (CMC) perspective, NDA 208424 (Nitroglycerin Sublingual Powder) is recommended for approval. The Agency has approved a shelf-life of 18 months for the product when stored in the approved commercial container closure system at 20°C - 25°C (68°F-77°F); with excursions permitted between 5°C – 40°C (41°F – 104°F).

Application Technical Lead Signature:

Mohan K. Sapru -A

Digitally signed by Mohan K. Sapru -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -A, 0.9.2342.19200300.100.1.1=2000589315
Date: 2016.05.24 17:36:05 -04'00'

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

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

The Applicant did not include an in vitro dissolution test in the drug product release specification. This is acceptable due to the nature of the dosage form and the fast drug release exhibited by the drug product. FDA recommends that the Applicant performs a comparative solubility study to support post-approval changes in formulation or drug product manufacturing process.

- **Solubility of nitroglycerin:**

The solubility of nitroglycerin is pH independent, and the solubility is approximately 1 mg/mL.

- **Formulation:**

The drug product contains the active drug substance nitroglycerin (GTN) in a powder dosage form to be administered by the sublingual route for the treatment of angina pectoris.

Table 38-1. The composition of the drug product (one unit/ (b) (4)

Ingredient	Quantity [mg]	Standard	Function
Active substance			
Nitroglycerin (b) (4) (b) (4)	8.0 (0.4)		active ingredient
Excipients	(b) (4)		(b) (4)
Medium chain triglycerides[2]		USP - NF	
Isomalt		USP - NF	
Anhydrous dibasic calcium phosphate[3]		USP - NF	
Oleoyl Polyoxylglycerides		USP - NF	
Peppermint oil		USP - NF	
Total	200		

- **Dissolution Test:**

The Sponsor claimed that no continuous control of dissolution for the drug product is necessary; because the sublingual powder rapidly releases the active drug substance. Therefore the Sponsor did not propose a dissolution test for the drug product batch release and stability study. Figure 38-1 illustrates the fast dissolution of the drug product.

The dissolution conditions are as follows: USP (b) (4)

Figure 38-1. Dissolution of the drug product

Reviewer's Assessment:

The dissolution test conducted during the development stage (b) (4) In lieu of dissolution test, the Agency recommended that the Sponsor explores the possibility of using a solubility test as a quality control test. A solubility study needs to be conducted using smaller volume of the medium in order to better mimic the in vivo sublingual environment. The following IR was sent on October 26, 2015.

We note that you are not proposing to include a dissolution test as part of the regulatory drug product specifications. In order for us to consider your proposal, we recommend that you conduct solubility studies (instead of dissolution) on the drug product under conditions that are closely relevant to the in vivo sublingual environments. Specifically, provide the following information: Solubility data (individual, mean, SD, n=6 or more) of your product in small volumes (e.g., 1 mL, 2 mL, 3 mL, 4 mL, and 5 mL) while stirring, as a function of time (e.g., 1 minute, 2 minutes, 3 minutes, 5 minutes, 10 minutes etc.) at pH 6.8 at 37°C for 3 batches of your proposed to-be-marketed drug product.

The following additional IR regarding solubility testing was conveyed to the Applicant on January 13, 2016.

1. We acknowledge the submission of the requested solubility studies for your drug product using smaller volumes of buffer pH 6.8 medium. However, the results of these studies are showing that only about (b) (4)% of the drug substance is dissolved in (b) (4)mL of the

medium. Therefore, in order to assess the complete solubility (100% dissolved) of your proposed Nitroglycerin sublingual powder product, we request that you conduct an additional solubility study under the same conditions, but using increased volumes of the medium. Specifically, provide the solubility data (individual, mean, SD, n=6 or more) of your drug product in volumes of 10 mL, 15 mL, 20 mL, and 25 mL buffer pH 6.8 medium at 37°C while stirring, as a function of time (e.g., 1 minute, 3 minutes, 5 minutes, 8 minutes, 10 minutes, etc.) for 3 batches of your proposed to-be-marketed drug product.

