

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**89884**

**BIOEQUIVALENCY REVIEW(S)**

JUN 24 1998

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

199.

ANDA #89-884  
ANDA #89-885  
ANDA #89-884

APPLICANT: Hercon Laboratories, Inc.

DRUG PRODUCT: Nitroglycerin Transdermal System, 0.6 mg/hr,  
0.4 mg/hr and 0.2 mg/hr

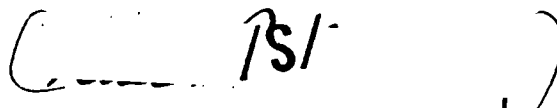
The Division of Bioequivalence has completed its review and has no further questions at this time. However, for the future applications, you are advised to submit data on the residual nitroglycerin contents in the used patches.

You should incorporate the dissolution testing into your manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 32°C using paddle over disk at 50 rpm. The test product should meet the tentative dissolution specifications:

| <u>Sampling Schedule</u> | <u>Limits</u> |
|--------------------------|---------------|
| 0.25 hr                  | %             |
| 0.5 hr                   | %             |
| 1.0 hr                   | %             |
| 4.0 hr                   | %             |

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.  
Director  
Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Nitroglycerin Transdermal System  
AND #89-886; NTS, 0.6 mg/hr  
AND #89-885; NTS, 0.4 mg/hr  
AND #89-884; NTS, 0.2 mg/hr  
Reviewer: Sikta Pradhan  
XWP #89886SDW.N97

Hercon Laboratories, Co.  
York, PA  
Submission Date:  
November 3, 1997  
June 2, 1998

## **Review of a Bioequivalence Study, Dissolution Data and Waiver Requests**

### **I. INTRODUCTION:**

Nitroglycerin is used for the acute relief of angina pectoris. It is used for long term therapy of cardiac insufficiency and cardiac infarction. When given orally, nitroglycerin is extensively metabolized during its first pass, hence alternate routes of administration such as transdermal, are often used. Nitroglycerin transdermal delivery systems are developed in order to control the surface area of application, and the rate of drug delivery, thereby maintaining sustained plasma levels of nitroglycerin over an extended period of time.

This submission is a major amendment to the firm's conditionally approved AND of Nitroglycerin Transdermal System. The firm had previously conducted a bioequivalence study on this product (0.4 mg/hr strength patch). The study (submission dated December 8, 1994) was found unacceptable by the Agency. In this current amendment, the firm has included the data of a new bioequivalence study conducted on the test product (0.6 mg/hr strength patch). The firm has also informed the Agency that the patch size of the test product(s) has recently been increased. The current amendment also contains waiver requests for its 0.2 mg/hr and 0.4 mg/hr products.

### **Objective:**

The objective of this Open-label, replicate design, two-treatment, four-period, randomized, crossover single dose study was to evaluate the bioequivalence of a re-sized (3.7% increased) Hercon's Nitroglycerin Transdermal System formulation relative to a commercially-available reference patch, Transderm-Nitro<sup>R</sup> of Novartis.

### In-Vivo Study:

The study was conducted in healthy, male volunteers under fasting conditions. The clinical study was conducted at \_\_\_\_\_ under the supervision of \_\_\_\_\_ Principal Investigator. The analytical study was conducted at \_\_\_\_\_

### Study Dates:

Group I(subj. 28): 7/14/97, 7/18/97, 7/22/97, 7/26/97

Group II(subj. 21): 7/28/97, 8/1/97, 8/5/97, 8/9/97

### Study Design:

A randomized, open-label, replicate design, two-treatment, four-period, crossover single dose bioequivalence study including a Hercon nitroglycerin patch formulation and a commercially available nitroglycerin reference patch manufactured by Novartis was conducted according to protocol # HERC-9701.

Subjects: Forty- nine (49) healthy male volunteers between 18-55 years of age and within  $\pm 15\%$  of their ideal body weight according to Metropolitan Life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Tests (hematology, blood chemistry, urinalysis, etc.). The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 48 hours before dosing and throughout the period of sample collection.

### Treatments:

- A. Administration of a single Nitroglycerin Transdermal System, 0.6 mg/hr (111.9 mg/21.0 cm<sup>2</sup> patch) of the test formulation (Hercon), Lot # L0597NG/613; Potency: 99.6%, Lot size: \_\_\_\_\_ patches; Duration of patch application 12 hrs.
- B. Administration of a single Nitroglycerin Transdermal System, 0.6 mg/hr (75.0 mg/30 cm<sup>2</sup> patch) of the reference formulation (Transderm-Nitro<sup>R</sup>, Novartis), Lot # 1F193881; Potency: 98.2%, Expiration Date: 7/99; Duration of patch application 12 hrs.

Dose Administration: Subjects were assigned to one of two treatment sequences (ABBA or BAAB) according to the randomization schedule. Each subject received two (2) treatments during the study with a 4-day washout period between them.

Drug Washout Period: Four days

Site of Patch Application: The skin at the site of application was clean and dry. Each patch was applied to the chest of each subject approximately halfway between the nipple and medio-clavicular line for 12 hours.

Vital signs: Vital signs such as, heart rate, blood-pressure, respiratory rate, etc. were determined periodically during the study. Times of measurement were: 0 (pre-dose), 0.5, 1, and 6 hours after application of each TNG-patch, and immediately after removal of each patch (12 hours post-dose). All vital sign measurements were taken within 10 minutes before or after the respective blood sampling.

Meal and Food Restrictions: All volunteers fasted for 8 hours prior to and 1 hours after drug administration. Fluids were restricted within one hour of dosing. Standard meal was served. No caffeine-containing food or beverage was served during the study.

Patch Removal:

The patch was removed within 5 minutes after collection of the 12-hour blood sample. Immediately after patch removed, the subject's skin was visually examined and rated for irritation. The patch from each individual subject was transferred into a protective pouch that was properly identified and sealed. Sealed pouches were sent to the sponsor for analysis of residual nitroglycerin content.

Blood Sample Collection:

Venous blood samples (5 ml) were collected in Vacutainer tubes containing sodium heparin prior to dosing (0 time) and at 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 12.5 and 13 hours after patch application. Plasma was separated and kept frozen at -70°C until analysis.

Assay Methodology:

Dates of Analysis: August 1, 1997 - September 5, 1997.

Method: Trinitrolycerin (TNG), 1,2 -dinitrolycerin (1,2-DNG) and 1,3 -dinitrolycerin (1,3-DNG) levels in plasma were estimated by method.

TNG, 1,2-DNG, and 1,3-DNG assay:

The calibration range, average correlation coefficient, overall percent coefficient of variation (%CV), and the number of analytical runs for each compound are summarized below:

Internal Standards: TNG-<sup>15</sup>N, 1,2-DNG-<sup>15</sup>N, and 1,3-DNG-<sup>15</sup>N,

Specificity: No interference was observed.

Linearity: The standard plots were linear in the concentration range of 0.01 ng/mL to 5.0 ng/mL for TNG and in the concentration range of 0.1 ng/mL to 10.0 ng/mL for 1,2-DNG and 1,3-DNG. The coefficient of determination of the calibration line was greater than 0.9996.

Sensitivity: The lower limit of quantitation (LLOQ) was 0.01 ng/mL for TNG and 0.10 ng/mL for both 1,2-DNG and 1,3-DNG; any value less than these was reported as zero.

Precision:

Within-study validation:

I. TNG

Interday Assay Precision from Standard Samples:

9.10% (CV) at 0.01 ng/mL; (N=45)

4.74% (CV) at 0.025 ng/mL; (N=49)

2.17% (CV) at 0.200 ng/mL; (N=49)

2.50% (CV) at 5.00 ng/mL; (N=49)

Interday Assay Precision from (QC) Control Samples:  
(N=75)

6.38% (CV) at 0.025 ng/mL;

4.22% (CV) at 0.25 ng/mL;

3.26% (CV) at 4.00 ng/mL

## II. 1,2-DNG

### Interday Assay Precision from Standard Samples:

4.54% (CV) at 0.10 ng/mL; (N=50)  
2.36% (CV) at 0.40 ng/mL; (N=50)  
2.96% (CV) at 2.50 ng/mL; (N=50)  
1.64% (CV) at 10.00 ng/mL; (N=49)

### Interday Assay Precision from (QC) Control Samples:

4.71% (CV) at 0.25 ng/mL; (N=77)  
4.72% (CV) at 1.50 ng/mL; (N=77)  
3.33% (CV) at 8.00 ng/mL; (N=76)

## III. 1,3-DNG

### Interday Assay Precision from Standard Samples:

5.46% (CV) at 0.10 ng/mL; (N=50)  
2.11% (CV) at 0.40 ng/mL; (N=50)  
2.33% (CV) at 2.50 ng/mL; (N=50)  
1.98% (CV) at 10.00 ng/mL; (N=49)

### Interday Assay Precision from (QC) Control Samples:

5.00% (CV) at 0.25 ng/mL; (N=77)  
4.63% (CV) at 1.50 ng/mL; (N=77)  
3.21% (CV) at 8.00 ng/mL; (N=76)

### Stability:

1. Frozen control samples were found to be stable through three freeze/thaw cycles for TNG, 1,2-DNG and 1,3-DNG. The test samples were compared with freshly thawed (once only) samples.
2. Frozen control samples for TNG, 1,2-DNG and 1,3-DNG were stable for at least forty weeks at -70°C.
3. Quality control samples for TNG, 1,2-DNG and 1,3-DNG were found to be stable at room temperature for 4 hours.
4. The firm did not provide the short term stability data at 0-4°C for TNG, 1,2-DNG and 1,3-DNG. However, the overall stability data are acceptable.

