CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-359

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA (Biopharmaceutics) Review

NDA Re-submission	21-359
Applicant:	ProStarkan, Inc.
Trademark:	To be determined
Stamp Date	12/20/10; 5/9/11; 5/20/11
Established Name:	Nitroglycerin 0.4%
Dosage Form:	Ointment
Route of Administration:	Intra-anal
Indication:	Relief of pain associated with chronic anal fissure
Reviewer	Tapash Ghosh, Ph.D.

Background:
ProStarkan, Inc. is seeking the approval of nitroglycerin (NTG) ointment, 0.4% for the treatment of chronic anal fissures. Nitroglycerin is an organic nitrate that is proposed to work by relaxing the smooth muscle of the internal anal sphincter. By vasodilating both arteries and veins, NTG reduces the maximal resting anal pressure caused by anal fissures, and increases blood flow to the anoderm.

Re-Submission:
The current re-submission to NDA 21-359 dated May 20, 2011, includes the Applicant's response to the issues raised by FDA in the Complete Response (CR) Letter dated March 30, 2010.

Note that in the previous review cycle, the Applicant changed the drug product manufacturers, but they did not submit sufficient stability data to bridge the drug product registration batches to batches from the previous drug product manufacturer, therefore a CR Letter was issued that time. The current re-submission provides the requested bridging stability data, but it also includes a commercial manufacturing scale-up proposal that will require different manufacturing equipment and process parameters. In order to bridge this larger manufacturing scale-up to the clinical and registration processes, the applicant submitted complete process comparisons, *in vitro* drug release profile comparisons, and stability data.

Biopharmaceutics:
The biopharmaceutics review will focus on the evaluation of the *in vitro* release studies provided in a previous submission dated May 5, 2011 and in this re-submission. In the may 5th document, ProStrakan, Inc. responded to the Agency's CR Question **5ii**, regarding a comparison of the *in vitro* release profile between [redacted] (b) (4) kg validation batches and the [redacted] (b) (4) kg registration batches. The FDA's Question 5ii, Applicant response, and Reviewer comments are described next.

FDA's Question. 5 ii.
If available, provide a comparison of the *in vitro* release rate between [redacted] (b) (4) kg validation batches and the [redacted] (b) (4) kg registration batches.

ProStrakan's Response (excerpted):

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*A [redacted] (b) (4) kg registration batch (**906495**) and a [redacted] (b) (4) kg validation batch (**100141**) were tested in accordance with the SUPAC-SS guidance, CMC 7, May 1977. Data from Stage **I** and **II** of the test are contained in reports **40002-1632-0311/1.0** and **40002-1645-0411/1.0** respectively. The results from the testing are summarized in Table 5 of Report **40002-1645-0411/1.0**. The testing established that there is no significant difference in vitro release rate between the registration batch and the validation batch tested (90% Confidence Interval 0.823-0.921).*

*In addition, Report **40002-1645-0411/1.0** (Table 4) provides data comparing the in vitro release rates of [redacted] (b) (4) validation batch **106195** to [redacted] (b) (4) commercial batch **452022** which utilized the same method of manufacture and formulation as the batch used in the confirmatory Phase III clinical study (REC-C-001). No significant difference was seen in the in vitro release rate (90% Confidence Interval 1.021-1.219).*

*Report **4002-1645-0411/1.0** (Table 4) also provides the results of testing validation batches **100141**, **106195** and **106196** and establishes the equivalence of in vitro release of these three [redacted] (b) (4) kg [redacted] (b) (4) batches.*

Reviewer Comments:

1. During review of the above response information was lacking; therefore, an additional information requests (IR) was sent to the Applicant on May 16, 2011. The Applicant responded to this request on May 20, 2011. FDA asked mainly for the method development and validation report for the in-vitro release test (IVRT) used to generate the data included in the reports 40002-1632-0311/1.0 and 40002-1645-0411/1.0, and for the computational worksheets with all the data and statistical calculations involved in the same reports.
2. In comparing the *in vitro* release rates of Nitroglycerin from the various validation batches manufactured at [redacted] (b) (4) facility and between products manufactured at two different ([redacted] (b) (4) facilities, a statistical significant difference was not observed using the statistical procedure described in SUPACC-SS Guideline (statistical method Whitney U). Therefore, the results from this study support the product sameness for all the validation batches.

Recommendation:

Overall, the applicant's responses to the questions included in the IR and CR Letters were found satisfactory and they are acceptable.

The in vitro drug release data are showing that the [redacted] (b) (4) kg validation batches and the [redacted] (b) (4) kg registration batches have similar *in-vitro* release rate characteristics. Therefore, the sponsor's proposal for a scale-up in commercial manufacturing that would require different manufacturing equipment and process parameters at [redacted] (b) (4) is acceptable from Biopharmaceutics perspective.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT by Patrick Marroum, Ph. D. _____

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Biopharmaceutics Review

The review consists of three (3) sections:

- IVRT Method Development and Validation (Report # 40002-1051-0209)
- Stage I IVRT Report 40002-1632-0311/1.0 (referred as 1632)
- Stage II IVRT Report 40002-1645-0411/1.0 (referred as 1645)

IVRT Method Development and Validation (Report # 40002-1051-0209)

2.4. *In vitro* release method development

During the *in vitro* release method development following parameters were defined:

- membrane,
- applied amount of formulation,
- receptor medium,
- incubation time.

Moreover, the binding of the test substance to membrane material and to the syringes material used for sampling was investigated after confirmation of the receptor medium. (b) (4) (b) (4)

The development of the in vitro release method was conducted using the formulation Rectogesic® ((b) (4) ID: K12580).

Membrane

Two different membranes were tested for their suitability: a (b) (4) membrane (b) (4) membrane.

Applied amount of formulation

Two application doses (400 and 800 mg per diffusion area) were compared.

Receptor phase

As a receptor medium two different media were tested: (b) (4) .

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CRITERIA FOR MEMBRANE SELECTION

There are typically five different membrane types that are used most frequently worldwide for *in vitro* tests. Two of these were initially selected for Nitroglycerin 0.4% Ointment as (b) (4)

3.1.3. Comparison of the release using the (b) (4) membrane

The mean release of Nitroglycerin from the reference formulation (K12580) using (b) (4) membrane during the in vitro release method development is compared in Fig. 3.

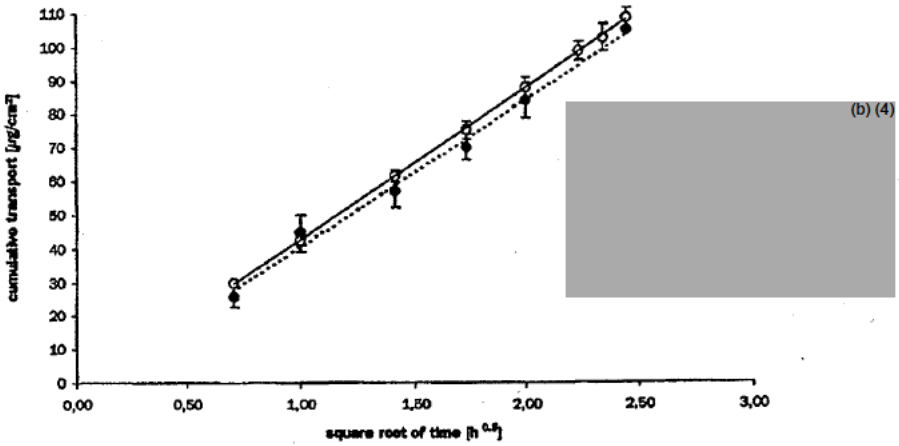

Fig. 3: Mean release of Nitroglycerin from the reference formulation (K12580) using two different membranes. The values shown are arithmetic mean values from experiments performed in triplicate ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

For both tested membranes similar results were observed. However, due to the better reproducibility and linearity of the data for (b) (4) membrane, this membrane was selected for further in vitro release testing.

- **Membrane resistance**

There were no significant changes to the membrane over this range as demonstrated by the linearity of the response as any variability in the membrane resistance would result in an inconsistent release rate with time. The gradient of the plots is very close to 1, and this suggests the right degree of resistance has been attained (Figure 2).

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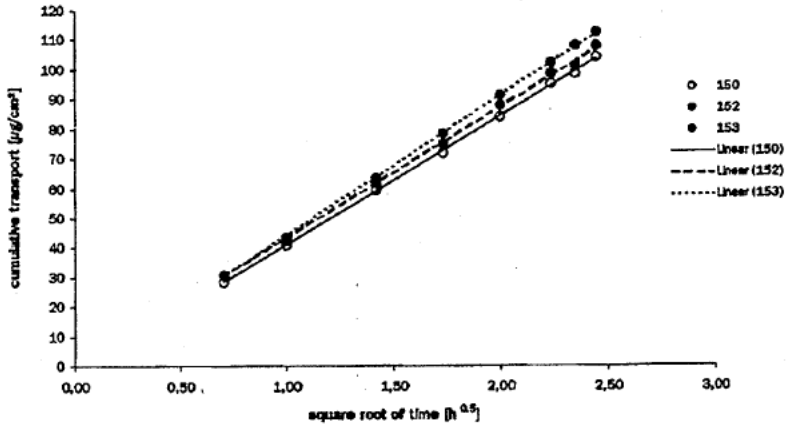

Fig. 2: Release of Nitroglycerin from the reference formulation (K12580) during the experiment 3 D. The values shown are the individual values from each Franz cell from experiment performed in triplicate. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

- **Membrane stability**

The linearity of the release rates for the duration of the experiment also suggests that the membrane is stable. If there were any opening or closing of the pores within the membrane, then this would manifest itself as a non-linearity in the data (Figure 2).

- **Membrane equilibrium**

Some membrane manufacturers recommend that their membranes are wetted before commencing the experiment [redacted] (b) (4)

- **Medium solubility**

Data on the solubility limit of nitroglycerin show that the compound was found to be completely dissolved in the acceptor medium, with a plateau concentration at about (b) (4) µg [redacted] (b) (4) (Table 33).

Tab. 33: Solubility of Nitroglycerin in acceptor medium.

Medium	[redacted] (b) (4)
Incubation time [h]	[redacted] (b) (4)
Measured concentration [µg·mL⁻¹]	[redacted]
Theoretical concentration [µg·mL⁻¹]	[redacted]
pH	[redacted]

The test compound was completely dissolved in the receptor medium. Therefore, the results show solubility of Nitroglycerin after 6 h at 32 °C was (b) (4) µg/mL⁻¹.

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3.2. Influence of formulation amount

3.2.3. Comparison of the release using two different formulation amounts

The mean release of Nitroglycerin from the reference formulation (K12580) using two different formulation amounts (400 mg and 800 mg) during the in vitro release method development is compared in Fig. 6.

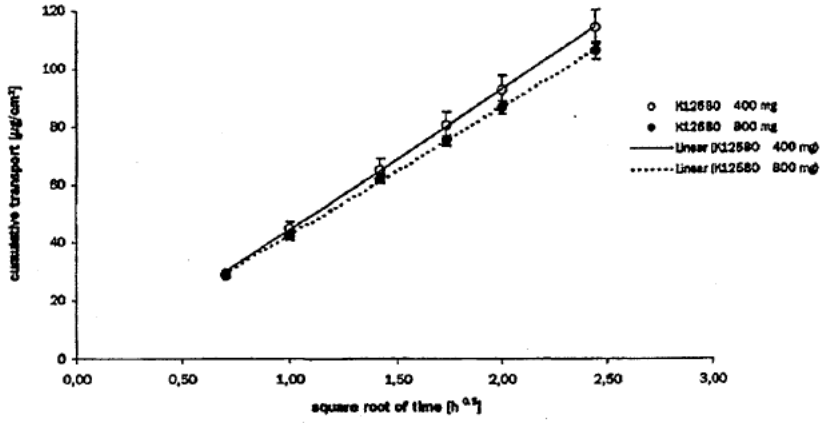

Fig. 6: Mean release of Nitroglycerin from the reference formulation (K12580) using two different formulation amounts (400 mg and 800 mg). The values shown are arithmetic mean values from experiments performed in triplicate ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

For both tested formulation amounts similar results were observed. However, due to the better linearity of the data for 400 mg and the fact that the use of the smaller sample size was not limiting to release rate obtained, this application dose was selected for further in vitro release testing.