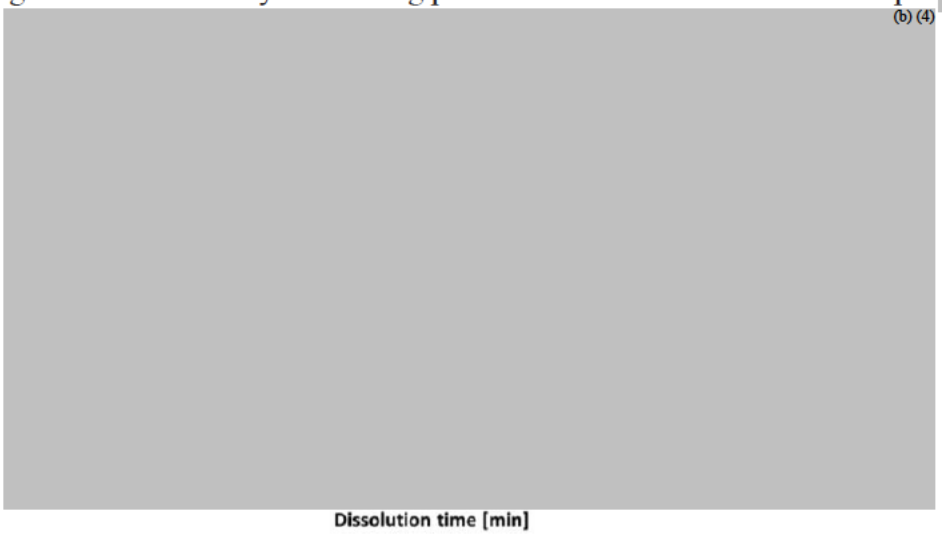
2. Other than a solubility test, is there any other quality control test that you can propose in order to assure the consistent release of drug from your drug product?

The IR responses were received on November 27, 2015, and February 26, 2016, respectively, and evaluated in the section below.

- **Solubility Studies:**

One (b) (4) was opened and the contents were transferred to (b) (4) Each experiment was performed in sextuplicate. For every sampling time point a separate test was performed, because the remaining volume in the vial is too small to continue the test. The following diagram shows the test results. The amount of dissolved GTN is between less than (b) (4)% with 1 mL of buffer and approximately (b) (4) % with 5 mL. The degree of solubility depends only on the volume of buffer added.

Figure 38-2. Solubility of the drug product in a small volume of buffer pH (b) (4)



The results appear to suggest that after the addition of buffer solution a certain amount of nitroglycerin is instantaneously available in aqueous solution. This amount depends on the volume of the added buffer solution.

(b) (4)

The above observations were further confirmed by the experiment carried out using higher volume of the buffer (10, 20, 30, 50, 100 mL). Samples were taken for analysis at 1, 5, and 10 minutes. Table 38-2 summarizes the results and the predicted values based on the partition coefficient.

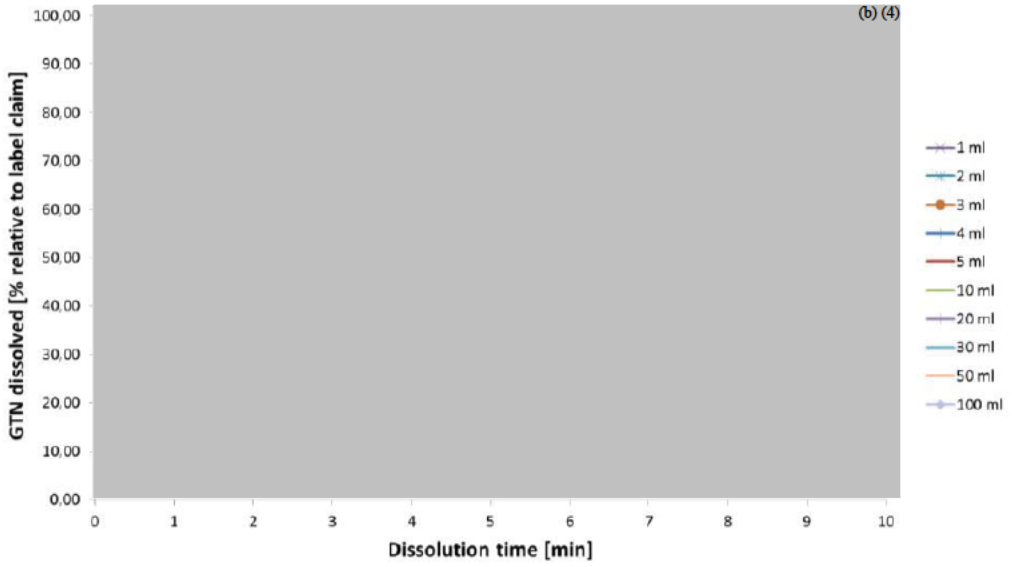
Table 38-2. Solubility of the drug product in the buffer of pH 6.8