### Results:

Forty-nine (49) male volunteers were enrolled in the study and 46 of them completed all phases of the study. The ANOVA analysis was conducted on 46 subjects. Subject# 33 withdrew from the study due

to adverse events such as headache, nausea, etc., and Subject #44 became tired of blood draws and voluntarily withdrew from the study prior to period 2. Subject# 45 was absent for period 2 of the study. A total of 25 different adverse events and the observed patch irritations were reported in Table 1A and 1B (attached). None of these adverse events reported were considered to be severe. All vital signs occurred during the study were measured and reported in the Appendix A (attached). The firm has reported, no clinically significant changes in clinical laboratory test results, physical examinations, or ECGs occurred during the study. It has been reported by the firm that no treatment effects were observed for the adverse events. Mean plasma TNG, 1,2-DNG and 1,3-DNG levels are presented in Tables 2 (and Fig.1&2), 3 (and Fig.3&4) and 4 (and Fig.5&6), respectively.

**Table 2**  
**Mean Plasma TNG Levels (pg/mL)**

| Time<br>(hour) | Reference<br>(B <sub>1</sub> )<br>N = 46 | Reference<br>(B <sub>2</sub> )<br>N = 46 | Test<br>(A <sub>1</sub> )<br>N = 46 | Test<br>(A <sub>2</sub> )<br>N = 46 |
|----------------|------------------------------------------|------------------------------------------|-------------------------------------|-------------------------------------|
| Pre-dose       | 0                                        | 0                                        | 0                                   | 0                                   |
| 0.5            | 107.18 (89)*                             | 139.82 (120)                             | 65.69 (127)                         | 115.80 (103)                        |
| 1.0            | 194.61 (65)                              | 263.58 (84)                              | 146.38 (83)                         | 258.89 (79)                         |
| 1.5            | 168.66 (56)                              | 207.69 (69)                              | 169.82 (100)                        | 220.53 (69)                         |
| 2.0            | 222.04 (72)                              | 222.00 (57)                              | 169.13 (62)                         | 285.05 (77)                         |
| 2.5            | 165.49 (58)                              | 191.96 (55)                              | 138.50 (61)                         | 251.71 (72)                         |
| 3.0            | 197.53 (72)                              | 200.44 (56)                              | 186.97 (80)                         | 250.65 (70)                         |
| 4.0            | 254.56 (79)                              | 271.42 (66)                              | 214.50 (67)                         | 355.29 (80)                         |
| 5.0            | 232.80 (59)                              | 251.05 (52)                              | 224.24 (78)                         | 352.41 (74)                         |
| 6.0            | 226.28 (57)                              | 261.61 (58)                              | 262.07 (96)                         | 417.23 (135)                        |
| 8.0            | 283.25 (72)                              | 226.82 (48)                              | 232.12 (71)                         | 337.87 (85)                         |
| 10.0           | 232.10 (61)                              | 229.54 (53)                              | 236.53 (66)                         | 310.12 (62)                         |
| 12.0           | 172.44 (80)                              | 175.94 (60)                              | 163.34 (61)                         | 222.49 (68)                         |
| 12.5           | 18.31 (61)                               | 18.23 (58)                               | 31.32 (64)                          | 39.00 (67)                          |
| 13.0           | 4.82 (184)                               | 6.0413 (135)                             | 43.25 (384)                         | 15.68 (81)                          |

\* Coefficient of Variation; N = Total Number of Subjects

**Table 3**  
**Mean Plasma 1,2-DNG Levels (ng/mL)**

| Time<br>(hour) | Reference<br>(B <sub>1</sub> )<br>N = 46 | Reference<br>(B <sub>1</sub> )<br>N = 46 | Test<br>(A <sub>1</sub> )<br>N = 46 | Test<br>(A <sub>1</sub> )<br>N = 46 |
|----------------|------------------------------------------|------------------------------------------|-------------------------------------|-------------------------------------|
| Pre-dose       | 0                                        | 0                                        | 0                                   | 0                                   |
| 0.5            | 0.51 (99)                                | 0.60 (111)                               | 0.26 (124)                          | 0.46 (101)                          |
| 1.0            | 1.84 (60)                                | 2.09 (63)                                | 1.19 (78)                           | 1.94 (68)                           |
| 1.5            | 2.71 (48)                                | 3.02 (49)                                | 2.00 (64)                           | 3.01 (62)                           |
| 2.0            | 3.21 (42)                                | 3.46 (39)                                | 2.52 (55)                           | 3.75 (57)                           |
| 2.5            | 3.43 (38)                                | 3.76 (35)                                | 2.91 (52)                           | 4.32 (57)                           |
| 3.0            | 3.39 (37)                                | 3.70 (35)                                | 3.00 (49)                           | 4.38 (55)                           |
| 4.0            | 3.63 (35)                                | 3.90 (34)                                | 3.37 (45)                           | 4.75 (54)                           |
| 5.0            | 3.77 (32)                                | 4.09 (34)                                | 3.65 (43)                           | 5.29 (57)                           |
| 6.0            | 3.97 (33)                                | 4.28 (31)                                | 3.92 (43)                           | 5.39 (52)                           |
| 8.0            | 3.81 (35)                                | 3.94 (33)                                | 3.78 (41)                           | 5.20 (54)                           |
| 10.0           | 3.90 (35)                                | 4.19 (33)                                | 4.07 (39)                           | 5.42 (50)                           |
| 12.0           | 3.63 (35)                                | 3.98 (32)                                | 3.78 (39)                           | 4.94 (50)                           |
| 12.5           | 2.38 (30)                                | 2.55 (26)                                | 2.62 (34)                           | 3.23 (40)                           |
| 13.0           | 1.39 (34)                                | 1.45 (29)                                | 1.57 (44)                           | 1.86 (40)                           |

\* Coefficient of Variation  
N = Total Number of Subjects

**Table 4**  
**Mean Plasma 1,3-DNG Levels (ng/mL)**

| Time<br>(hour) | Reference<br>(B <sub>1</sub> )<br>N = 46 | Reference<br>(B <sub>2</sub> )<br>N = 46 | Test<br>(A <sub>1</sub> )<br>N = 46 | Test<br>(A <sub>2</sub> )<br>N = 46 |
|----------------|------------------------------------------|------------------------------------------|-------------------------------------|-------------------------------------|
| Pre-dose       | 0                                        | 0                                        | 0                                   | 0                                   |
| 0.5            | 0.06 (158)                               | 0.087 (138)                              | 0.03 (215)                          | 0.07 (141)                          |
| 1.0            | 0.36 (59)                                | 0.40 (61)                                | 0.21 (87)                           | 0.36 (66)                           |
| 1.5            | 0.54 (47)                                | 0.59 (48)                                | 0.39 (58)                           | 0.55 (56)                           |
| 2.0            | 0.65 (43)                                | 0.68 (40)                                | 0.49 (49)                           | 0.68 (51)                           |
| 2.5            | 0.71 (39)                                | 0.77 (38)                                | 0.57 (46)                           | 0.78 (49)                           |
| 3.0            | 0.73 (40)                                | 0.78 (36)                                | 0.61 (43)                           | 0.82 (49)                           |
| 4.0            | 0.76 (36)                                | 0.81 (37)                                | 0.66 (39)                           | 0.87 (47)                           |
| 5.0            | 0.74 (34)                                | 0.80 (35)                                | 0.67 (40)                           | 0.91 (48)                           |
| 6.0            | 0.75 (34)                                | 0.80 (34)                                | 0.70 (41)                           | 0.93 (49)                           |
| 8.0            | 0.74 (36)                                | 0.77 (35)                                | 0.70 (40)                           | 0.92 (49)                           |
| 10.0           | 0.73 (38)                                | 0.78 (38)                                | 0.73 (41)                           | 0.92 (47)                           |
| 12.0           | 0.72 (39)                                | 0.78 (35)                                | 0.71 (41)                           | 0.89 (48)                           |
| 12.5           | 0.54 (35)                                | 0.57 (33)                                | 0.56 (36)                           | 0.71 (51)                           |
| 13.0           | 0.36 (39)                                | 0.37 (33)                                | 0.37 (33)                           | 0.45 (39)                           |

\* Coefficient of Variation  
N = Total Number of Subjects

The mean pharmacokinetic parameters derived from the plasma data are presented in Tables 5-7.

**Table 5**  
**Mean Pharmacokinetic Parameters for Plasma TNG**

| <b>Parameters</b>                                   | <b>Test (A)<br/>NOT-FA (21.0 cm<sup>2</sup>)<br/>of Hercon<br/>N=46<br/>Mean<math>\pm</math>SD</b> | <b>Reference (B)<br/>Transderm-Nitro<sup>®</sup><br/>(Novartis)<br/>N=46<br/>Mean<math>\pm</math>SD</b> | <b>Ratio<br/>A/B</b> | <b>90% C.I.<br/>Based on<br/>LSM.<br/>N=46</b> |
|-----------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------|------------------------------------------------|
| <b>AUC<sub>0-7</sub><br/>(pg.hr/mL)</b>             | 3087.66 $\pm$ 2225.3<br>LSM: 3038.42                                                               | 2690.03 $\pm$ 1382.5<br>LSM: 2581.37                                                                    |                      |                                                |
| <b>AUC<sub>0-inf</sub><br/>(pg.hr/mL)</b>           | 3154.01 $\pm$ 2245.7<br>LSM: 3049.22                                                               | 2806.16 $\pm$ 1410.6<br>LSM: 2585.86                                                                    |                      |                                                |
| <b>C<sub>max</sub> (pg/mL)</b>                      | 460.16 $\pm$ 458.0<br>LSM: 454.93                                                                  | 380.70 $\pm$ 224.5<br>LSM: 358.55                                                                       |                      |                                                |
| <b>C<sub>ss</sub> (pg/mL)</b>                       | 271.61 $\pm$ 197.5<br>LSM: 267.29                                                                  | 236.81 $\pm$ 12<br>LSM: 227.01                                                                          |                      |                                                |
| <b>T<sub>max</sub> (hour)</b>                       | 6.02 $\pm$ 2.6                                                                                     | 4.77 $\pm$ 2.92                                                                                         |                      |                                                |
| <b>KE (1/hour)</b>                                  | 2.763 $\pm$ 0.99                                                                                   | 3.655 $\pm$ 1.22                                                                                        |                      |                                                |
| <b>t<sub>1/2</sub> (hour)</b>                       | 0.29 $\pm$ 0.13                                                                                    | 0.21 $\pm$ 0.08                                                                                         |                      |                                                |
| <b>%Fluctuation</b>                                 | 110.7 $\pm$ 40.0                                                                                   | 109.7 $\pm$ 56.75                                                                                       |                      |                                                |
| <b>LnAUC<sub>0-7</sub><br/>Geometric<br/>mean</b>   | 7.82081<br>2491.92                                                                                 | 7.75575<br>2334.96                                                                                      | 1.07                 | 100, 114                                       |
| <b>LnAUC<sub>0-inf</sub><br/>Geometric<br/>mean</b> | 7.82878<br>2511.86                                                                                 | 7.77069<br>2370.11                                                                                      | 1.06                 | 99, 114                                        |
| <b>LnC<sub>max</sub><br/>Geometric<br/>mean</b>     | 5.84212<br>344.51                                                                                  | 5.77310<br>321.53                                                                                       | 1.07                 | 98, 117                                        |
|                                                     |                                                                                                    |                                                                                                         |                      |                                                |