3.3. Influence of receptor medium

Comparison of the release using different acceptor media

The mean release of Nitroglycerin from the reference formulation (K12580) using (b) (4) (b) (4) medium during the in vitro release method development is compared in Fig. 9.

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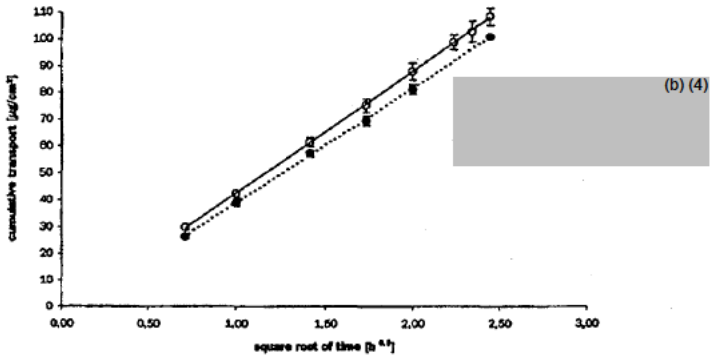

Fig. 9: Mean release of Nitroglycerin from the reference formulation (K12580) using (b) (4) (b) (4) medium. The values shown are arithmetic mean values from experiments performed in triplicate ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

For both tested receptor media similar results were observed. However, due to the better linearity of the data for (b) (4), this receptor medium was selected for further in vitro release testing.

3.4. Influence of chosen sampling time points

The results of the release studies of Nitroglycerin from the reference formulation (K12580) during the in vitro release method development with 8 sampling time points are shown in Fig. 10.

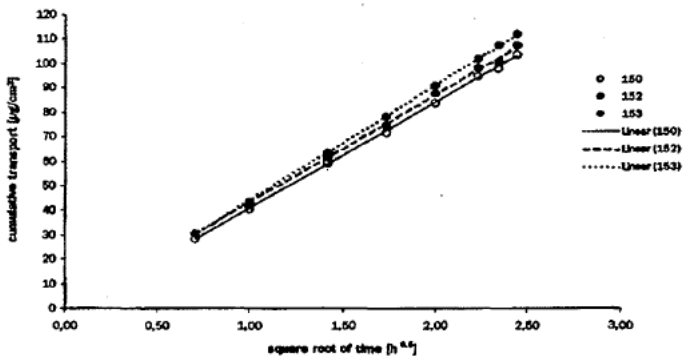

Fig. 10: Release of Nitroglycerin from the reference formulation (K12580) during the experiment 3 D. The values shown are the individual values from each Franz cell from experiment performed in triplicate. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

Since a sufficient linearity of the data expressed as cumulative transport into the acceptor compartment in µg per cm² of membrane area against the square root of time was observed for 8 sampling time points described above as well as for 6 sampling time points (see 3.3.1), the sampling time points suggested by the SUPAC-SS guideline (6 time points: 0.5, 1, 2, 3, 4 and 6 hours) were selected for further in vitro release testing.

3.5. Binding to the membrane material and to syringes material

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➢ **Membrane binding**

An assessment of the potential for nitroglycerin to bind to the membrane material was carried out as described below. The results indicate that there were no issues with binding.

The binding of the test substance to membrane material and to the syringes material used for sampling was investigated. The determined concentration in the samples and the corresponding recoveries are summarized in Tab. 23 and Tab. 25.

Tab. 23: Binding to the membrane material

	Initial at t=0 h [µg/mL]	After filtration [µg/mL]	Recovery [%]
(b) (4) **membrane**	10.34	10.44	100.97
(b) (4)	10.26	10.06	98.05

Tab. 24: Binding to syringes material

	C initial at t=0 h [µg/mL]	After 5 Minutes	After 30 Minutes
Concentration	10.44	10.24	10.65
Recovery [%]	-	98.08	102.01

IN VITRO RELEASE METHOD VALIDATION

➢ **Method Precision**

A comparison of the release from the same formulation determined separately in two experiments on the same day (intra-day, Figure 10, Table 34) indicate that the gradients (slopes) of the plots were very similar, resulting in a maximum %RSD of (b) (4) This indicates that the release rates were equivalent.

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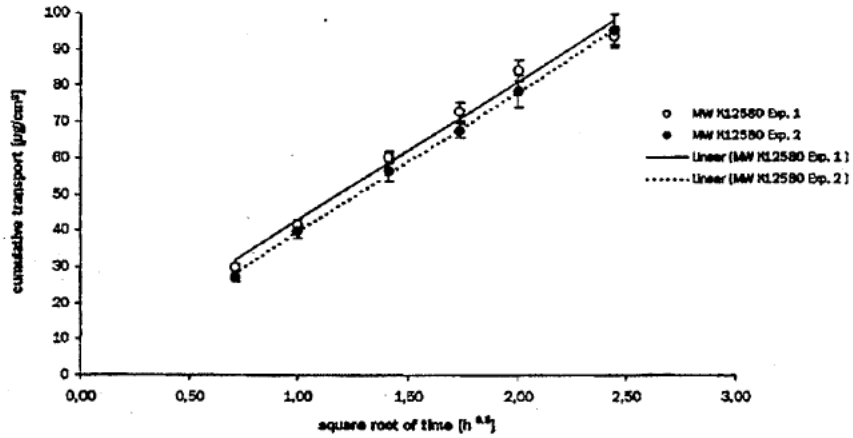

Fig. 10: Mean release of Nitroglycerin from the reference formulation (K12580) during the intra-day repeatability. The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

Tab. 34: Mean slope of the straight line resulting from plotting of the amount of drug released per unit area against the square root of time

Experiment			Slope [µg/cm²-h^0.5]	
Experiment	(b) ID	Batch No.	Mean	RSD [%]
Experiment 1	K12580	436930	45.08	3
Experiment 2	K12580	436930	44.07	6

The precision of the method was also assessed on different days (inter-day). The release profile of the reference formulation on different days were found equivalent (Figure 19, Table 37).

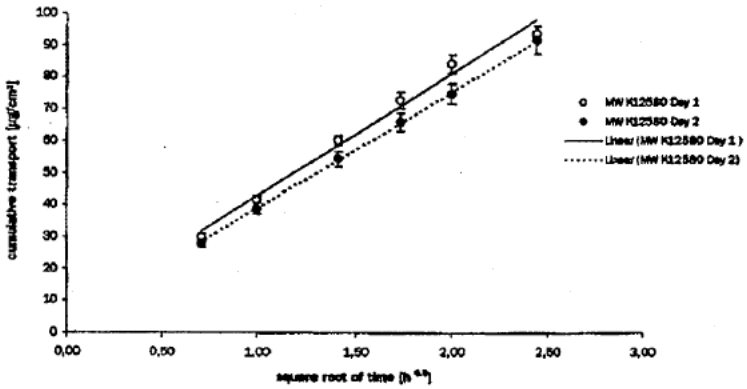

Fig. 19: Mean release of Nitroglycerin from the reference formulation (K12580) during experiments performed on two different days. The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

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Tab. 37: Mean slope of the straight line resulting from plotting of the amount of drug released per unit area against the square root of time

Day			Slope [$\mu g/cm^2 \cdot h^{0.5}$]	
Day	(b) ID	Batch No.	Mean	RSD [%]
Day 1 (06.05.09)	K12580	436930	45.08	3
Day 2 (07.05.09)	K12580	436930	41.77	5

- **Method Sensitivity**

As part of the manufacturing technical transfer activities from (b) (4) , a number of (b) kg lab-scale batches were prepared, for assessment of the impact on *in vitro* release of nitroglycerin when some of the excipient grades were changed. One of these formulations used a grade of (b) (4) that had been previously used in another product by (b) (4). (b) (4) When these batches were assessed for *in vitro* release, there was one batch (Test Formulation 3) out of the nine tested that was not equivalent, and this was the batch containing the (b) (4). This difference in viscosity in the one batch, and the resulting non-equivalence in *in vitro* release rate, demonstrates that the *in vitro* method is sufficiently sensitive.

Tab. 1: Summary of reference formulation and test formulations employed.

Formulation	(b) ID	Batch No.
Reference formulation (Rectogesic® batch 441406)	K14818	441406
Reference formulation (Rectogesic® batch 441406)	K14819	441406
Test formulation 1	K14782	08010709
Test formulation 2	K14783	08020709
Test formulation 3	K14820	08030709
Test formulation 4	K14821	08050709
Test formulation 5	K14822	08060709
Test formulation 6	K14947	08070709
Test formulation 7	K14948	08080709
Test formulation 8	K14949	08090709
Test formulation 9	K14950	08100709

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Release profile of Nitroglycerin from the test formulation 3 (K14820) and from the reference formulation (K14818) during the in vitro release comparison is presented in Fig. 12.

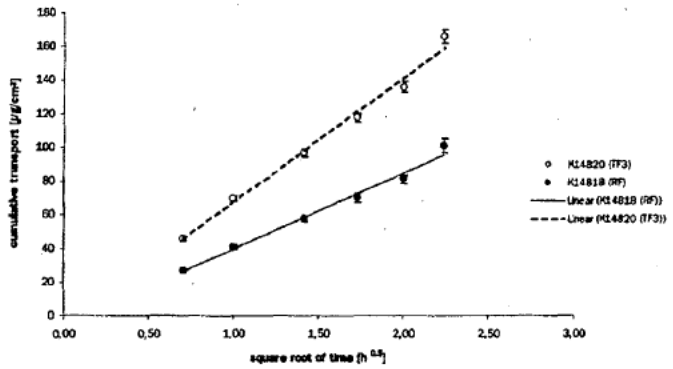

Fig. 12: Mean release of Nitroglycerin from the test formulation 3 (K14820) and from the reference formulation (K14818). The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

Tab. 40: Mean slope of the straight line resulting from plotting of the amount of drug released per unit area against the square root of time

Test products			Slope [µg/cm²·h^0.5]	
Test and reference	(b)I-ID	Batch No.	Mean	RSD [%]
Test formulation 3	K14820	08030709	68.48	3
reference formulation	K14818	441406	41.87	3

Tab. 41: Results of the 90% confidence interval.

(b) (4)ID	Batch No.	(b) ID	Batch No.	Lower limit 8-th value	Upper limit 29-th value	Significant different
K14820	08030709	K14818	441406	(b) (4)		yes

➢ Method Reproducibility

A comparison of data of the *in vitro* method when assessed over two days is presented in Figure 19. The results indicate that there was no significant difference between the two profiles.

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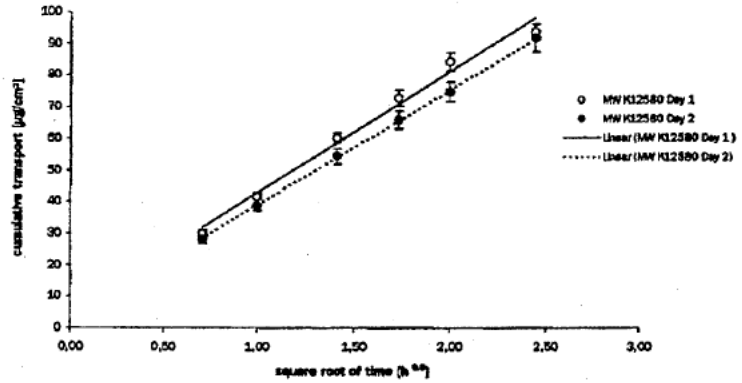

Fig. 19: Mean release of Nitroglycerin from the reference formulation (K12580) during experiments performed on two different days. The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

- **Selection of Time-Points**

The *in vitro* release experiments were run over a six hour period, with sampling every hour to provide a statistically meaningful number of data points. In addition, a sample was taken at the 30 minute timepoint – principally as a means of checking Franz cell operation when it can be assured that there would be a detectable HPLC response for nitroglycerin from the acceptor medium.