Dissolution [% of label claim]				
Lot No. – amount of buffer used	1 minute	5 minutes	10 minutes	predicted from log P
238940 - 10 ml	(b) (4)			
238990 - 10 ml				
239123 - 10 ml				
mean – 10 ml				(b) (4)
238940 - 20 ml				
238990 - 20 ml				
239123 - 20 ml				
mean – 20 ml				(b) (4)

238940 - 30 ml	(b) (4)
238990 - 30 ml	
239123 - 30 ml	
mean – 30 ml	(b) (4)
238940 - 50 ml	
238990 - 50 ml	
239123 - 50 ml	
mean – 50 ml	(b) (4)
238940 - 100 ml	
238990 - 100 ml	
239123 - 100 ml	
mean – 100 ml	(b) (4)

Figure 38-4 shows all volumes used throughout the two sets of experiments.

Figure 38-4. Solubility of the drug product in various volumes of buffer pH 6.8



Reviewer's Assessment:

- The solubility studies conducted indicates that the drug substance is distributed (b) (4) more than (b) (4)% was dissolved when the buffer volume was larger than 30 mL. The solubility of the drug product is not increasing as a function of time, indicating the fast equilibrium (b) (4).
- Based on the results of the solubility study, it is possible that the small volume of liquid present in the sublingual environment is not able to fully dissolve the drug

(b) (4)

As demonstrated by the bioequivalence study comparing the bioavailability of the sublingual powder and the pumpspray formulations, the sublingual powder actually resulted in higher exposure (both C_{max} and AUC).

- The drug product is in powder dosage form for sublingual use, and it is analogous to an oral disintegrating tablet (ODT) or a sublingual tablet which has already disintegrated. It is also noted that the use of a disintegration test in lieu of a dissolution test is recommended for ODT and sublingual tablet (b) (4) FDA agrees that neither a dissolution test nor a solubility test is needed for drug product batch release.
- Though a dissolution or a solubility test is not needed for batch release, changes in formulation (b) (4) and manufacturing process (b) (4) f the drug product. Therefore, in cases when post-approval changes in formulation or manufacturing process are proposed, the Applicant will need to conduct a comparative solubility test to demonstrate the consistent solubility of the drug product between pre-change and post-change batches. Therefore, the following General Advice Comment needs to be conveyed to the Applicant:

General Advice Comment:

FDA agrees that a dissolution test or solubility test is not needed for drug product batch release. However, in order to ensure the consistent quality of the drug product, for post-approval changes in formulation or manufacturing process, we recommend that you compare the solubility of the pre-change and post-change batches using a validated method. It is recommended that for the pre-change and post-change drug product batches, not less than (b) (4) % of the drug product should be dissolved in 30 mL of the phosphate buffer (pH 6.8) in 5 minutes.

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

No bridging is needed. The formulation of the clinical batch and the proposed commercial batch is the same (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From a Biopharmaceutics perspective, NDA 208424 for Nitroglycerin sublingual powder, 400 mcg, is recommended for **APPROVAL.**

3/18/2016

Jing Li, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Concurrence and Signature:

I Concur with Dr. Li's assessment and recommendation.

3/22/2016

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response:
The following micro specification is proposed for the drug product.

Test	Acceptance criterion	
Microbiological purity** (Oromucosal preparations)	TAMC	nmt [redacted] CFU/g
	TYMC	nmt [redacted] CFU/g
	Staphylococcus aureus	absent [redacted] g)
	Pseudomonas aeruginosa	absent [redacted] g)

** Microbiological purity:

Release:

Microbiological purity will be tested on every batch

Stability:

a) Microbiological purity will be investigated at every sampling for the 3 validation batches.

b) Subsequently microbiological purity will be investigated once per year during routine stability (GMP on-going stability).

Reviewer's Assessment: Acceptable

The applicant includes microbial enumeration tests in accordance with USP <61> for microbial enumeration and USP <62> for specified micro-organisms. The acceptance criteria agree with the recommendations in USP <1111> for non-aqueous preparations for Oromucosal use.

2.3.P.7 Container/Closure System

39. 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:

The packaging material is a standard material used for the manufacturing of [redacted]

Reviewer's Assessment: Acceptable.

The [redacted] (b) (4) thus is not likely to be permeable for microbial. The applicant checks the integrity of the [redacted] (b) (4) with dye ingression method which is commonly used for container closure integrity test for sterile products.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

40. 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:
No excipients of animal or human origin are used for the drug substance or drug product manufacturing. Drug substance information was referred to DMF [redacted] (b) (4) and DMF [redacted] (b) (4).