N = Total Number of Subjects

**Table 6**  
**Mean Pharmacokinetic Parameters for Plasma 1,2-DNG**

| Parameters                                  | Test(A)<br>NOT-FA (21.0 cm <sup>2</sup> )<br>of Hercon<br>N=46<br>Mean $\pm$ SD | Reference(B)<br>Transderm-Nitro <sup>a</sup><br>(Novartis)<br>N=46<br>Mean $\pm$ SD | Ratio<br>A/B | 90% C.I.<br>Based on<br>LSM.<br>N=46 |
|---------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------|--------------------------------------|
| AUC <sub>0-r</sub><br>(ng.hr/mL)            | 49.67 $\pm$ 25.79<br>LSM: 49.77                                                 | 44.89 $\pm$ 14.81<br>LSM: 43.87                                                     |              |                                      |
| AUC <sub>0-inf</sub><br>(ng.hr/mL)          | 51.75 $\pm$ 26.28<br>LSM: 51.50                                                 | 46.38 $\pm$ 14.99<br>LSM: 45.37                                                     |              |                                      |
| C <sub>max</sub> (ng/mL)                    | 5.04 $\pm$ 2.62<br>LSM: 4.68                                                    | 4.42 $\pm$ 1.40<br>LSM: 4.33                                                        |              |                                      |
| C <sub>ss</sub> (ng/mL)                     | 4.67 $\pm$ 2.40<br>LSM: 4.68                                                    | 4.12 $\pm$ 1.32<br>LSM: 4.02                                                        |              |                                      |
| T <sub>max</sub> (hour)                     | 8.20 $\pm$ 2.27                                                                 | 7.48 $\pm$ 2.79                                                                     |              |                                      |
| KE (1/hour)                                 | 0.920 $\pm$ 0.22                                                                | 0.986 $\pm$ 0.17                                                                    |              |                                      |
| t <sub>1/2</sub> (hour)                     | 0.79 $\pm$ 0.19                                                                 | 0.73 $\pm$ 0.15                                                                     |              |                                      |
| %Fluctuation                                | 32.21 $\pm$ 10.45                                                               | 29.65 $\pm$ 25.51                                                                   |              |                                      |
| LnAUC <sub>0-r</sub><br>Geometric<br>mean   | 3.79267<br>44.37                                                                | 3.73733<br>41.99                                                                    | 1.06         | 101; 111                             |
| LnAUC <sub>0-inf</sub><br>Geometric<br>mean | 3.82948<br>46.04                                                                | 3.77305<br>43.51                                                                    | 1.06         | 101; 111                             |
| LnC <sub>max</sub><br>Geometric<br>mean     | 1.51004<br>4.53                                                                 | 1.42724<br>4.17                                                                     | 1.09         | 104; 114                             |
|                                             |                                                                                 |                                                                                     |              |                                      |

N = Total Number of Subjects

**Table 7**  
**Mean Pharmacokinetic Parameters for Plasma 1,3-DNG**

| <b>Parameters</b>                                   | <b>Test (A)<br/>NOT-FA (21.0 cm<sup>2</sup>)<br/>of Hercon<br/>N=46<br/>Mean<math>\pm</math>SD</b> | <b>Reference (B)<br/>Transderm-Nitro<sup>®</sup><br/>(Novartis)<br/>N=46<br/>Mean<math>\pm</math>SD</b> | <b>Ratio<br/>A/B</b> | <b>90% C.I.<br/>Based on<br/>LSM.<br/>N=46</b> |
|-----------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------|------------------------------------------------|
| <b>AUC<sub>0-T</sub><br/>(ng.hr/mL)</b>             | 9.03 $\pm$ 4.32<br>LSM: 9.00                                                                       | 8.83 $\pm$ 3.15<br>LSM: 8.64                                                                            |                      |                                                |
| <b>AUC<sub>0-inf</sub><br/>(ng.hr/mL)</b>           | 9.73 $\pm$ 4.44<br>LSM: 9.64                                                                       | 9.43 $\pm$ 3.19<br>LSM: 9.20                                                                            |                      |                                                |
| <b>C<sub>max</sub> (ng/mL)</b>                      | 0.88 $\pm$ 0.40<br>LSM: 0.87                                                                       | 0.85 $\pm$ 0.30<br>LSM: 0.84                                                                            |                      |                                                |
| <b>C<sub>ss</sub> (ng/mL)</b>                       | 0.84 $\pm$ 0.40<br>LSM: 0.84                                                                       | 0.80 $\pm$ 0.28<br>LSM: 0.79                                                                            |                      |                                                |
| <b>T<sub>max</sub> (hour)</b>                       | 8.01 $\pm$ 2.60                                                                                    | 6.20 $\pm$ 3.02                                                                                         |                      |                                                |
| <b>KE (1/hour)</b>                                  | 0.66 $\pm$ 0.22                                                                                    | 0.73 $\pm$ 0.16                                                                                         |                      |                                                |
| <b>t<sub>1/2</sub> (hour)</b>                       | 1.16 $\pm$ 0.38                                                                                    | 1.01 $\pm$ 0.27                                                                                         |                      |                                                |
| <b>%Fluctuation</b>                                 | 22.44 $\pm$ 7.30                                                                                   | 24.28 $\pm$ 25.36                                                                                       |                      |                                                |
| <b>LnAUC<sub>0-T</sub><br/>Geometric<br/>mean</b>   | 2.09334<br>8.112                                                                                   | 2.09892<br>8.157                                                                                        | 0.99                 | 95; 103                                        |
| <b>LnAUC<sub>0-inf</sub><br/>Geometric<br/>mean</b> | 2.16999<br>8.76                                                                                    | 2.16767<br>8.74                                                                                         | 1.00                 | 96; 104                                        |
| <b>LnC<sub>max</sub><br/>Geometric<br/>mean</b>     | -0.22793<br>0.796                                                                                  | -0.23158<br>0.793                                                                                       | 1.00                 | 97; 104                                        |
|                                                     |                                                                                                    |                                                                                                         |                      |                                                |

**N = Total Number of Subjects**

### Statistical Analysis:

The firm has included a term for simple first-order residual (carryover) effects in their statistical model without giving any reason. The Model used was:

$T = \text{sequence} + \text{group} + \text{sequence} * \text{group} + \text{subject}(\text{sequence} * \text{group}) + \text{period}(\text{group}) + \text{treatment} + \text{treatment} * \text{group} + \text{residual}$

A reduced ANOVA model excluding the group-by-treatment interaction term (when this term was not significant) was then employed to evaluate the bioequivalence of the pharmacokinetic parameters of interest.

However, according to the Agency statistician's opinion, if the first-order residual effects are to be considered, the sponsor's model is inadequate to examine all of the possible residual effects. The sponsor's experimental design (as shown below) with four periods and two sequences was carried out in two groups of subjects. However, the group structure of the study does not affect the issues involving possible residual effects.

|            |   | Periods |   |   |   |
|------------|---|---------|---|---|---|
|            |   | 1       | 2 | 3 | 4 |
| Sequence 1 | T | R       | R | T |   |
| Sequence 2 | R | T       | T | R |   |

The sponsor's model incorrectly assumed that the effect of T on T was the same as the effect of T on R, and that the effect of R on T was the same as the effect of R on R.

Regarding the residual effect, one possible cause is direct carryover of the drug substance from one period into the next. There is essentially no evidence of such direct carryover in this study, with the time zero concentrations of the parent compound, the 1,2 metabolite, and the 1,3 metabolite reported as 0 for all subjects and periods except for subject 47, period 1, and subject 48, period 1. In those two cases, the time zero concentrations are reported as missing.

reported as missing.