Analytical Validation Report of HPLC Parameters

Validation of the HPLC method (method transfer with partial validation) is described in the Report no. 4002-1051-0209, '*In vitro release of Nitroglycerin from different batches of one formulation of nitroglycerin ointment 0.4%: method validation and in vitro release comparison*'. The HPLC method for nitroglycerin that was used by (b) (4) (contract testing laboratory for (b) (4)), 'Method (b) (4)-0571-LC for the (b) (4) ', was also supplied to (b) (4), and a partial validation was performed following the transfer of this method.

2.3.2. HPLC method development and validation

The first step of the study was to develop an analytical HPLC method for quantification of Nitroglycerin in the samples from in vitro release experiments (in receptor medium used in the release method). The development of the analytical method was based on the information published in the literature and on the method sent by the customer.

Prior to the HPLC method validation the first in vitro release experiment was performed. Based on the results from this run a concentration range for HPLC method validation was chosen.

The analytical parameters of the developed HPLC method are summarizedin Tab. 20.

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Tab. 20: Summary of the analytical parameters for HPLC method

System	(b) (4)
Software	
Column	
Guard column	
Mobile Phase	
Mode	
Flow rate	
Temperature	
Detector wavelength	
Injection volume	
Run time	
Retention time	

a. **Linearity**

It was found that with five data points, the method is linear in the nitroglycerin concentration range (b) (4).

b. **Range**

The range in nitroglycerin concentration over which the method is validated is restricted to the range of linearity of response – i.e. (b) (4)

c. **Detection limit**

A separate assessment of detection limit was not carried out. However, it was found that the lower end for nitroglycerin concentration linearity of the HPLC method was (b) (4) and the release data at all timepoints from investigation of release rates of the Nitroglycerin 0.4% Ointment batches were always greater than this lower limit.

d. **Specificity (Selectivity and Sensitivity)**

In validating the method, no interference with the nitroglycerin peak was detected. Therefore, the method is considered as specific, selective and sensitive.

e. **Precision**

The mean value of three replicate samples was determined for three concentration levels: approximately (b) (4). The results indicated

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that the values for precision of the method complied with relative standard deviation limit requirements.

f. Robustness

Robustness of the method was not evaluated, although the conditions for the analysis such as pH, flow rate, temperature, wavelength, injector volume etc. are fixed and do not change when using the fully qualified HPLC equipment at (b) (4). Nevertheless, a system suitability and linearity test is carried out before the running of each experimental set.

Tab. 1: Summarized results of the HPLC method validation.

Parameter	Detail	Limits	Result	Compliance
System suitability test	6 injections of standard solution	RSD ≤ (b)	(b)%	Yes
Selectivity	Visual comparison of chromatograms of the test compound in eluent mixture and extraction medium	No interferences with eluent mixture and acceptor medium	No interferences with eluent mixture and acceptor medium	Yes
Linearity	1st Order regression model r 5 calibration levels	R^2: (b) (4)	R^2: (b) (4)	Yes
	Linear range	-	(b) (4) µg mL^{-1}	Yes
	Deviation conc. Measured/ theor. conc.:	± (b)%	(b) (4)	Yes
Accuracy	3 concentration levels (b) (4) n=3 deviation mean value/true value	Recovery ± (b) (4)%	Recovery: (b) (4)	Yes
Precision	3 concentration levels (b) (4) n=3 RSD%	RSD (n=3) ± (b)	RSD: (b) (4)	Yes
Robustness (stability in receptor medium)	Recovery in acceptor medium n=3	Recovery > (b) (4)%	Recovery Acceptor medium over 24 h: RT: (b) (4)	Yes

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1.2.1. In vitro method development

The test conditions selected for in vitro release method validation and for further in vitro release testing are summarized in Tab. 1.

Tab. 1: Test conditions for in vitro release method validation

Test condition	
Receptor medium	(b) (4) (v/v, %)
Sampling time points	6: after 0.5, 1, 2, 3, 4 and 6 hours
Membrane	(b) (4) Membrane, (b) (4) µm thickness
Test formulation amount in mg	400

Reviewer Comment:

The above proposed IVRT method (4002-1051-0209) using the validated analytical method (Method (b) (4)'-0571-LC) is adequate and acceptable.

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Stage I IVRT Report 40002-1632-0311/1.0 (referred as 1632)

In vitro release of Nitroglycerine from 2 batches of one formulation - (b) (4) release testing for commercial batches no. 906495-0 and 100141-0

Report number: 40002-1632-0311/1.0

Contract laboratory: (b) (4)

1.1. Objectives

An in vitro release rate can reflect the combined effect of several physical and chemical parameters including solubility and particle size of the active ingredient and rheological properties of the dosage form. Therefore, in vitro release rate is a useful test to assess product sameness between pre change and post change products.

The aim of the present study was to determine the in vitro release of Nitroglycerine from two batches of the Rectogesic formulation. The investigations were performed in six-fold (n=6) per formulation as suggested by the FDA Guidance (SUPAC-SS, CMC 7, May 1977). The study was carried out using static Franz diffusion cells according to the study design validated in studies 40002-1135-0509 and 40002-1051-0209. A comparison between the batches has been performed.

1.2. Summarized results

1.2.1. Analytics

Previously to the analytical series a system suitability test (SST) has been performed. Within the analytical series the precision of quality control (QC) samples has been determined in terms of area and retention time. The specification of (b) (4) % relative standard deviation was fulfilled in the series for SST as well as for the precision of the QC samples.

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1.2.2. In vitro release

The results of the in vitro release study (comparison of the release from the test and reference formulation are summarized in in Tab. 1 and Tab. 2.

Tab. 1: Mean slope of the straight line, determined from the plot of the amount of released drug compound per unit area versus the square root of time.

In vitro release comparison			Slope [$\mu g/cm^2 \cdot h^{0.5}$]	
Formulation	(b) (4) ID	Batch	Mean	RSD [%]
Rectogesic	K16972 TF	906495-0	39.39	6
Rectogesic	K16973 RF	100141-0	51.46	9

Tab. 2: Results of the 90% confidence interval.

Test formulation		Reference formulation		Limits of the 90% confidence interval		
(b) (4) ID	Batch No.	(b) (4) ID	Batch No.	Lower limit 8-th value	Upper limit 29-th value	Significant different
K16972	906495-0	K16973	100141-0	(b) (4)		yes

1.3. Conclusion

Comparing the in vitro release rates of Nitroglycerin from the test product and reference product a significant difference was observed according to statistical procedure described in SUPACC-SS Guideline (statistical method Whitney U).

Therefore no product sameness can be assumed.

Reviewer's Comment:

Since the batches 906495-0 ((b) (4) Kg registration batch) and 100141 ((b) (4) Kg validation batch) were significantly different during this first stage of the evaluation of release testing, a second stage evaluation according to the SUPAC-SS guideline was performed. As the second stage evaluation includes the data generated from the previous study (see report 40002-1632-0311), report 40002-1632-0311 were not reviewed in detail. The review of the second stage study 40002-1645-0411/1.0 is presented next.

Reference ID: 2957532

Reference ID: 2969428

Stage II IVRT Report 40002-1645-0411/1.0 (referred as 1645)

In vitro release of nitroglycerine from 5 batches of Rectogesic – [redacted] (b) (4) batches no. 906495-0 (Pilot Scale Batch 3), 100141-0 (Validation Batch 1), 106195-0 (Validation Batch 2), 106196-0 (Validation Batch 3) and [redacted] (b) (4) [redacted] Commercial Batch 452022

Report number: 40002-1645-0411/1.0

Contract laboratory: [redacted] (b) (4)

1.1. Objectives

An in vitro release rate can reflect the combined effect of several physical and chemical parameters including solubility and particle size of the active ingredient and rheological properties of the dosage form. Therefore, in vitro release rate is a useful test to assess product sameness between pre change and post change products.

The aim of the present study was to determine the in vitro release of Nitroglycerine from three batches of the Rectogesic formulation. For all three batches the statistical comparison has been performed. Additionally one of these batches has been compared to another production batch. The investigations were performed in six-fold (n=6) per formulation as suggested by the FDA Guidance (SUPAC-SS, CMC 7, May 1977). The study was carried out using static Franz diffusion cells according to the study design validated in studies 40002-1135-0509 and 40002-1051-0209. A comparison between the batches has been performed.

The following batches were tested and compared as shown in the table below:

Tab. 1: Batches tested for rele3ase of Nitroglycerin and comparison (first stage evaluation)

Formulation		Formulation	
[redacted] (b) ID	Batch No.	[redacted] (b) (4) ID	Batch No.
K16987 (B)	106195-0	K16973 (A)	100141-0
K16988 (C)	106196-0	K16973 (A)	100141-0
K16988 (C)	106196-0	K16987 (B)	106195-0
K170006 (D)	452022	K16987 (E)	106195-0

Reference ID: 2957532

Reference ID: 2969428

Tab. 2: Second stage evaluation of

Formulation		Formulation	
(b) (4) ID	Batch No.	(b) (4) ID	Batch No.
K16972 (F)	906495-0	K16973 (G)	100141-0

Release testing

In the calculations the individual values of Franz cells used in the experiments were considered. All calculations were performed using the program EXCEL from Microsoft Corporation. USA. The calculations were performed using the full number of digits handled by the EXCEL 2000 program. The results were rounded only for printing and for the presentation in the report. Release is theoretically proportional to the square root of time. This assumption based on the relation of Higuchi (Higuchi 1961) as shown in the following equiation:

$$Q = A\sqrt{D * c_s * (2c_0 - c_s)} * \sqrt{t} \qquad \text{Eq. 3}$$

Q Released amount of API at time t [g]

A Diffusion area [cm^2]

D Diffusion coefficient [cm min^{-1}]

c_s Saturation solubility of API in the formulation [g mL^{-1}]

C_0 API concentration in the matrix [g mL^{-1}]

t Time [min]

A plot of the amount of drug released per unit area [µg·cm^{-2}] against the square root of time yields a straight line. The slope of the line represents the release rate. This release rate measure is formulation specific. For all individual cells. the release rates were calculated from the linear part of the cumulative amount released.

$$m = \frac{dQ}{A\sqrt{dt}} \qquad \text{Eq. 4}$$

Q Released amount of API at time t [g]

A Diffusion area [cm^2]

t Time [min]

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Comparison of release rate was performed according to the SUPAC-SS guideline. The two experiments were compared to each other. The lower limit (8-th ratio) of the 90 % confidence interval should be greater than (b) (4) and the upper limit (29-th) lower than (b) (4). If the confidence interval does not fall within the limits. the results of the two experiments are significant different.

For the second stage evaluation the 12 additional slopes per batch (906495-0 and 100141-0) has been evaluated together with the six slopes from stage one evaluation (see report 40002-1632-0311). For total 18 slopes per batch (906495-0 and 100141-0) were evaluated. All 324 (=18x18) individual Batch 906495-0/Bacht 100141-0 ratios were calculated and ranked.

The lower limit (110th ratio) of the 90 % confidence interval should be greater than (b) (4) and the upper limit (215th ratio) lower than (b) (4)

1.2.2. In vitro release

The results of the in vitro release study comparison of the release from the formulations are summarized in Tab. 3 and Tab. 2.

Tab. 3: Mean slope of the straight line, determined from the plot of the amount of released drug compound per unit area versus the square root of time.