Reviewer's Assessment: Acceptable.

Drug substance reviewer, Dr. Sithamalli Chandramouli, confirms that no raw materials used during drug substance manufacturing are from human or animal sources. Although, some raw material and excipient, such as [redacted] (b) (4), may come from vegetable sources, they are unlikely to introduce human virus or prion contamination.

41. 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: NA

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Acceptable
Xuhong Li
Branch I/Division I,
Office of Process & Facility (OPF)

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

42. Is the applicant's claim for categorical exclusion acceptable?

43. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

The sponsor updated the environmental assessment section during the review cycle and claims categorical exemption from the environmental assessment in accordance with 21 CFR 25.31(a) (please see seq. 0019, dated 29-Mar-2016). In addition, in accordance with 21 CFR 25.15(a) and (d), they declare to have no knowledge of any extraordinary circumstances that could warrant the preparation of the environmental assessment.

Reviewer's Assessment: Adequate

The proposed drug product is a new dosage form of the already marketed nitroglycerin drug products. Therefore, sponsor's claim for categorical exemption under 21 CFR 25.31(a) is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
Categorical exclusion from the environmental assessment may be granted.

Mariappan Chelliah
04-Apr-2016

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee
Branch Chief (Acting), ONDP/OPQ 04-APR-2016

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

Labeling & Package Insert

1. Package Insert

(b) (4)

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

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		Currently under review
Dosage form, route of administration		Adequate
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		Adequate

Conclusion: Adequate

In the original filing, the sponsor referred to the container closure system as '(b) (4) throughout the application and the labeling. However, it is not an accepted regulatory term for describing a package type for the labeling purpose (Please refer to FDA's Data Standards Manual (monographs) for Package Type, which can be accessed at the following URL link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071748.htm.). This was communicated to the sponsor during the review cycle and they replaced the term (b) (4) with 'packet' in the package insert and the C/C, carton labels (please see the sponsor's response in seq. 018, dated 11-Mar-2016.

(b) "Full Prescribing Information" Section

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

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		Adequate
Strengths: in metric system	400 mcg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Adequate

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

11 DESCRIPTION

Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate ($C_3H_5N_3O_9$). The compound has a molecular weight of 227.09. The chemical structure is:

$CH_2–ONO_2$
|
$CH–ONO_2$
|
$CH_2–ONO_2$

[Brand name] is a (b) (4) powder containing nitroglycerin. (b) (4) delivers (b) (4) (400 mcg (b) (4) (b) (4) Inactive ingredients: medium-chain triglycerides, peppermint oil, isomalt, anhydrous dibasic calcium phosphate, oleoyl polyoxylglycerides.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Currently under review
Dosage form and route of administration		Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		Adequate
Statement of being sterile (if applicable)		N/A
Pharmacological/ therapeutic class	vasodilator	Adequate
Chemical name, structural formula, molecular weight		Adequate
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		Adequate

Conclusion: Adequate

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

16 HOW SUPPLIED/STORAGE AND HANDLING
Each box of [Brand name] contains 12, 36 or 96 packets.
Each packet contains 400 mcg of nitroglycerin.

[Brand name] is available as:
- Box of 12 packets NDC 70007-400-12
- Box of 36 packets NDC 70007-400-36
- Box of 96 packets NDC 70007-400-96

Store up to 25 °C (77 °F); excursions permitted between 5° – 40 °C (41° – 104 °F).

Rx Only.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate
Special handling (e.g., protect from light, do not freeze)		N/A
Storage conditions		Adequate