Since the Division has not yet developed definitive procedures to analyze the residual effect, and the Agency has previously approved applications on Nitroglycerin Transdermal Patches, where the pharmacokinetic data were analyzed using a statistical model of replicate design without including a term for residual, the data of the current application were also reanalyzed using a similar model by the Agency statistician and found acceptable. The study data of all three analytes met the usual bioequivalence criterion of 80- 125% for 90% CI for all three PK parameters, AUCt, Cmax, and AUCinf as shown below:

|          | <u>Parent compound</u> | <u>1.2 Metabolite</u> | <u>1.3 Metabolite</u> |
|----------|------------------------|-----------------------|-----------------------|
| LnAUCt   | 99.60% , 113.39%       | 99.75% , 109.06%      | 94.50% , 102.46%      |
| LnCmax   | 97.58% , 115.68%       | 102.60% , 112.06%     | 95.43% , 102.89%      |
| LnAUCinf | 98.70% , 112.94%       | 100.19% , 109.33%     | 95.59% , 103.37%      |

Dissolution:

The dissolution (drug release) testing data are presented in Table 8 below:

**Table 8. In Vitro Dissolution Testing (drug release)**

Drug: NTS-FA Transdermal System  
Dose Strengths: 0.6 mg/hr (21.0 cm<sup>2</sup> patch)  
AND No.: 89-886-  
Firm: Hercon Lab.  
Submission Date: November 3, 1997

**I. Conditions for Dissolution Testing:**

USP XXIII Paddle (USP modified Apparatus 5, paddle over disk) RPM: 50  
No. Units Tested: 12  
Medium: Water at 32 °C; Volume: 500 mL  
Specifications: Has been proposed  
Reference Drug: Transderm-Nitro<sup>®</sup> (0.6 mg/hr); Label Claim: 75 mg/30 cm. sq.  
Assay Methodology:

**II. Results of In Vitro Dissolution Testing:**

| Sampling Times (Hour) | Test Product: Patch<br>Lot # LO597NG/613<br>Strength 0.6 mg/hr; 111.9 mg /21cm <sup>2</sup> |       |     | Reference Product: Patch<br>Lot # 1F193881<br>Strength 0.6 mg/hr ; 75.0 mg/30 cm <sup>2</sup> |       |     |
|-----------------------|---------------------------------------------------------------------------------------------|-------|-----|-----------------------------------------------------------------------------------------------|-------|-----|
|                       | Mean %                                                                                      | Range | %CV | Mean %                                                                                        | Range | %CV |
| 0.25                  | 41.0                                                                                        |       | 3.6 | 3.8                                                                                           |       | 3.3 |
| 0.5                   | 61.0                                                                                        |       | 1.6 | 4.4                                                                                           |       | 2.8 |
| 1                     | 76.0                                                                                        |       | 1.8 | 5.6                                                                                           |       | 2.5 |
| 2                     | 82.9                                                                                        |       | 1.9 | 8.0                                                                                           |       | 2.5 |
| 4                     | 83.5                                                                                        |       | 3.6 | 12.5                                                                                          |       | 2.4 |
| Sampling Times (Hour) | Test Product: Patch<br>Lot # LANG/612<br>Strength 0.4 mg/hr; 74.6 mg/14.0 cm <sup>2</sup>   |       |     | Reference Product: Patch<br>Lot # 1M205516<br>Strength 0.4 mg/hr ; 50.0 mg/20 cm <sup>2</sup> |       |     |
| 0.25                  | 37.4                                                                                        |       | 4.2 | 3.4                                                                                           |       | 1.7 |
| 0.5                   | 57.6                                                                                        |       | 4.4 | 4.2                                                                                           |       | 1.1 |
| 1                     | 74.0                                                                                        |       | 3.1 | 5.5                                                                                           |       | 1.3 |
| 2                     | 83.0                                                                                        |       | 2.9 | 7.7                                                                                           |       | 1.5 |
| 4                     | 87.9                                                                                        |       | 2.0 | 11.9                                                                                          |       | 1.7 |

| Sampling Times (Hour) | Test Product: Patch<br>Lot # LANG/614<br>Strength 0.2 mg/hr; 37.3 mg/ 7 cm <sup>2</sup> |  |     | Reference Product: Patch<br>Lot #1M010951<br>Strength 0.2 mg/hr ; 25.0 mg/10 cm <sup>2</sup> |  |     |
|-----------------------|-----------------------------------------------------------------------------------------|--|-----|----------------------------------------------------------------------------------------------|--|-----|
| 0.25                  | 36.3                                                                                    |  | 5.2 | 3.4                                                                                          |  | 2.5 |
| 0.5                   | 57.6                                                                                    |  | 5.8 | 4.2                                                                                          |  | 2.2 |
| 1                     | 75.2                                                                                    |  | 4.3 | 5.6                                                                                          |  | 2.4 |
| 2                     | 85.9                                                                                    |  | 2.9 | 7.5                                                                                          |  | 1.9 |
| 4                     | 90.5                                                                                    |  | 2.3 | 11.4                                                                                         |  | 2.1 |

### Formulations:

The compositions of three proposed strengths of Hercon's Nitroglycerin Transdermal System are presented below:

| <u>AND</u>  | <u>Strength</u> | <u>Old Size</u>       | <u>New Size</u>      |
|-------------|-----------------|-----------------------|----------------------|
| AND #89-884 | 0.2 mg/hr       | 6.75 cm <sup>2</sup>  | 7.0 cm <sup>2</sup>  |
| AND #89-885 | 0.4 mg/hr       | 13.5 cm <sup>2</sup>  | 14.0 cm <sup>2</sup> |
| AND #89-886 | 0.6 mg/hr       | 20.25 cm <sup>2</sup> | 21.0 cm <sup>2</sup> |

### Components

#### Delivery Rate

### Strengths

#### 0.2 mg/hr

#### 0.4 mg/hr

#### 0.6 mg/hr

Patch size

7.0 cm<sup>2</sup>

14.0 cm<sup>2</sup>

21.0 cm<sup>2</sup>

Nitroglycerin

37.3 mg

74.7 mg

111.9 mg

#### Adhesive

Polymer

13.6 mg

26.2 mg

39.3 mg

#### Adhesive

Polymer

16.6 mg

32.04 mg

48.01 mg

#### Backing Film

7.0 cm<sup>2</sup>

14.0 cm<sup>2</sup>

21.0 cm<sup>2</sup>

Coated Reservoir Weight

68.9 mg

132.9 mg

199.2 mg

Comments:

1. For nitroglycerin (TNG), 1,2-dinitroglycerin and 1,3-dinitroglycerin of the test product, the 90% confidence interval for  $\text{LnAUC}_T$ ,  $\text{LnAUC}_{0-\text{inf}}$  and  $\text{LnC}_{\text{MAX}}$  were within the 80% to 125% limit.
2. The firm has also conducted an acceptable skin irritation study.
3. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.6 mg/ml, Lot #LO597NG/613 comparing it to Transderm-Nitro<sup>®</sup>, 0.6 mg/hr, Lot #1F193881 manufactured by Novartis has been found acceptable.

The tentative specifications for the test product should be:

| <u>Sampling Schedule</u> | <u>Limits</u> |
|--------------------------|---------------|
| 0.25 hr                  | %             |
| 0.5 hr                   | %             |
| 1.0 hr                   | %             |
| 4.0 hr                   | %             |

4. The dissolution (drug release) data of 0.2 mg/hr and 0.4 mg/hr patches are acceptable. The formulations for the 0.2 mg/hr and 0.4 mg/hr strengths are proportionally similar to the 0.6 mg/hr patch, and therefore, the waivers on 0.2 mg/hr and 0.4 mg/hr patches are granted.

**Recommendations:**

1. The in vivo bioequivalence study conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch (111.9 mg /21.0 cm<sup>2</sup>) of 0.6 mg/hr, Lot #LO597NG/613 comparing it to Transderm-Nitro<sup>R</sup> patch (75 mg/30 cm<sup>2</sup>) of 0.6 mg/hr, Lot #1F193881 manufactured by Novartis has been found acceptable by the Division of Bioequivalence. The study demonstrates that Hercon's Nitroglycerin Transdermal System Face Adhesive Patch (111.9 mg /21.0 cm<sup>2</sup>) of 0.6 mg/hr is bioequivalent to the reference product, Transderm-Nitro<sup>R</sup> Patch (75 mg /30 cm<sup>2</sup>) of 0.6 mg/hr.
2. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.6 mg/ml, Lot #LO597NG/613 comparing it to Transderm-Nitro<sup>R</sup>, 0.6 mg/hr, Lot #1F193881 manufactured by Novartis has been found acceptable.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 32°C using paddle over disk at 50 rpm. The test product should meet the tentative dissolution specifications:

| <u>Sampling Schedule</u> | <u>Limits</u> |
|--------------------------|---------------|
| 0.25 hr                  | 5 %           |
| 0.5 hr                   | 5 %           |
| 1.0 hr                   | 5 %           |
| 4.0 hr                   | 5 %           |

3. The firm has also conducted an acceptable skin irritation study.
4. The dissolution (drug release) testings conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patches of 0.2 mg/hr (37.3 mg /7.0 cm<sup>2</sup>), Lot #LO557NG/614, and 0.4 mg/hr (74.6 mg/14.0 cm<sup>2</sup>), #LANG/612 are acceptable. The formulations for the 0.2 mg/hr and 0.4 mg/hr strengths are proportionally similar to the 0.6 mg/hr patch of the test product which underwent bioequivalency testing. The

waivers of in vivo bioequivalence study requirements for the  
0.2 mg/hr (37.3 mg /7.0 cm<sup>2</sup>) and 0.4 mg/hr (74.6 mg /14.0 cm<sup>2</sup>)  
patches of the test product are granted.

( /S/ )  
Sikta Pradhan, Ph. D.  
Division of Bioequivalence  
Review Branch I

RD INITIALED YCHUANG  
FT INITIALED YCHUANG

( /S/ )

6/17/98

Concur:

( /S/ )

Date: 6/18/98

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

cc: AND # 89-886 (original, duplicate), HFD-652 (Huang,  
Pradhan), HFD-650 (Director), Drug File, Division File.