In vitro release comparison			Slope [$\mu g/cm^2 \cdot h^{0.5}$]	
Formulation	Batch	(b) (4) ID	Mean	RSD [%]
Rectogesic	100141-0	K16973 (A)	46.66	7
Rectogesic	106195-0	K16987 (B)	46.71	8
Rectogesic	106196-0	K16988 (C)	47.35	17
Rectogesic	452022	K170006 (D)	40.99	8
Rectogesic	106195-0	K16987 (E)	45.81	5
Rectogesic (second stage)	906495-0	K16972 (F)	41.07	11
Rectogesic (second stage)	100141-0	K16973 (G)	46.81	11

Tab. 4: Results of the 90% confidence interval for the first stage evaluation

Formulation		Formulation		Limits of the 90% confidence interval		
(b) (4) ID	Batch No.	(b) (4) ID	Batch No.	Lower limit 8-th value	Upper limit 29-th value	Significant different
K16987 (B)	106195-0	K16973 (A)	100141-0	(b) (4)		no
K16988 (C)	106196-0	K16973 (A)	100141-0			no
K16988 (C)	106196-0	K16987 (B)	106195-0			no
K170006 (D)	452022	K16987 (E)	106195-0			no
Comparison 100141-0 study 1632 vs. study 1645						
K16973	100141-0	K16973	100141-0	(b) (4)		no

Reference ID: 2957532

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In table 5 the results of the second stage evaluation for batch 906495-0 and 100141-0 are depicted. The release of Nitroglycerin has been tested during project 40002-1632-0311. This first relase testing (first stage evaluation) showed a significant difference. Therefore the two batches were tested again (second stage evaluation) according the SUPAC-SS guideline.
The experiments have been performed using the same equipment by the same operators in the laboratory. Therefore any influence by different material or operator can be excluded.

Tab. 32: Measured release rate (µg/cm²h $^{0.5}$) in individual Franz diffusion cells at different time points. release from formulation A; 100141-0 (K16973)

Root of Time [h]	247	227	251	261	233	256
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

Tab. 34: Measured release rate (µg/cm²h $^{0.5}$) in individual Franz diffusion cells at different time points. release from formulation B; 106195 (K16987)

Root of Time [h]	224	222	241	219	259	260
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

Reference ID: 2957532

Reference ID: 2969428

3.2.8. Comparison of the release from formulation A; 100141-0 (K61973) and formulation B; 106195-0 (K16987)

The mean release of Nitroglycerin from formulation B; 106195-0 (K16987) and from formulation A; 100141-0 (K16973) during the in vitro release comparison is compared in Fig. 9.

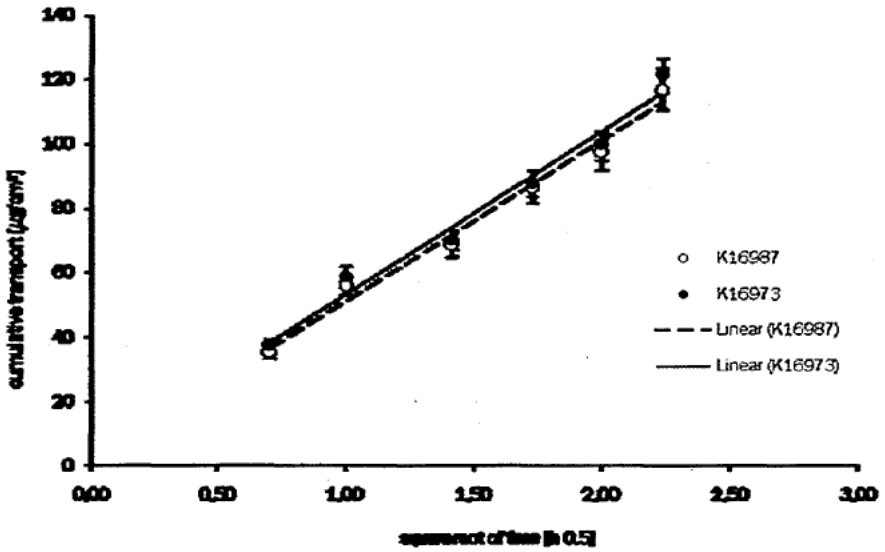

Fig. 9: Mean release of Nitroglycerin from formulation B; 106195-0 (K16987) and from formulation A; 100141-0 (K16973). The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

Tab. 36: Measured release rate (µg/cm²h $^{0.5}$) in individual Franz diffusion cells at different time points. release from formulation C; 106196 (K16988)

Root of Time [h]	236	62	253	257	160	248
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

Reference ID: 2957532

Reference ID: 2969428

3.2.9. Comparison of the release from formulation A; 100141-0 (K16973) and formulation C; 106196-0 (K16988)

The mean release of Nitroglycerin from formulation C; 106196-0 (K16988) and from formulation A; 100141-0 (K16973) during the in vitro release comparison is compared in Fig. 10.

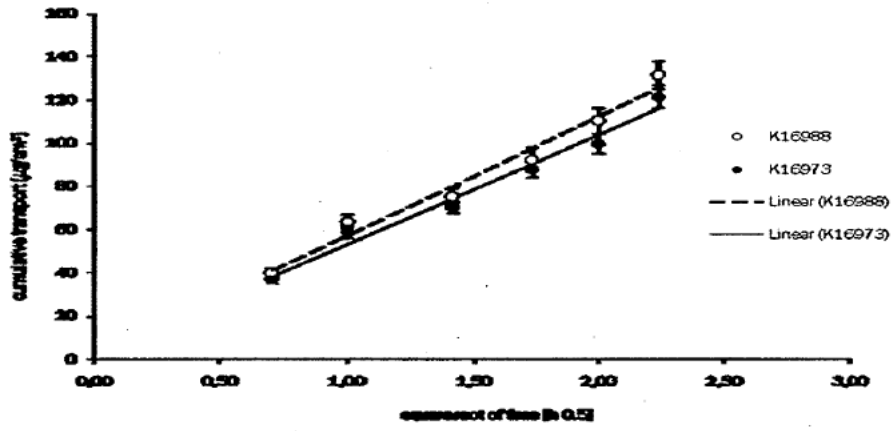

Fig. 10: Mean release of Nitroglycerin from formulation C; 106196-0 (K16988) and from formulation A; 100141-0 (K16973). The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

3.2.10. Comparison of the release from formulation B; 106195-0 (K16987) and formulation C; 106196-0 (K16988)

The mean release of Nitroglycerin from formulation C; 106196-0 (K16988) and from formulation B; 106195-0 (K16987) during the in vitro release comparison is compared in Fig. 11.

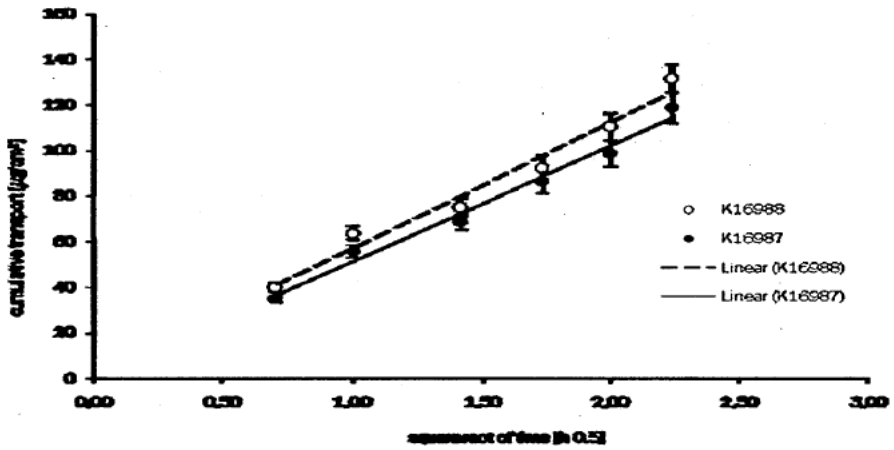

Fig. 11: Mean release of Nitroglycerin from formulation C; 106196-0 (K16988) and from formulation B; 106195-0 (K16987). The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

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Tab. 38: Measured release rate (µg/cm²h $^{0.5}$) in individual Franz diffusion cells at different time points. release from formulation D; 452022 (K170006)

Root of Time [h]	255	252	67	258	216	55
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

Tab. 40: Measured release rate (µg/cm²h 0.5) in individual Franz diffusion cells at different time points. release from formulation E; 106195 (K16987)

Root of Time [h]	66	250	210	161	235	218
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

Reference ID: 2957532

Reference ID: 2969428

3.2.11. Comparison of the release from formulation D; 452022 (K170006) and formulation E; 106195-0 (K16987)

The mean release of Nitroglycerin from formulation E; 106195-0 (K16987) and from formulation D; 452022 (K170006) during the in vitro release comparison is compared in Fig. 12.

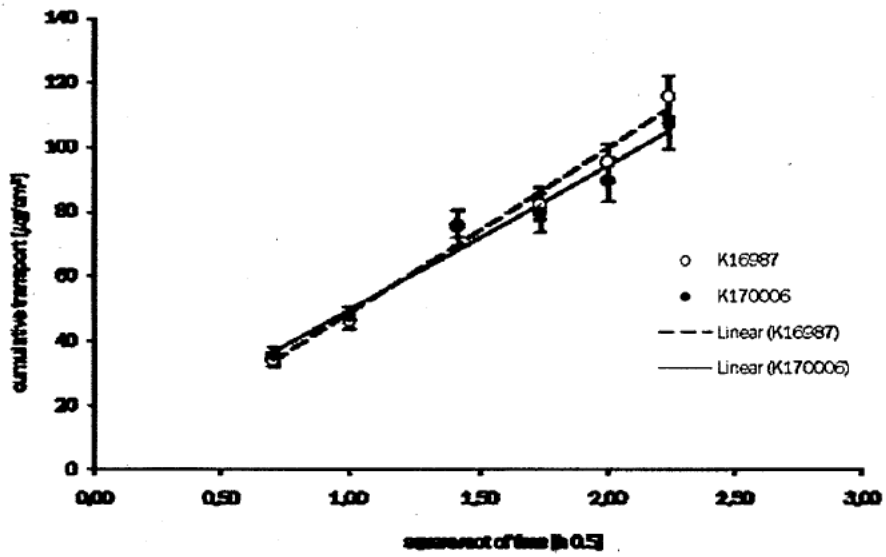

Fig. 12: Mean release of Nitroglycerin from formulation E; 106195-0 (K16987) and from formulation D; 452022 (K170006). The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

Tab. 44: Measured release rate (µg/cm²h $^{0.5}$) in individual Franz diffusion cells at different time points. release from formulation G; 100141-0 (K16973)

Root of Time [h]	256-1632	220-1632	260-1632	254-1632	261-1632	222-1632
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

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Root of Time [h]	251-1645-	219-1645-	220-1645-	235-1645-	255-1645-	161-1645-
0.71	(b) (4)					
1.00						
1.41						
1.73						
2.00						
2.24						
Slope $\mu g/(cm^2 \cdot h^{0.5})$						

Root of Time [h]	216-1645-	252-1645-	258-1645-	250-1645-	55-1645-	66-1645-
0.71	(b) (4)					
1.00						
1.41						
1.73						
2.00						
2.24						
Slope $\mu g/(cm^2 \cdot h^{0.5})$						

Reference ID: 2957532

Reference ID: 2969428

3.2.12. Comparison of the release from formulation 100141-0 K16973 (report 1632) and formulation 100141-0 K16973 (report 1645)

The mean release of Nitroglycerin from formulation 100141-0 K16973 (report 1632) and from formulation 100141-0 K16973 (report 1645) during the in vitro release comparison is compared in Fig. 13.