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

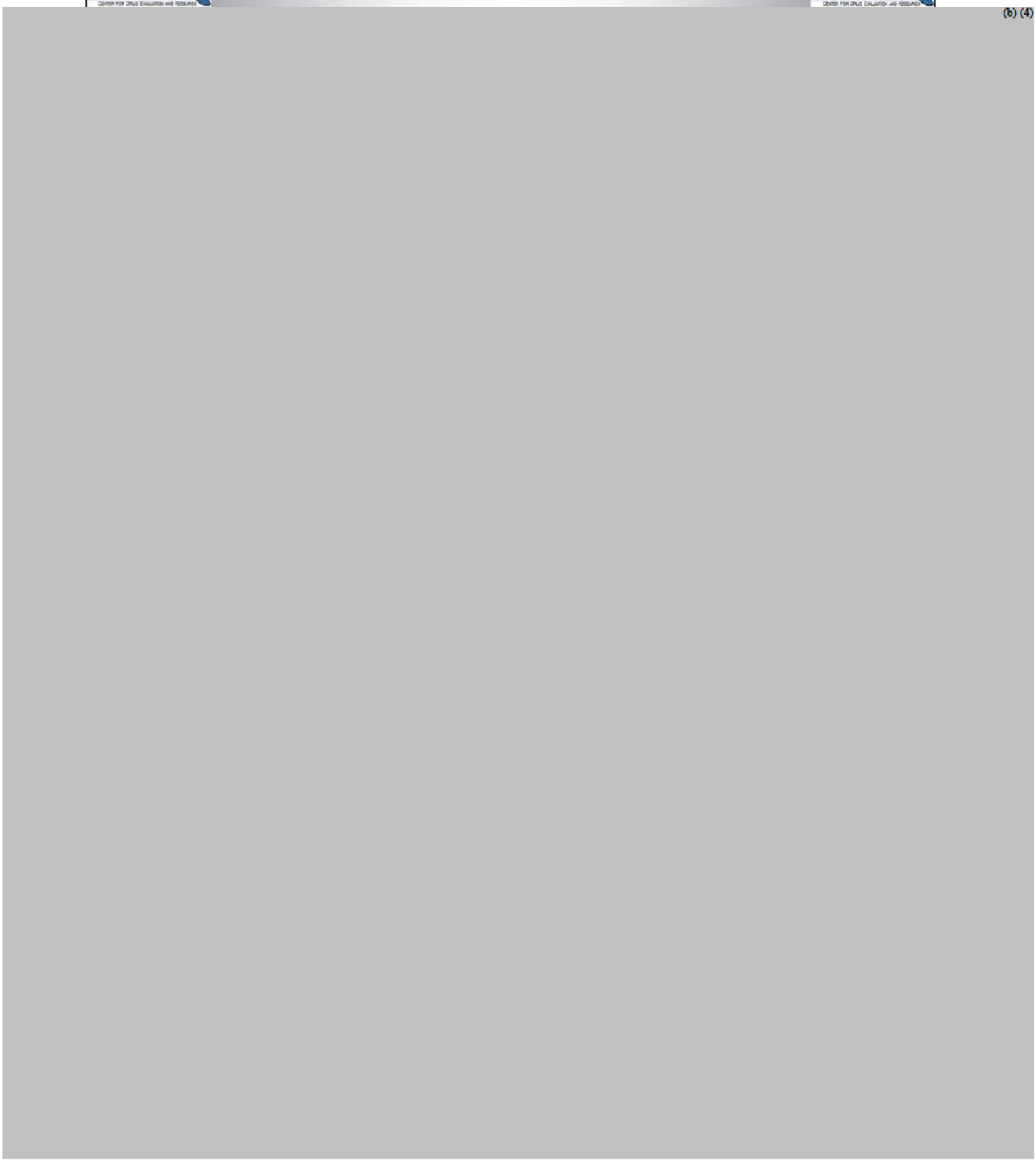
Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		Adequate

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration 21.CFR 201.100(b)(3))		Adequate
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Container labels do not list the inactive ingredients. However, this is acceptable as per 21 CFR 201.10(i)(2) (too small a label to print all the details required by 21.CFR 201.100(b)(3))	Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)	Storage is not listed.	Not required
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Container label is not printed with the NDC. But this is acceptable.	Not required
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		N/A