*Table - 1(a)*  
**NUMBER OF SUBJECTS REPORTING ADVERSE EVENTS  
 FOR THE DIFFERENT TREATMENTS**

| Adverse Event               | Test Formulation | Reference Formulation |
|-----------------------------|------------------|-----------------------|
| Body Aches                  | 1                | -                     |
| Burning at Patch Site       | 4                | 2                     |
| Chest Pain                  | 1                | -                     |
| Chest Tightness             | -                | 1                     |
| Cold Sensation              | 1                | 1                     |
| Dizziness                   | 1                | 1                     |
| Drowsiness                  | 1                | -                     |
| Emesis                      | -                | 4                     |
| Erythema at Dose Site       | 2                | 2                     |
| Fatigue                     | 6                | 2                     |
| Headache                    | 89               | 88                    |
| Indigestion                 | 1                | -                     |
| Irritation at Patch Site    | 2                | 1                     |
| Leg Pain                    | -                | 1                     |
| Lightheadedness             | 2                | 3                     |
| Nausea                      | 6                | 9                     |
| Neck Pain                   | 1                | -                     |
| Neck Pressure               | -                | 1                     |
| Neck Tension                | -                | 2                     |
| Pain at Patch Site          | -                | 1                     |
| Painful Eyes                | 1                | -                     |
| Sensation of Swollen Throat | -                | 1                     |
| Stomach Ache                | 1                | -                     |
| Syncope                     | 1                | -                     |
| Weakness                    | -                | 1                     |

APPEARS THIS WAY  
 ON ORIGINAL

*Table - 1(b)*  
**OBSERVED PATCH IRRITATIONS**

| Time Point                          | Test Formulation |      |          | Reference Formulation |      |          |
|-------------------------------------|------------------|------|----------|-----------------------|------|----------|
|                                     | Absent           | Mild | Moderate | Absent                | Mild | Moderate |
| Immediately Following Patch Removal | 14               | 72   | 6        | 4                     | 68   | 23       |
| 1 Hour Following Patch Removal      | 89               | 3    | 0        | 86                    | 7    | 0        |
| 2 Hours Following Patch Removal     | 91               | 1    | 0        | 87                    | 6    | 0        |