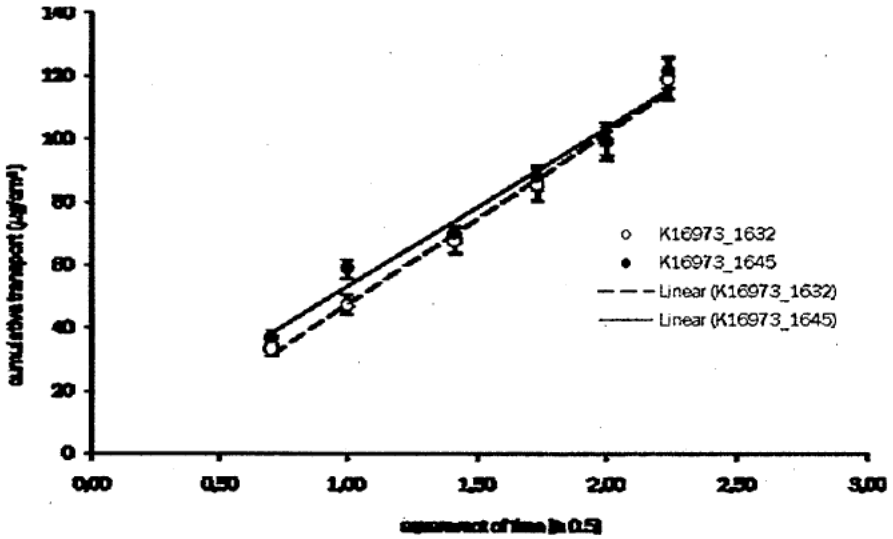

Fig. 13: Mean release of Nitroglycerin from formulation 100141-0 K16973 (report 1632) and from formulation 100141-0 K16973 (report 1645). The values shown are arithmetic mean values from experiments performed in six-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

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Tab. 42: Measured release rate (µg/cm²h $^{0.5}$) in individual Franz diffusion cells at different time points. release from formulation F; 906495-0 (K16972)

Root of Time [h]	235-1632	251-1632	250-1632	247-1632	233-1632	253-1632
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

Root of Time [h]	260-1645-	222-1645-	248-1645-	224-1645-	253-1645-	241-1645-
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

Root of Time [h]	261-1645-	247-1645-	236-1645-	227-1645-	233-1645-	256-1645-
0.71						(b) (4)
1.00						
1.41						
1.73						
2.00						
2.24						
Slope µg/(cm²·h$^{0.5}$)						

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Reference ID: 2969428

3.2.13. Comparison of the release from formulation F; 906495 (K16972) and formulation G; 100141-0 (K16973) – second stage

The mean release of Nitroglycerin from formulation G; 100141-0 (K16973) and from formulation F; 906495 (K16972) during the in vitro release comparison is compared in Fig. 14.

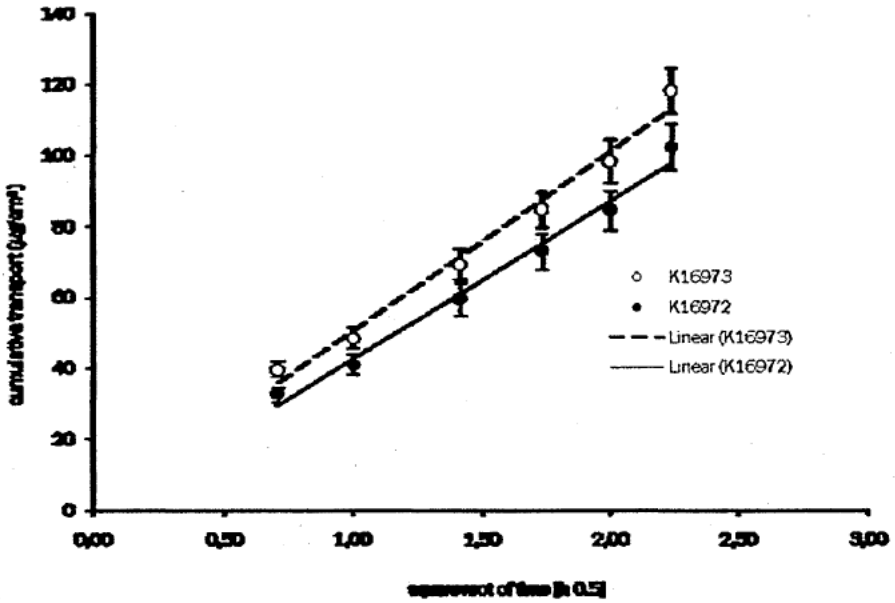

Fig. 14: Mean release of Nitroglycerin from formulation G; 100141-0 (K16973) and from formulation F; 906495 (K16972). The values shown are arithmetic mean values from experiments performed in 18-fold ± SD. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

The figure shows the mean values from 18th slopes.

Tab. 5: Results of the 90% confidence interval for the second stage evalution with 18th slopes

Formulation		Formulation		Limits of the 90% confidence interval		
(b) (4) ID	Batch No.	(b) (4) ID	Batch No.	Lower limit 110-th value	Upper limit 215-th value	Significant different
K16972 (F)	906495-0	K16973 (G)	100141-0	(b) (4)		no

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Tab 6: Results of the 90% confidence interval for the second stage evaluation with 18th slopes (alternating "Test" and "Reference")

Reference formulation		Test formulation		Limits of the 90% confidence interval		
(b) (4) ID	Batch-Nr.	(b) (4) ID	Batch-Nr.	Lower-limit 110th value	Upper-limit 215th value	Signifiant difference
K16973	100141-0	K16972	906495-0	(b) (4)		no

Reviewer Comments:

1. *The same IVRT and analytical procedure described in the Method Development and Validation Report # 40002-1051-0209 was used for both studies 1632 and 1645. Therefore, the procedures were not described in detail in the review of these studies.*

2. *During the first phase testing (Report 40002-1632-0311/1.0) as per SUPAC-SS, (b) (4) batches 906495-0 ((b) (4) kg scale registration) and 100141 ((b) (4) kg scale validation) had in vitro release rates of (b) (4) (RSD = 6%) and (b) (4) (RSD = 9%) $\mu g/cm^2 * h^{0.5}$ respectively. Limits of the 90% confidence intervals were significantly different, so no product sameness could be assumed.*

3. *SUPAC-SS acknowledges that in vitro release rate testing often encounters outliers in testing (i.e. due to air bubbles between the product sample and membrane). Therefore, a second stage testing is not uncommon to establish product sameness. The second phase evaluation (Report 40002-1645-0411/1.0) repeated the comparison between batches 906495 and 100141 as per SUPAC-SS guidelines. The report also included additional comparisons of (b) (4) batches 906495 (pilot, (b) (4) kg scale), 100141 (validation, (b) (4) kg), 106195 (validation, (b) (4) kg), 106196 (validation, (b) (4) kg), and (b) (4) 452022 (commercial, (b) (4) kg, same process as clinical batch) as tabulated below:*

4.

Manufacturer	Batch #	Batch Amount	Batch Description
(b) (4)	452022	(b) (4) Kg	Commercial
	906495	Kg	Registration/Pilot
	100141	Kg	Validation
	106195	Kg	Validation
	106196	Kg	Validation

4. *Overall, the second stage evaluation comparing the pilot batch (906495) and validation batch (100141) was performed according to the guideline (Nonsterile Semisolid dosage forms SUPAC- SS) with 18 slopes shows that the two products are similar in contrast to the first evaluation with 6 slopes for each product. The reason that the difference is no*

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longer statistically significant is probably due to the larger number of replicate slopes required for the second stage.

5. *Comparison of the in vitro release rates of Nitroglycerin from the additional test products demonstrated no significant difference according to the statistical procedure described in SUPACC-SS Guideline (statistical method Whitney U) reinforcing sameness of different batches of the products manufactured at (b) (4) facility and between products manufactured at two different (b) (4) and (b) (4) facilities.*

6. *There is no evidence of a run-to-run effect.*

7. *Based on their in-vitro release data, it can be concluded that the products manufactured at (b) (4) kg pilot batches and at (b) (4) kg at (b) (4) have similar release rate characteristics. Therefore, the scale-up data from (b) (4) is acceptable from Biopharmaceutics perspective.*

OTHER ADDITIONAL ISSUES

During review of the IVRT reports, in response of the Agency's IRs, the sponsor responded to some other issues as excerpted follows:

In both reports, please identify clearly the "Test" and the "Reference" formulations and justifications for their designation.

In report 40002-1632-0311/1.0 (submitted on May 5, 2011 in Attachment 1), the pilot batch (Batch no. 906495-0) was designated as the Test batch, and the validation batch (Batch no. 100141-0) was designated as the Reference batch. The purpose of the experiment was to directly compare the batches with each other, and in that sense there is no practical difference as to which batch is ***designated 'Test' and which is designated 'Reference'. In other words****, if the designation were the other way around, it would make no difference to the conclusion of the experiment. Nevertheless, if it is considered that the* ***pilot batch is the 'pre-change' (Reference) lot, and the validation batch is the 'postchange'*** *(Test) lot, then the calculations in report 40002-1632-0311/1.0 were actually performed as per the SUPAC-SS Guidance requirements, with the T/R ratios being validation lot/pilot lot.*

For the Stage II testing (report 40002-1645-0411/1.0, submitted on May 5, 201,1 in ***Attachment 2), there was no 'Test' or 'Reference' designation*** *assigned for the batches evaluated as such, because the batches were all compared directly with each other, and therefore no such designation was deemed necessary . However, the way the calculations were performed indicates that the T/R ratios were determined as pilot lot/validation lot. Calculating in this way produced the 90%* ***confidence interval limits*** *(b) (4).*

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Tab. 5: Results of the 90% confidence interval for the second stage evalution with 18th slopes

Formulation		Formulation		Limits of the 90% confidence interval		
(b) (4) ID	Batch No.	(b) (4) ID	Batch No.	Lower limit 110-th value	Upper limit 215-th value	Significant different
K16972 (F)	906495-0	K16973 (G)	100141-0	(b) (4)		no

Consequently, a recalculation of the 90% confidence interval was performed using the reverse ratio of validation lot/pilot lot. This resulted in revised limits (b) (4)*, with the same conclusion that there was no significant difference in release rate between the two batches.*

Reference formulation		Test formulation		Limits of the 90% confidence interval		
(b) (4) ID	Batch-Nr.	(b) (4) ID	Batch-Nr.	Lower-limit 110th value	Upper-limit 215th value	Significant difference
K16973	100141-0	K16972	906495-0	(b) (4)		no

Explain why there is a difference in the shapes of the release profiles from batch 100141 between the two studies (refer to Fig. 3 of study 40002-1632-0311/1.0 and Fig 2 of study 40002-1645-0411/1.0).

The difference in the shapes is within the limits of normal variation. Submitted on May 5, 2011 in Attachment 2, report 40002-1645-0411/1.0, Table 2 on Page 7 (Section 1.2.2 (In vitro release)) includes a statistical comparison of these two release plots of batch 100141. This shows that the 90% confidence interval limits were (b) (4)*, and therefore the plots are not significantly different.*

Also clarify how many points were taken into consideration in calculating the slopes from Fig 2 of study 40002-1645-0411/1.0 as all points are not linear.

*All the data points were used for calculation of the slopes. The SUPAC guideline ('**Nonsterile Semisolid Dosage** Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro release Testing and In Vivo **Bioequivalence Documentation**', May 1997) states on Page 23 (Chapter VII, In Vitro Release Test) that a nonparametric method can be used, due to the possibility of outliers in the event of, for example, air bubble formation. The performance of the statistical method tends to be resistant to the presence of outliers, and therefore it was deemed appropriate in this case to calculate the slopes across all data points using this robust method.*

Reviewer Comment:

The sponsor's responses to the other additional issues presented above are acceptable.