*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

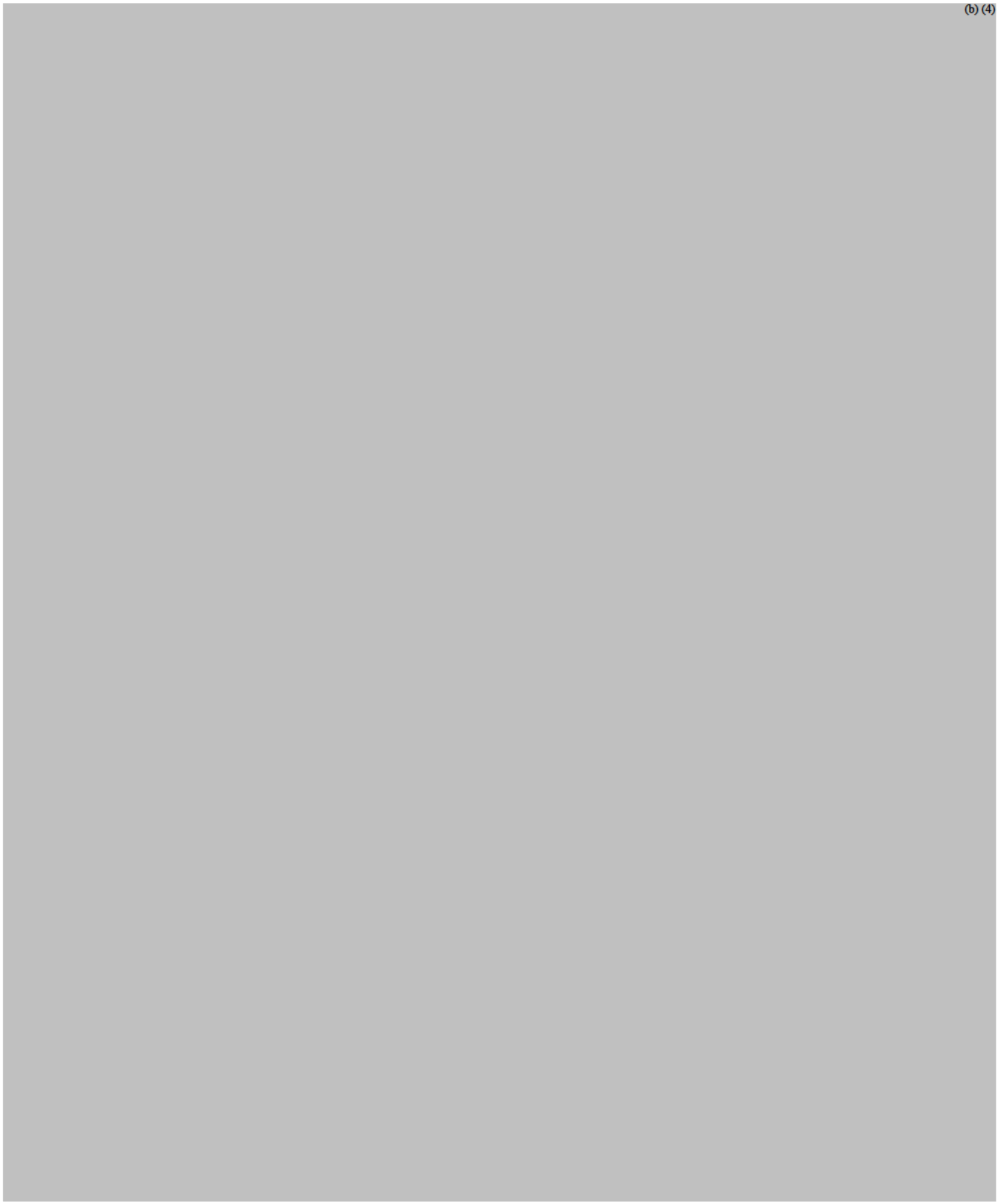
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code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

Conclusion: Adequate

2) Carton Labeling

(b) (4)

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		**Adequate**
Sterility Information (if applicable)		**N/A**
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		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)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)	The following language is used: (b) (4)	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		Not required

Conclusion: Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The labeling is adequate.

Mariappan Chelliah, 16-Mar-2016

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, 23-MAR-2016
Branch Chief (Acting), Branch 1/DNDP1/ONDP

Lifecycle Knowledge Management: Please refer to final risk assessment tables on pages 11-12.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208424	**Submission Type: The 505(b)(1)**	**Established/Proper Name: Nitroglycerin**
Applicant:G. Pohl-Boskamp GmbH & Co.	**Letter Date:08/06/2015**	**Dosage Form: Powder for Sublingual Use**
Chemical Type:	**Stamp Date:08/10/2015**	**Strength:400 Mcg** (b) (4)

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			No

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other _____	☒	☐	Powder for subligual use

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☒	☐	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other_____		☐	☐	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Facilities and Equipment ○ Adventitious Agents Safety Evaluation ○ Novel Excipients ❑ Regional Information ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols				
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be	☒	☐	☐	

C. FILING CONSIDERATIONS					
	licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☒	☐	The submitted relative BA study will be reviewed by OCP as per current MOU.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	No bridging is needed. The formulation of the clinical batch and the proposed commercial batch is the sam (b) (4)
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☐	☒	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☒	

Mohan K. Sapru -A

Digitally signed by Mohan K. Sapru -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -A, 0.9.2342.19200300.100.1.1=2000589315
Date: 2016.01.03 12:31:20 -05'00'