APPEARS THIS WAY  
ON ORIGINAL

Figure 1

# Trinitrolycerin

Trinitrolycerin (Protocol No. HERC-9701)  
Mean Plasma Concentration Profile

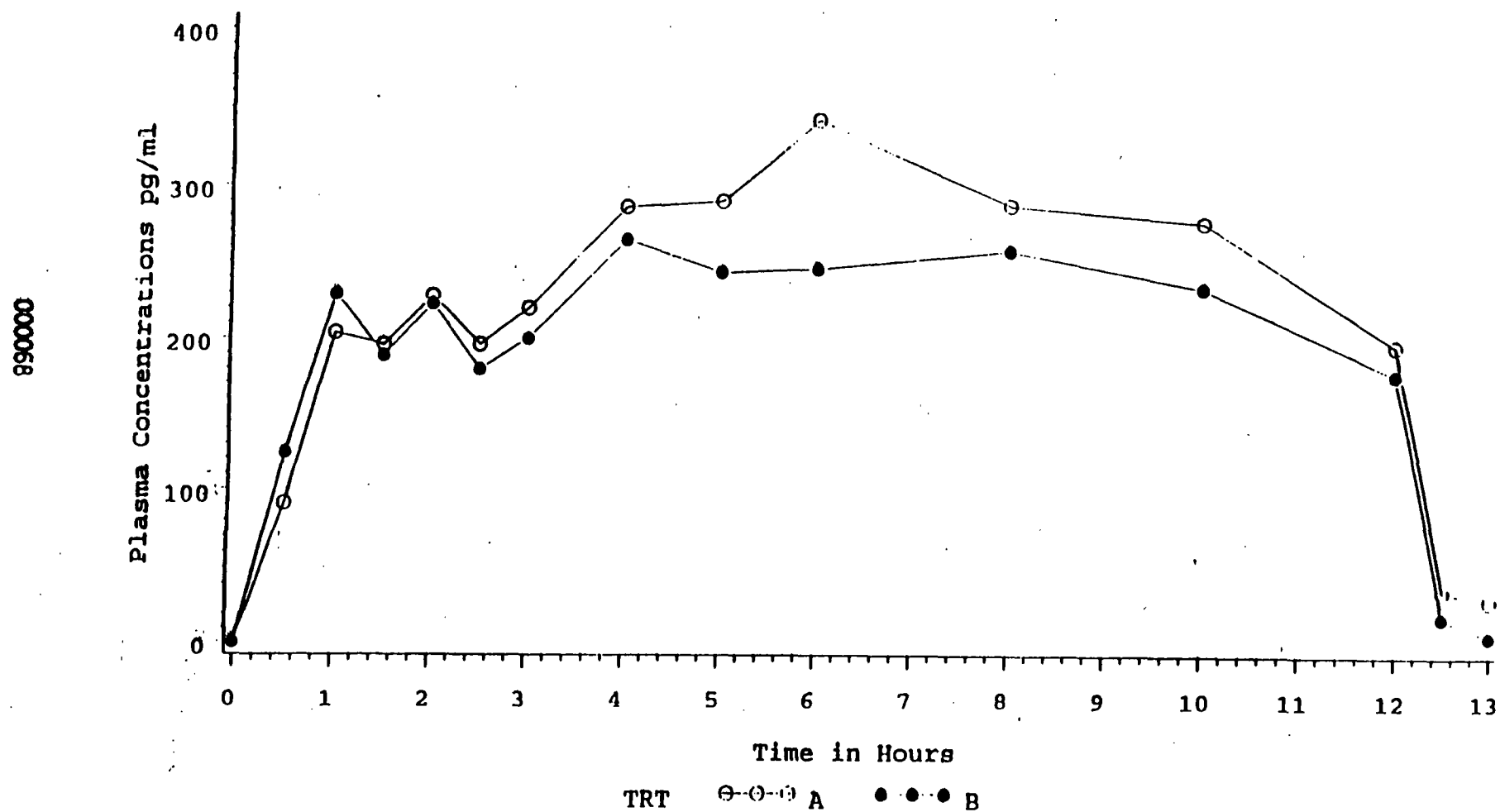


Figure 2

# Trinitroglycerin

Trinitroglycerin (Protocol No. HERC-9701)  
Mean Plasma Concentration Profile

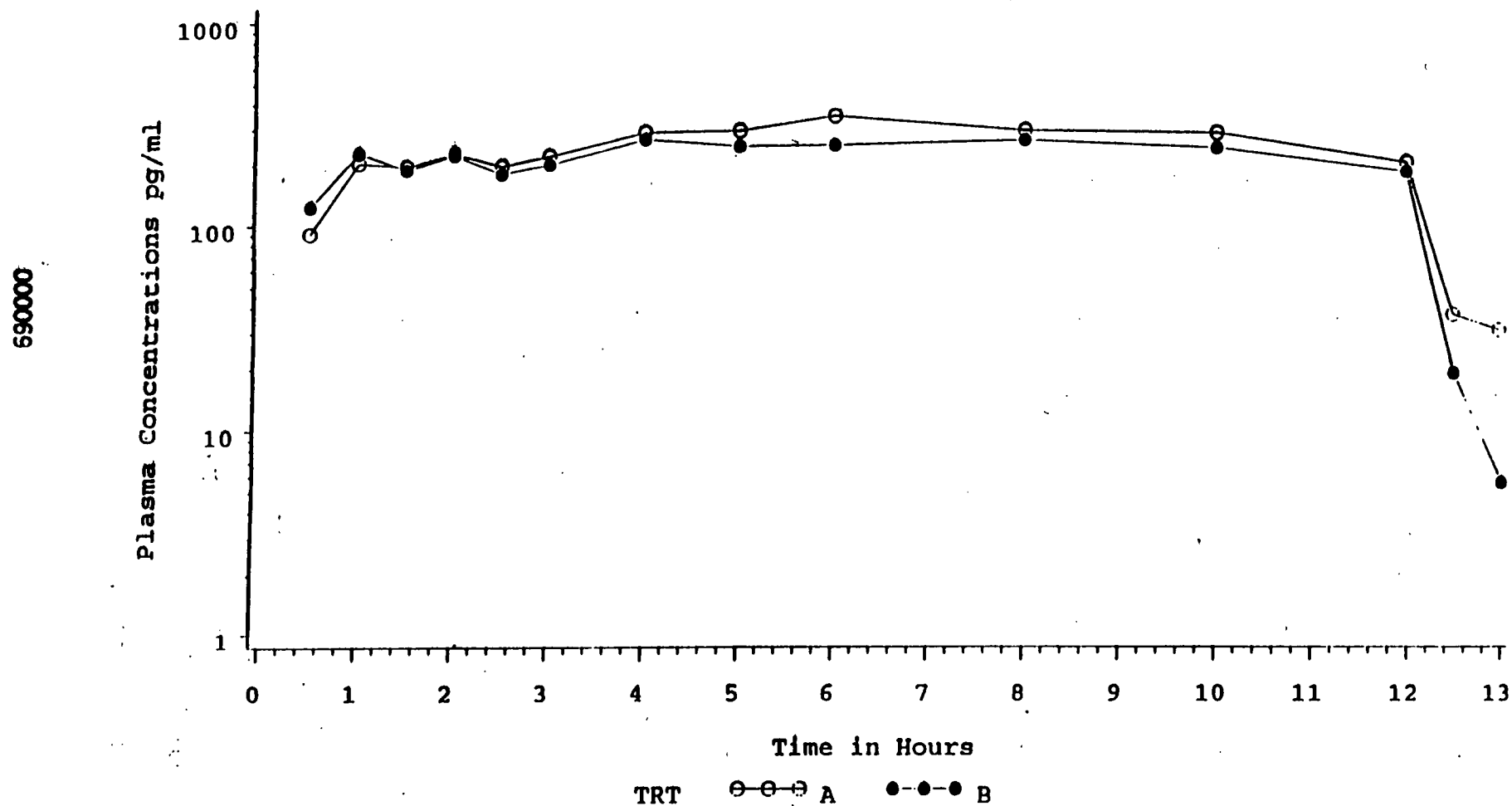
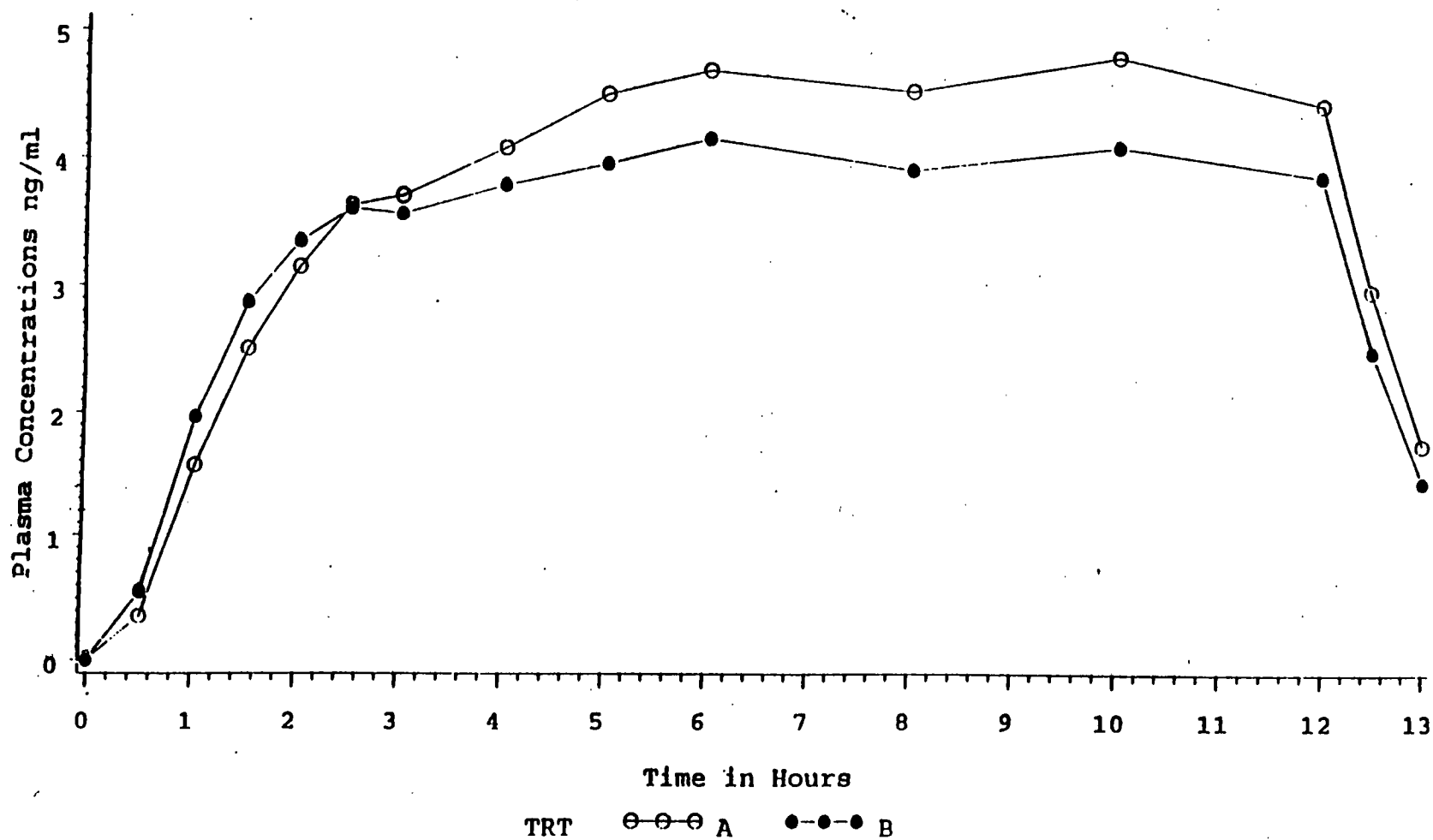