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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/

TAPASH K GHOSH
06/08/2011

ANGELICA DORANTES
06/08/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**21-359**	**SUBMISSION DATES**
TYPE:	P	June 30, 2004
BRAND NAME:	Cellegesic™ (was also known as Anogesic)	September 3, 2004
GENERIC NAME:	Nitroglycerin	
DOSAGE FORM:	Ointment	
DOSAGE STRENGTH:	0.4%	
INDICATION:	Relief of pain associated with chronic anal fissure	
SPONSOR:	Cellegy Pharmaceuticals	
OCPB DIVISION:	I	
ORM DIVISION:	Cardio-renal drug products	
PRIMARY REVIEWER:	B. Nhi Nguyen, Pharm.D.	
TEAM LEADER:	Patrick Marroum, Ph.D.	

MEMO

On March 12, 2002, the Office of Clinical Pharmacology and Biopharmaceutics reviewed NDA 21-359, Anogesic, for the treatment of chronic anal fissures and found that the clinical pharmacology and biopharmaceutics section was acceptable for approval provided that the assay validation be found acceptable. The current resubmission contains acceptable assay information.

No new PK data are contained in the current submission. The sponsor resubmitted study NTG 98-02-02 entitled, "A study to determine the pharmacokinetics and bioavailability of Anogesic 0.2 % (0.75 mg) applied to the anal canal". This study number was changed to 98-03-02 in the current submission, however it is the same study.

Labeling comments (page 9) for the Pharmacokinetics section of the 2002 review are still applicable to this submission.

B. Nhi Beasley, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary reviewer

FT Initialed by Patrick Marroum, Ph.D._____
CC list: HFD-110: NDA 21-359; HFD-860: (Mehta, Rahman); CDER Central Document Room

Office of Clinical Pharmacology and Biopharmaceutics

II. *NEW DRUG APPLICATION FILING AND REVIEW FORM*

General Information About the Submission

	Information		Information
NDA Number	21-359	Brand Name	Anogesic
OCPB Division (I, II, III)	I	Generic Name	Nitroglycerin
Medical Division	Cardio-Renal Drug Products	Drug Class	nitrate
OCPB Reviewer	B. Nhi Beasley	Indication(s)	Relief of pain associated with chronic anal fissure
OCPB Team Leader	Patrick Marroum	Dosage Form	0.4% Ointment
		Dosing Regimen	1.5 to 4.5 mg /day
Date of Submission	June 30, 2004	Route of Administration	Topical to anal fissure
Estimated Due Date of OCPB Review	October 30, 2004	Sponsor	Cellegy
PDUFA Due Date	December 30, 2004	Priority Classification	P
a. Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
A. Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				

Reference ID: 2969428

Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
	0			**The sponsor submitted 70 published nitroglycerin reports.**

Filability and QBR comments

b.	"X" if yes	***Comments***
c. Application filable ?	**y**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
d. Comments sent to firm ? e.		Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered	
Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-359, HFD-850(Electronic Entry or Lee), HFD-110(CSO), HFD-860(Marroum, Mehta, Rahman), CDR (B. Murphy)

Reference ID: 2969428

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

/s/

Nhi Beasley
10/22/04 11:13:04 AM
BIOPHARMACEUTICS

Patrick Marroum
10/25/04 01:54:09 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**21-359**	**SUBMISSION DATES**
TYPE:	S	Original NDA 06/22/01
BRAND NAME:	Cellegesic (was also known as Anogesic)	(N-BZ) 11/16/01
GENERIC NAME:	Nitroglycerin	
DOSAGE FORM:	Ointment	
DOSAGE STRENGTH:	0.2% and 0.4%	
INDICATION:	Relief of pain associated with chronic anal fissure	
SPONSOR:	Cellegy	
OCPB DIVISION:	I	
ORM DIVISION:	Cardio-renal drug products	
PRIMARY REVIEWER:	B. Nhi Nguyen, Pharm.D.	
TEAM LEADER:	Patrick Marroum, Ph.D.	
ACTING TEAM LEADER:	Angelica Dorantes, Ph.D.	

I. EXECUTIVE SUMMARY

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-359, Anogesic for the treatment of chronic anal fissures and finds that the clinical pharmacology and biopharmaceutics section is acceptable for approval provided that the assay validation is found acceptable.

The clinical pharmacology of nitroglycerin has been previously described since it is commercially available in various dosage forms and has been used for many years for the treatment of angina. Nitroglycerin vasodilates both arterial and venous systems. When dosed intra-anally it is proposed to heal anal fissures and relieve the pain.

The sponsor conducted one pharmacokinetic study. This study characterizes the absorption of nitroglycerin when given by the intra-anal route. The assay validation information is missing from the NDA. Additionally, the sponsor did not provide drug release information about the ointment.

B. Comments to the Sponsor

The sponsor is requested to submit the assay validation information for the pharmacokinetic study.

The sponsor may want to consider conducting an in-vitro study to characterize the drug release of Anogesic.

C. Comments to the Medical Officer

NDA 21-359 is acceptable from a clinical pharmacology and biopharmaceutics perspective. The to-be-marketed formulation contains a (b)(4)% overage of nitroglycerin, whereas the clinical

formulation contained a (b)(4)% overage. The difference in overage is acceptable according to the USP monograph.

OCPB briefing held on March 12, 2002. Mehul Mehta, Patrick Marroum and John Lazor were present.

B. Nhi Nguyen, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary reviewer

FT Initialed by Patrick Marroum, Ph.D._____
CC list: HFD-110: NDA 21-359; HFD-860: (Mehta); CDER Central Document Room

Reference ID: 2969428

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III. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AUC	area under the curve
AUMC	area under the first moment (C*t) curve
bid	twice a day
Conc.	concentration
F	systemic availability
GC/MS/MS	gas chromatography/mass spectrometry/mass spectrometry
inf	infusion
iv	intravenous
mg	milligram
mL	milliliter
NTG	nitroglycerin, glyceryl trinitrate
pg	picogram
PK	pharmacokinetic
qd	daily
tid	three times a day

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IV. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Cellegy Pharmaceuticals, Inc is seeking the approval of nitroglycerin ointment, for the treatment of chronic anal fissures. The 0.2% ointment (or 0.75 mg of NTG) would be applied twice daily to the anal fissures. The proposed total daily dose is 1.5 to 4.5 mg of nitroglycerin, administered in two divided doses.

Nitroglycerin vasodilates both arterial and venous systems and has been approved for angina for many years. It is known that nitroglycerin metabolism is extremely rapid and widely spread throughout the body tissues. Headaches are a common adverse effect of nitroglycerin.

The sponsor conducted one pharmacokinetic study to characterize the absorption of intra-anal nitroglycerin ointment. The average absolute bioavailability of intra-anal nitroglycerin is ~50%. The information submitted for the review of the assay validation was insufficient.

In addition to the provided pharmacokinetic study, the sponsor also referenced 69 publications in Section 6. These publications included 16 review articles, 29 clinical studies, 20 animal or in-vitro studies, two abstracts and two letters to the editor. None of these studies were reviewed because either they did not measure NTG concentrations, administered NTG by a different route (e.g., transdermal, oral), or used a different formulation of NTG ointment.

The sponsor conducted two pivotal clinical studies. Study NTG 98-02-01 did not find a difference between intra-anal NTG and placebo with respect to fissure healing (primary endpoint). There was a statistically significant effect in pain relief (secondary endpoint) between the 0.4% ointment and placebo, but not between the lower strength (0.1% and 0.2%) ointments and placebo. The relief of pain (primary endpoint) in Study NTG 00-02-01 was questionable, and many patients dropped out because of headaches. (See medical/statistical review for final conclusions.)

The to-be-marketed formulation contains a (b) (4)% overage of nitroglycerin, whereas the clinical formulation contained a (b) (4)% overage. This difference in overage is acceptable since the maximum allowed overage by the USP monograph is 15%. The sponsor states that the increase in overage in the to-be-marketed formulation is due (b) (4) Aside from this difference in overage, the two formulations are identical.

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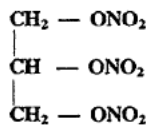
V. QUESTION BASED REVIEW

A. General Attributes

1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?*

STRUCTURE
chemical name: 1,2,3-propanetriol, trinitrate



molecular formula: $C_3H_5N_3O_9$
molecular weight: 227.09

Anogesic is an off-white, smooth, opaque ointment that contains 0.2% or 0.4% w/w nitroglycerin in a white petrolatum and lanolin base.

The to-be-marketed formulation contains a (b)(4)% overage of nitroglycerin, whereas the clinical formulation contained a (b)(4)% overage. This difference in overage is acceptable since the maximum allowed overage by the USP monograph is 15%. The sponsor states that the (b) (4) It is not known if the sponsor conducted any tests to address the absorption of nitroglycerin to the tubes. Aside from this difference in overage, the two formulations are identical. It is noted that the 0.4% formulation does not contain (b) (4), however it is in the 0.2% formulation.

Table 1. Composition of the to-be-marketed formulation

Excipient	0.2% (%w/w)	0.4% (%w/w)	Function
(b) (4) Nitroglycerin in (b) (4) (b) (4), USP	2.0	4.0	Active ingredient
White petrolatum, USP	(b) (4)		
Lanolin, USP			
Propylene glycol, USP			
Paraffin, NF			
Sorbitan sesquioleate, NF			

(b) (4)

Anogesic ointment will be manufactured and packaged by (b) (4). A typical batch size is (b) (4)kg.

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The product is supplied in a 30-gram, [redacted] (b) (4) unlined printed aluminum tube with a white low density polyethylene, non-piercing, cap. A metered dose pump comprised of an [redacted] (b) (4) lined aluminum canister and a pumping mechanism will be used to supply the nitroglycerin ointment.

2. *What is the proposed therapeutic indication and mechanism of action?*

The proposed indication is for the relief of pain associated with chronic anal fissures. Anogesic is an organic nitrate, nitroglycerin, that is proposed to work by relaxing the smooth muscle of the internal anal sphincter. By vasodilating both arteries and veins, NTG reduces the maximal resting anal pressure caused by anal fissures, and increases blood flow to the anoderm.

3. *What is the proposed dosage and route of administration? What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data?*

The sponsor's proposed total dose of nitroglycerin ointment for the treatment of chronic anal fissures is 1.5 to 4.5 mg of nitroglycerin to be applied intra-anally per day. A measuring device filled from the tube of a metered dose dispenser contains approximately 374 mg of ointment for delivery. This amount is equivalent to a nitroglycerin dose of 0.75 mg for the 0.2% NTG ointment and 1.5 mg for the 0.4% NTG ointment. The sponsor's proposed treatment is for two or three applications a day for (b) (4) weeks until anal pain is gone or anal fissure is healed. According to the proposed labeling, treatment should start [redacted] (b) (4) [redacted] 0.4% ointment.

Study NTG 98-02-01 found no difference between two and three applications a day for fissure healing or pain relief. A total daily Anogesic dose of 0.75 mg, 1.1 mg, 1.5 mg, 2.3 mg, 3.0 mg, and 4.5 mg was given to 304 patients. The dose was applied twice or three times daily and 0.1%, 0.2% and 0.4% strengths were used. Because of the results of Study NTG 98-02-01, study NTG 00-02-01, administered the dose twice daily in 229 patients. The patients were randomized to placebo, Anogesic 0.2% (or 0.75 mg NTG) or 0.4% (or 1.5 mg NTG) twice daily.

Study NTG 98-02-01 found no difference in fissure healing between placebo and Anogesic (primary endpoint).

With respect to pain relief, the first pivotal study, NTG 98-02-01, found a statistically significant effect in pain relief (secondary endpoint) between the 0.4% ointment and placebo, but not between the lower strength (0.1% and 0.2%) ointments and placebo. The second pivotal clinical study, NTG 00-02-01, found questionable relief of pain (primary endpoint), partly because of patient drop outs from headaches. (See medical/statistical review for additional information and final conclusions.) Therefore, the pain relief from intra-anal nitroglycerin is questionable.

B. General Clinical Pharmacology

Reference ID: 2969428

1. *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?*

The response endpoints of anal fissure healing and pain relief are related to the clinical pharmacology of nitroglycerin. An independent examiner assessed healing. Pain was assessed by the patient's response to a 100-mm visual analog scale.

2. *Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

The active moieties in plasma are appropriately identified. It is known that nitroglycerin has two active metabolites. The sponsor did not submit information to determine if nitroglycerin and its metabolites were appropriately assayed.

3. *What are the characteristics of the exposure-response relationships for efficacy and safety?*

The PK study was conducted in six healthy volunteers. AUCs were similar with single and multiple dose intra-anal NTG. With repeated dosing, concentrations were undetectable prior to the next dose, indicating no accumulation. Cmax of NTG was less variable with multiple doses.

C. General Biopharmaceutics

1. *What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?*

The proposed to-be-marketed formulation and the formulation used in the clinical studies are identical except for the (b) (4)% (b) (4) overage in the to-be-marketed formulation compared to the clinical formulation. (See Table 1)

D. Analytical Section

1. *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Plasma levels of glyceryl trinitrate (NTG) and two principal metabolites, 1,2-glyceryl dinitrate and 1,3-glyceryl dinitrate were determined by GC/MS/MS. The two principal metabolites are less effective vasodilators than NTG, but they last longer in the serum. Their net contribution to the overall effect of chronic NTG is unknown.

Reviewer Comment: The provided analytical information is less than appropriate. The only information provided is that the lower limit of quantification was 10 ng/L and the assay was linear over the concentration range of 25 – 2000 pg/mL. Therefore, it is recommended that the sponsor provides complete analytical validation and quality control data for the GC/MS/MS assay that was used.

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VIII. DETAILED LABELING RECOMMENDATIONS

The proposed labeling recommendations for Anogesic ointment is provided in Appendix A. The following changes are recommended for the "Pharmacokinetics" section of the labeling.

PHARMACOKINETICS

Absorption: In six healthy subjects, the average absolute bioavailability of nitroglycerin applied to the anal canal as a 0.2% ointment was approximately 50% of the 0.75 mg nitroglycerin dose.

Distribution: The volume of distribution of nitroglycerin following intravenous administration is about 3 L/kg. At plasma concentration between 50 and 500 ng/mL, the binding of nitroglycerin to plasma proteins is approximately 60%, while that of 1,2- and 1,3-dinitroglycerin is 60% and 30%, respectively.

Metabolism: Nitroglycerin is metabolized by a liver reductase enzyme to glycerol di- and mononitrate metabolites and ultimately to glycerol and organic nitrate. Known sites of extrahepatic metabolism include red blood cells and vascular walls. In addition to nitroglycerin, the two major metabolites, 1,2- and 1,3- dinitroglycerols are found in plasma. The dinitrates are less effective vasodilators than nitroglycerin, but they are eliminated slower. The contribution of metabolites to the relaxation of the internal anal sphincter is unknown. The dinitrates are further metabolized to nonvasoactive mononitrates and ultimately to glycerol and water.

Elimination: Metabolism is the primary route of drug elimination. Nitroglycerin plasma concentrations decrease rapidly with a mean elimination half-life of two to three minutes. Half-life values range from 1.5 to 7.5 minutes. Clearance (13.6 L/min) greatly exceeds hepatic blood flow.

8 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

Reference ID: 2969428

B. Clinical Pharmacology and Biopharmaceutics Individual Study Review

Reference ID: 2969428

A study to determine the pharmacokinetics and bioavailability of Anogesic® 0.2% (nitroglycerin ointment) applied to the anal canal

PROTOCOL: NTG 98-02-02 **VOLUME:** 1 **PAGES:** 28 – 190
2 1 – 85

PRINCIPAL INVESTIGATOR: Stephen L. Shafer, MD.
STUDY CENTER: Palo Alto Veterans Administration, Palo Alto, CA
PHARMACOKINETIC CONSULTANT: Thomas N. Tozer, PhD, UCSF

CITATION: not applicable
STUDY INITIATED: January 5, 1999
STUDY COMPLETED: February 23, 1999

OBJECTIVES: To determine the pharmacokinetics and bioavailability of a single and multiple dose of 0.2% nitroglycerin ointment applied to the anal canal, compared to the PK and bioavailability of a constant rate intravenous infusion of nitroglycerin

STUDY DESIGN: open label, three treatment, three period, cross over study

POPULATION: Six healthy subjects (four males and two females), ages 25 to 45 years were studied. Five subjects were Caucasian and one was Hispanic/American.

One subject (1100) with chronic sinusitis took Allegra twice daily and Flonase daily. Another subject (1103) took Levoxyl 150 μg daily for hypothyroidism.

Subjects abstained from smoking for at least 6 months and were required to have negative results on a urine drug screen test.

PROCEDURE: Each subject received three different phases of NTG treatment. The subjects were randomized to a treatment phase order. A seven day washout period separated each treatment phase.

There were no fluid or food restrictions prior to arrival at the study site. Subjects were provided low fat meal four hours after administration of study drug.

Prescription or over-the-counter drugs were not allowed from seven days prior to the first treatment until after the last blood sample was obtained at the end of the last treatment phase. Alcoholic beverages were not allowed from 48 hours prior to each treatment phase until the last blood sample was obtained for that phase. Acetaminophen (two 325 mg tablets every 6 hours) was allowed for intolerable headaches.

For treatment phase II, the baseline period began after the sixth dose on Day 2 and before administration of the seventh dose on Day 3.

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During Treatment phase III, subjects remained supine for at least the first four hours after iv NTG and preferably throughout the entire period of the PK arterial blood sampling.

TREATMENT: The treatment phases are shown in Table NTG 98-02-02_1.

Table NTG 98-02-02_1: Treatment phases

Phase	Conc.	Frequency	Total NTG	Total amount	route
I	0.2%	qd x1	0.75 mg	~374 mg	Intra anal
II	0.2%	tid x 7 doses	5.25 mg	~2618 mg	Intra anal
III	10 µg/mL	1 mL/min constant infusion over 30 minutes	0.3 mg	30 mL	iv

Cellegy Pharmaceuticals, Inc provided a lotion loader containing a plunger. This was used to deliver a metered dose of NTG. The lotion loader was attached over the nozzle of the tube of NTG ointment, and the plunger was slowly extended. The tube was squeezed until the ointment filled the plunger to the mark on the barrel. The ointment was expelled onto a finger covered by a finger cot. The finger with the ointment was to be gently inserted into the anus to approximately the first interphalangeal joint and the ointment was spread over the anoderm. Ointment on the skin outside the anus was to be gently removed with a tissue.

The exact weight of dispensed study drug for Treatment Phases I and II were calculated as follows:

Quantity applied to the finger cot = weight of lotion loader filled with ointment - weight of empty lotion loader

Quantity of ointment not applied = weight of finger cot after application to the anoderm - weight of unused finger cot

Actual weight applied to anoderm = Quantity applied to the finger cot - Quantity of ointment not applied

The protocol specified that non-NTG absorbing tubing be used for the iv NTG administration, however, this was not done because the hospital pharmacist told the investigator that it was satisfactory to use the tubing the pharmacy routinely provided for administration of IV NTG. Because of drug loss by the tubing, the actual rate of infusion was determined from the concentrations entering the antecubital vein (entrance site) at the time the infusion was stopped (30 minutes).

The rate of infusion was calculated as follows:

(b) (4)

FORMULATION: 0.2% NTG ointment came from batch 8e059d. This batch was manufactured by (b) (4) and was packaged, labeled, and shipped to the investigator by (b) (4)

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Study drug consisted of 0.2% NTG, USP (w/w), white petrolatum, lanolin, propylene glycol, paraffin wax, and sorbitan sesquioleate.

The intravenous NTG was commercially available nitroglycerin for infusion, USP, 5 mg/mL, containing nitroglycerin USP 50 mg, propylene glycol, and alcohol. Nitroglycerin for infusion was prepared by removing 5 mg aseptically from the vial and adding to a sterile glass bottle containing 500 mL 0.9% saline, USP. Following gentle inversion several times to mix the solutions, the final concentration of NTG in the 500 mL bottle was ~0.01mg/mL

PHARMACOKINETICS: Blood samples were collected at the time points shown in the table below.

Table NTG 98-02-02_2: Collection times for nitroglycerin concentration

Treatment Phase	Blood collection time (minutes)
I and II	predose, and at 15, 30, 60, 90, 120, 180, 240, 300, 360, and 480 minutes post dose.
III	Predose, and at 1, 2, 4, 6, 10, 15, 20, 30, 31, 32, 34, 36, 40, 45, 50, 60, 70, 90, 150, 210, and 270 minutes after the start of the infusion

ASSAY: Plasma levels of glyceryl trinitrate (NTG) and two principal metabolites, 1, 2-glyceryl dinitrate and 1, 3-glyceryl dinitrate were determined by GC/MS/MS. The sample analysis were performed by (b) (4).

Information on the precision and accuracy of the assay was omitted. The assay sensitivity was 10 ng/L and the assay was linear over the concentration range of 25 – 2,000 pg/mL.

PHARMACOKINETIC ANALYSIS: Concentration-time profiles were evaluated by modeling and modeling-independent approaches. The usual PK parameters were determined.

AUC and AUMC (area under the first moment (C*t) versus time curve) of NTG and its two principal metabolites were calculated by the trapezoidal rule. The clearance of NTG was estimated from $Dose_{inf} / AUC_{inf}$. The mean absorption times of NTG following single and multiple dose were determined from AUMC/AUC. The sponsor concluded that the calculation of mean NTG absorption time following the seventh dose in Treatment Phase II was appropriate since on drug or metabolite was found in arterial plasma at the time of the seventh application.

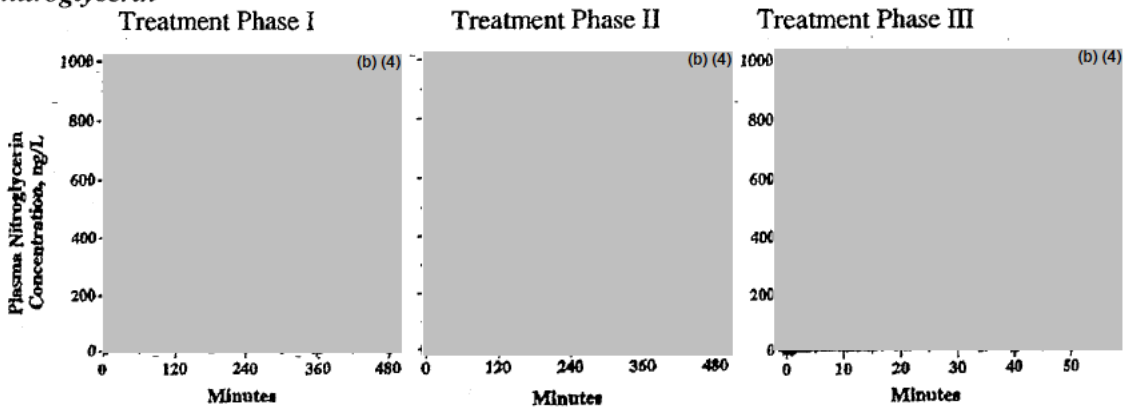
Systemic availability (F) of NTG following anal application was calculated by:

$$F = (AUC_{anal} / AUC_{iv}) * (Dose_{iv} / Dose_{anal})$$

PHARMACOKINETIC RESULTS: The plasma nitroglycerin concentrations are shown in Figure 1.