Figure 3

# 1,2-Dinitrolycerin

1,2-Dinitrolycerin (Protocol No. HERC-9701)  
Mean Plasma Concentration Profile

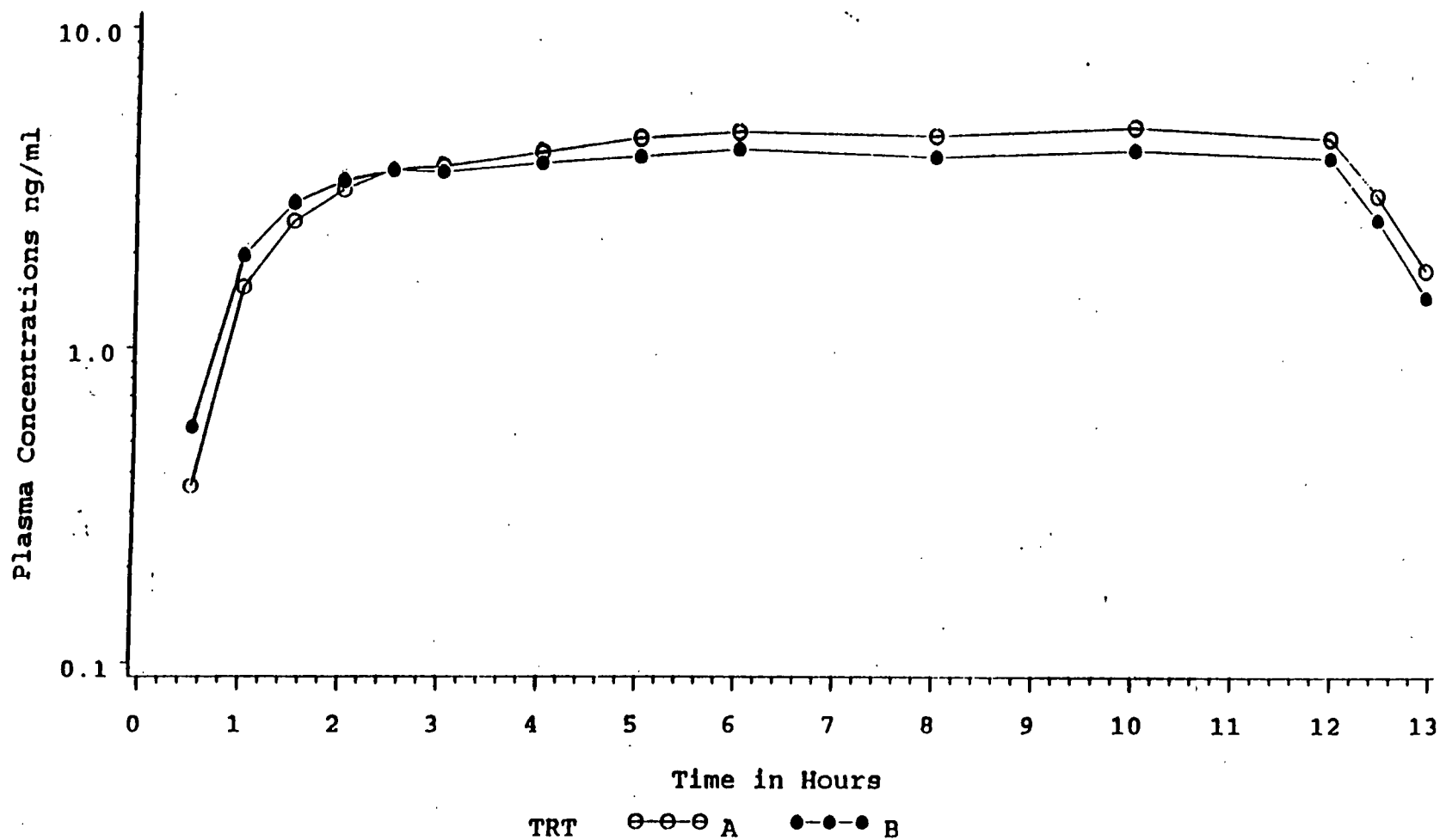


000070

Figure 4

# 1,2-Dinitrolycerin

1,2-Dinitrolycerin (Protocol No. HERC-9701)  
Mean Plasma Concentration Profile

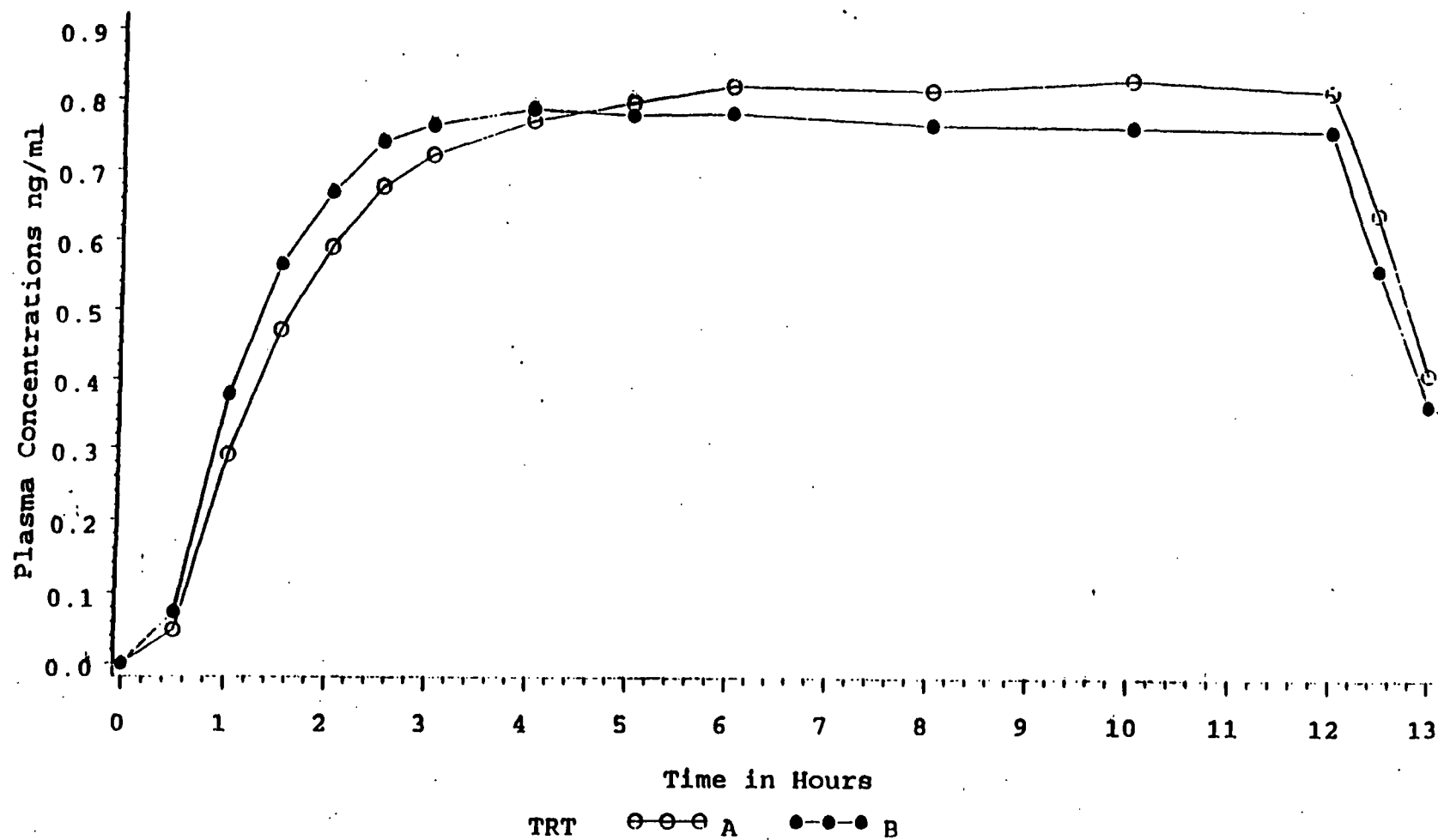


000071

Figure 5

# 1,3-Dinitrolycerin

1,3-Dinitrolycerin (Protocol No. HERC-9701)  
Mean Plasma Concentration Profile

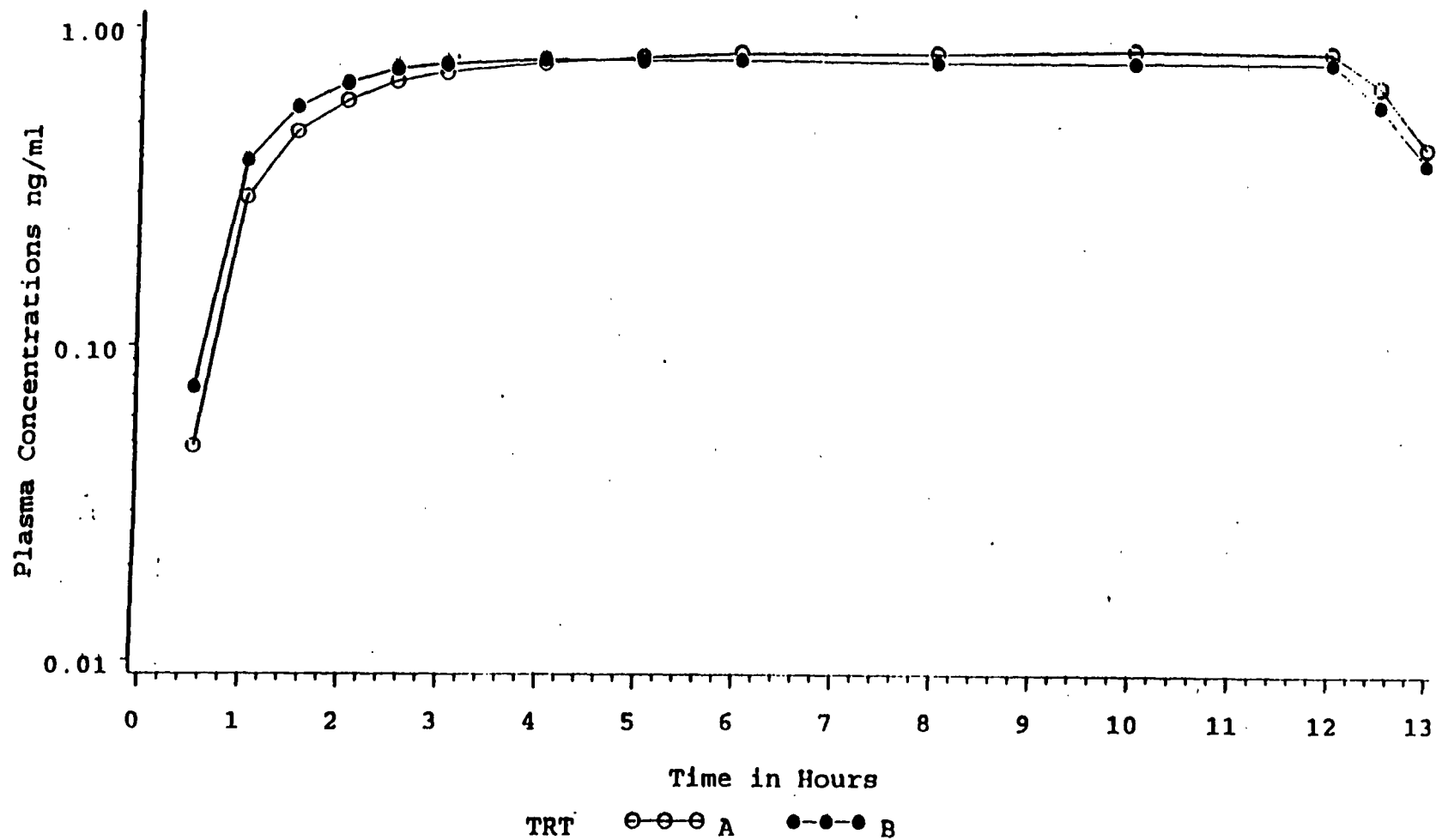


000072

Figure 6

# 1,3-Dinitrolycerin

1,3-Dinitrolycerin (Protocol No. HERC-9701)  
Mean Plasma Concentration Profile



ATTACHMENT # 1

VITAL SIGNS OUTPUT

000710

**SUMMARY STATISTICS FOR VITAL SIGNS AT EACH SAMPLING POINT  
(BY TREATMENT)**

Mercon Laboratories, Inc.  
 Nitroglycerin (Protocol No. Herc9701)  
 Fasting Single-Dose In Vivo Bioequivalence Study  
 Arithmetic Mean of Vital Signs  
 Versus Time (CV%) in 46 Subjects

----- VITSIGN=' DIASTOLIC' -----

| Time | Reference<br>Treatment B1 | Reference<br>Treatment B2 | Test<br>Treatment A1 | Test<br>Treatment A2 | Ratio<br>(A1+A2/B1+B2) |
|------|---------------------------|---------------------------|----------------------|----------------------|------------------------|
| 0    | 80.3(8.7%)                | 79.1(10.0%)               | 81.7(9.3%)           | 79.0(10.0%)          | 1.008                  |
| 0.5  | 80.4(9.1%)                | 80.8(11.1%)               | 79.2(9.3%)           | 80.0(10.9%)          | 0.988                  |
| 1    | 80.5(12.7%)               | 74.6(13.0%)               | 80.7(9.8%)           | 78.9(10.8%)          | 1.017                  |
| 2    | 79.0(7.5%)                | 76.9(12.6%)               | 79.2(10.1%)          | 78.4(9.8%)           | 1.011                  |
| 4    | 79.0(8.6%)                | 78.0(10.8%)               | 78.7(11.2%)          | 78.0(10.0%)          | 1.011                  |
| 8    | 74.3(9.8%)                | 71.2(11.7%)               | 73.4(9.4%)           | 71.2(10.6%)          | 0.994                  |
| 12   | 75.7(12.8%)               | 73.3(12.8%)               | 75.2(10.8%)          | 74.5(12.7%)          | 1.005                  |
| 13   | 73.3(8.8%)                | 72.3(9.0%)                | 70.7(8.3%)           | 73.5(11.5%)          | 0.990                  |

----- VITSIGN=' SYSTOLIC' -----

| Time | Reference<br>Treatment B1 | Reference<br>Treatment B2 | Test<br>Treatment A1 | Test<br>Treatment A2 | Ratio<br>(A1+A2/B1+B2) |
|------|---------------------------|---------------------------|----------------------|----------------------|------------------------|
| 0    | 111.8(8.5%)               | 111.5(7.6%)               | 115.1(9.2%)          | 109.0(7.5%)          | 1.004                  |
| 0.5  | 107.5(8.3%)               | 109.3(7.6%)               | 111.2(10.9%)         | 106.3(9.3%)          | 1.012                  |
| 1    | 107.5(9.6%)               | 103.9(8.6%)               | 110.8(9.1%)          | 103.9(9.1%)          | 1.016                  |
| 2    | 105.1(10.5%)              | 102.7(8.7%)               | 105.1(9.4%)          | 101.7(7.6%)          | 0.995                  |
| 4    | 105.4(9.8%)               | 103.1(9.7%)               | 106.7(9.3%)          | 106.1(9.6%)          | 1.021                  |
| 8    | 104.9(9.3%)               | 104.0(9.8%)               | 104.3(9.1%)          | 106.0(10.4%)         | 1.007                  |
| 12   | 113.9(9.1%)               | 109.6(11.0%)              | 112.0(8.3%)          | 112.5(9.4%)          | 1.005                  |
| 13   | 113.7(8.8%)               | 112.7(8.5%)               | 112.0(8.7%)          | 115.1(10.9%)         | 1.003                  |