Reference ID: 2969428

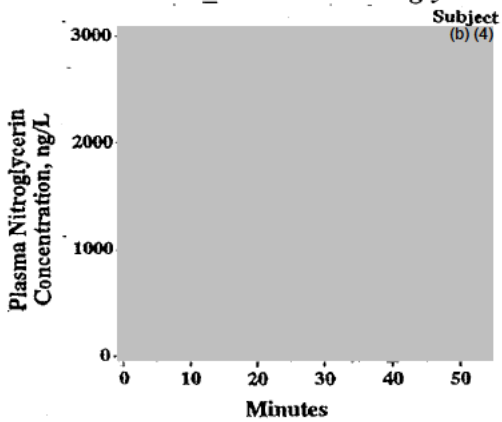
Figure NTG 98-02-02_1. Plasma nitroglycerin concentrations for intra-anal and i.v. nitroglycerin



Treatment Phase I = intra-anal NTG, one dose
Treatment Phase II=intra-anal NTG, 7th dose
Treatment Phase III=intravenous NTG
Note: The x-axis is the same for all three graphs. The y-axis is different for Treatment Phase III.

ID 1102 (subject 3) received twice the dose of intravenous NTG (by mistake). Her concentrations are higher than the scale in Figure 1. (See Figure 2.)

Figure NTG 98-02-02_2. Plasma nitroglycerin concentrations for i.v. nitroglycerin

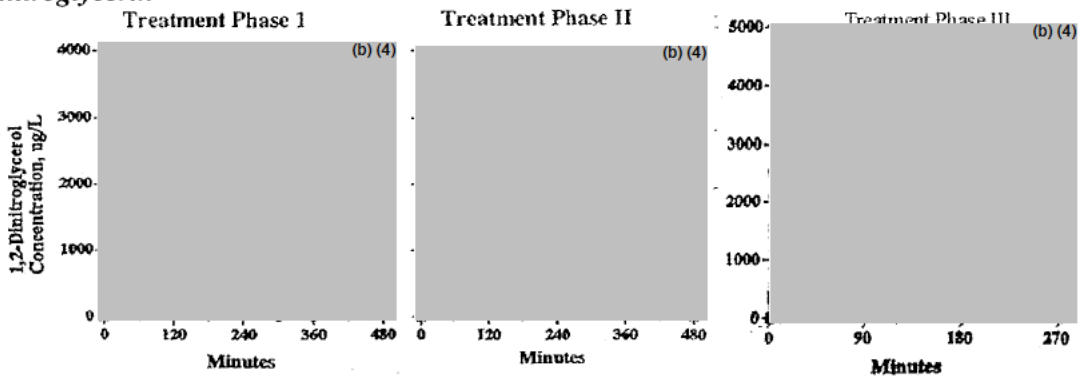


Subject Key: 1=1100; 2=1101; 3=1102; 4=1103; 5=1104; 6=1105

The plasma concentrations for 1,2-glyceryl dinitrate and 1,3-glyceryl dinitrate for Treatment Phase I, II and III are shown in Figure NTG 98-02-02_3 and NTG 98-02-02_4, respectively.

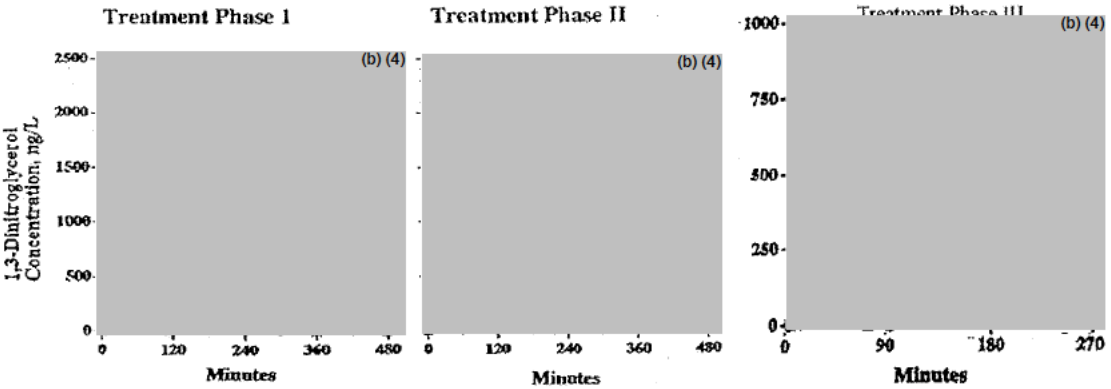
Reference ID: 2969428

Figure NTG 98-02-02_3. Plasma 1,2-glyceryl dinitrate concentrations for intra-anal and i.v. nitroglycerin



Treatment Phase I = intra-anal NTG, one dose
Treatment Phase II=intra-anal NTG, 7th dose
Treatment Phase III=intravenous NTG
Note: The x-axis for Treatment Phase I and II have the same scale.

Figure NTG 98-02-02_4. Plasma 1,3-glyceryl dinitrate concentrations for intra-anal and i.v. nitroglycerin



Treatment Phase I = intra-anal NTG, one dose
Treatment Phase II=intra-anal NTG, 7th dose
Treatment Phase III=intravenous NTG
Note: The x-axis for Treatment Phase I and II have the same scale.

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The individual and mean AUCs for intra-anal NTG are shown in Table NTG 98-02-02_3.

Table NTG 98-02-02_3: AUC (μg*min/L) for single and multiple dose intra-anal nitroglycerin

Subject ID	Single dose	Multiple dose
1100	(b) (4)	
1101		
1102		
1103		
1104		
1105		
Mean (± SD)	41.3 (± 18.9)	41.8 (± 8.8)

The AUC for single and multiple dose are similar. This was because concentrations in the multiple dose study were unmeasurable prior to the seventh dose. Thus, the concentration time profile of multiple dose looks like that of single dose. Subject 1105 had a measurable concentration at 480 minutes in Treatment Phase II.

The comparison of the metabolites after single and multiple dose show that concentrations of 1,3-glyceryl dinitrate was approximately three-fold higher after multiple dose compared to single dose. However, concentrations were not detectable prior to the seventh dose, thus accumulation is an unlikely explanation. See Table NTG 98-02-02_4 for the ratio of AUC(m) (Multiple dose/Single dose) for the metabolites.

Table NTG 98-02-02_4: Ratio of multiple dose:single dose for nitroglycerin metabolites

Subject ID	1,2-glyceryl dinitrate	1,3-glyceryl dinitrate
1100	(b) (4)	
1101		
1102		
1103		
1104		
1105		
Mean (± SD)	1.00 (± 0.57)	3.36 (± 2.44)

Table duplicated from 6; v01; p059

The clearance ranged from 2.6 to 11.9 L/min for the 30 minute intravenous NTG. Individual clearances are listed in Table NTG 98-02-02_5. These clearances are lower than previously published clearance values (plasma samples obtained from an antecubital vein) of approximately 70 L/min. This difference may be due to the steady state arterial-venous difference across the superficial tissues of the arm. That is, the venous concentration of NTG in an arm vein is much lower (by ~10 fold) than that on the arterial side.

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Table NTG 98-02-02_5: Clearance of intravenous nitroglycerin

Subject ID	Clearance (L/min)
1100	(b) (4)
1101	
1102	
1103	
1104	
1105	
Mean (± SD)	7.0 (± 3.6)

Table duplicated from 6; v01; p060

The bioavailability following single and multiple dose was approximately 50% (see Table 6). The lower bioavailabilities observed for Subjects 1102 and 1104 were due to the large AUCs observed for these subjects following the intravenous infusion. Slower absorption was observed in Subjects 1100 and 1105 due to measurable NTG plasma concentrations between 300 and 480 minutes in these two subjects.

Table NTG 98-02-02_6: Bioavailability of intra-anal nitroglycerin

	Mean Absorption Time (min)		Bioavailability (F)	
	Treatment Phase		Treatment Phase	
Subject ID	I	II	I	II
1100				(b) (4)
1101				
1102				
1103				
1104				
1105				
Mean (± SD)	108 (± 59)	110 (± 69)	0.46 (± 0.28)	0.47 (± 0.31)

Treatment Phase I = single dose
Treatment Phase II= multiple dose
Table duplicated from 6; v01; p061

Check appendix 2.1.1.

The amount of NTG infused and applied are presented in Table 7. The amount of NTG infused intravenously ranged from 0.045 – 0.162 mg. The amount of NTG applied intra-anally ranged from 0.540 – 0.780 mg (single dose) and 0.485 – 0.820 mg (multiple dose).

Reference ID: 2969428

Table NTG 98-02-02_7. Amount (mg) of nitroglycerin applied or infused

Subject ID	Treatment Phase I (mg)	Treatment Phase II (mg)	Treatment Phase III (mg)
1100			(b) (4)
1101			
1102			
1103			
1104			
1105			

Treatment Phase I = single dose
Treatment Phase II= multiple dose
Treatment Phase III= infusion
Table duplicated from 6; v01; p062

ADVERSE EVENTS: The most frequently reported adverse event was headache. Most (18/24) were mild, five were moderate and one was severe. Four subjects during the multiple dose phase (II) experienced more than one headache. Only one headache was experienced in two subjects during the intravenous phase and five subjects during the single dose phase. Four headaches were treated with acetaminophen.

Subject 1105 did not report any adverse event during the study. No subjects withdrew from the study because of an adverse event. There were no serious adverse events reported during the study.

REVIEWER'S COMMENTS: The clearance of NTG when administered intravenously in this study was considerably lower than previously published reports. Nitroglycerin concentrations in this study were measured in arterial plasma, whereas, previous studies have determined NTG concentrations from venous plasma.

Information on the precision and accuracy of the assay was omitted.

On p. 43 vol 6.1, the sponsor states the final concentration of the iv NTG was 0.01 mg/mL. The infusion was to be delivered at a rate of 0.01 mg/minute for 30 minutes. Thus, the total amount of NTG should be 0.30 mg, yet the sponsor states the total dose should be 0.3 g.

SPONSOR'S CONCLUSIONS:

- Approximately 50% of intra-anally applied 0.2% NTG ointment (approximately 0.75 mg NTG) was bioavailable. Because there was considerable interindividual variability in mean absorption time and bioavailability, it is possible that absorption of NTG from the anal canal may not be a simple first order process.

REVIEWER'S CONCLUSIONS:

- The reviewer agrees with the sponsor's conclusion that the systemic bioavailability of 0.2% NTG ointment when applied intra-anally was approximately 50%.

Reference ID: 2969428

C. Cover Sheet and OCPB Filing / Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-359**	**Brand Name**	**Anogesic**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Nitroglycerin**
Medical Division	**Cardio-Renal Drug Products**	**Drug Class**	**nitrate**
OCPB Reviewer	**B. Nhi Nguyen**	**Indication(s)**	**Relief of pain associated with chronic anal fissure**
OCPB Team Leader	**Patrick Marroum**	**Dosage Form**	**0.2% and 0.4% Ointment**
		Dosing Regimen	**1.5 to 4.5 mg /day**
Date of Submission	**June 22, 2001**	**Route of Administration**	**Topical**
Estimated Due Date of OCPB Review	**November 30, 2001**	**Sponsor**	**Cellegy**
PDUFA Due Date	**June 26, 2002**	**Priority Classification**	**S**
Division Due Date	**April 26, 2002**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	X	X	
multiple dose:	X	x	X	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				

Reference ID: 2969428

Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability:	X			
Relative bioavailability -				
solution as reference:	X			
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
	1	**1**	**1**	**The sponsor submitted 70 published nitroglycerin reports.**

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**y**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**n**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered	**Are the PK of 0.2% nitroglycerin ointment similar to other topical nitroglycerin products currently available?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-359, HFD-850(Lee), HFD-110 (FrommE), HFD-860(MarroumP, Mehta), CDR (B. Murphy)

Reference ID: 2969428

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/s/

Nhi Nguyen
3/12/02 03:13:30 PM
BIOPHARMACEUTICS

Patrick Marroum
3/12/02 04:16:59 PM
BIOPHARMACEUTICS