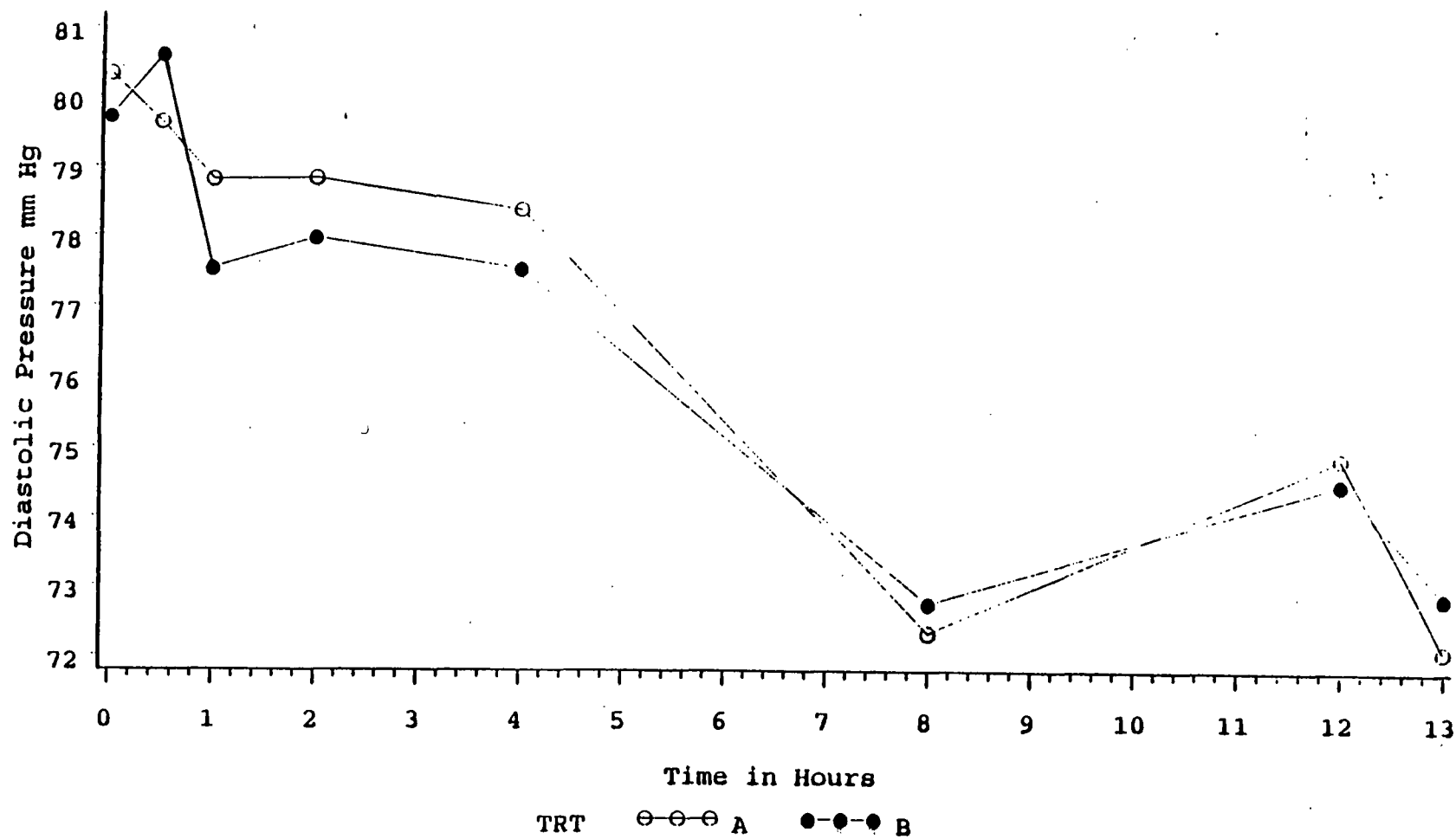
----- VITSIGN='PULSE' -----

| Time | Reference<br>Treatment B1 | Reference<br>Treatment B2 | Test<br>Treatment A1 | Test<br>Treatment A2 | Ratio<br>(A1+A2/B1+B2) |
|------|---------------------------|---------------------------|----------------------|----------------------|------------------------|
| 0    | 61.8(11.7%)               | 62.8(11.9%)               | 61.8(15.2%)          | 63.2(11.8%)          | 1.003                  |
| 0.5  | 64.4(13.9%)               | 66.0(13.4%)               | 65.7(13.4%)          | 64.4(12.2%)          | 0.998                  |
| 1    | 66.0(13.6%)               | 68.7(15.5%)               | 64.0(15.1%)          | 69.4(13.7%)          | 0.990                  |
| 2    | 65.1(10.6%)               | 68.7(12.0%)               | 64.7(12.1%)          | 69.8(12.0%)          | 1.004                  |
| 4    | 76.7(12.7%)               | 77.2(14.5%)               | 76.5(12.9%)          | 79.3(12.6%)          | 1.013                  |
| 8    | 69.7(13.4%)               | 69.2(12.1%)               | 68.0(11.4%)          | 69.3(13.4%)          | 0.989                  |
| 12   | 74.8(11.9%)               | 71.7(13.9%)               | 74.1(11.1%)          | 73.5(14.2%)          | 1.008                  |
| 13   | 70.0(12.2%)               | 71.2(10.9%)               | 70.4(9.9%)           | 70.2(11.3%)          | 0.996                  |

## MEAN AND INDIVIDUAL DIASTOLIC BLOOD PRESSURE PROFILES

# Hercon Laboratories, Inc.

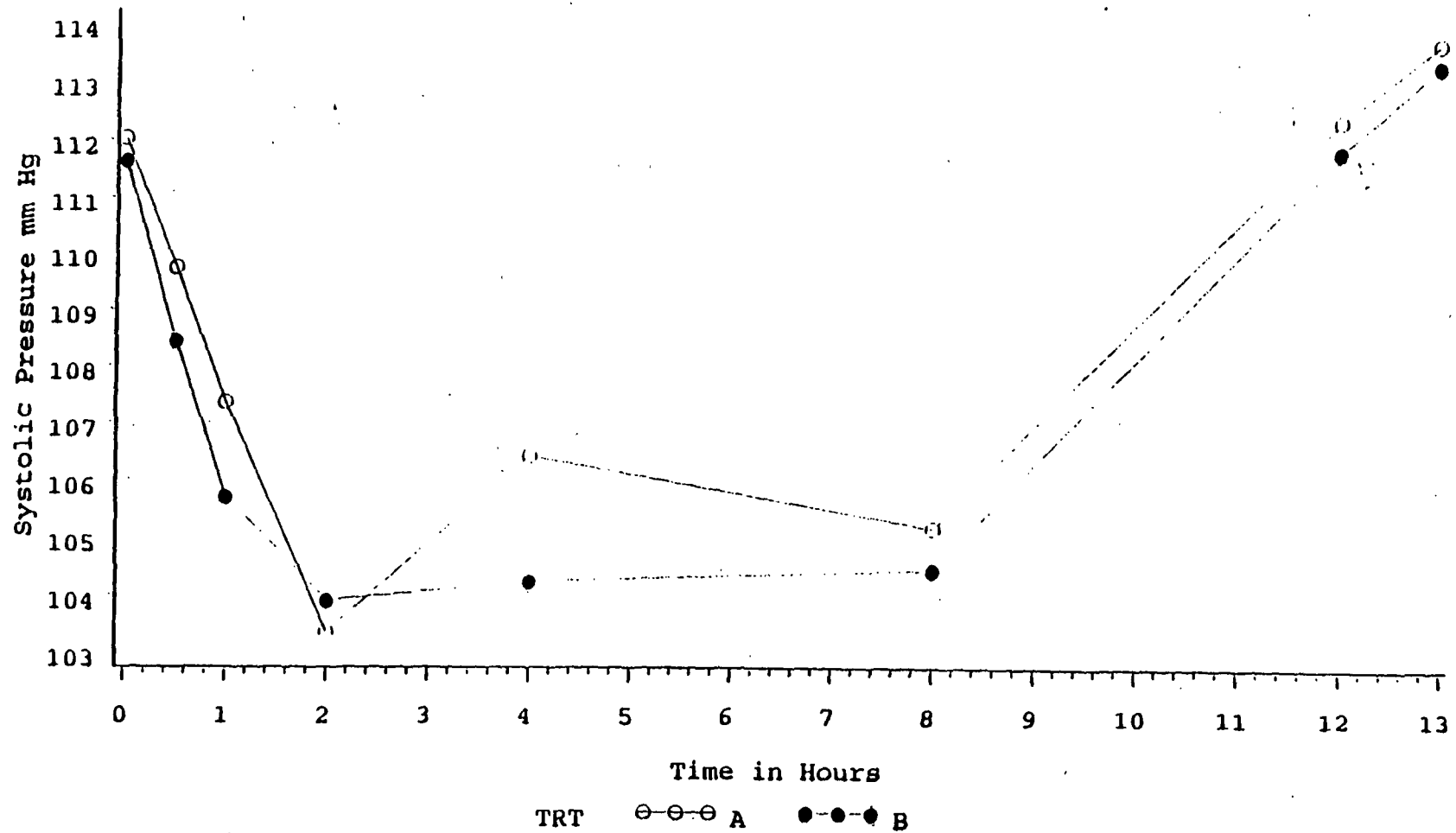
Nitroglycerin (Protocol No. Herc9701)  
Mean Blood Pressure Profiles



## MEAN AND INDIVIDUAL SYSTOLIC BLOOD PRESSURE PROFILES

# Hercon Laboratories, Inc.

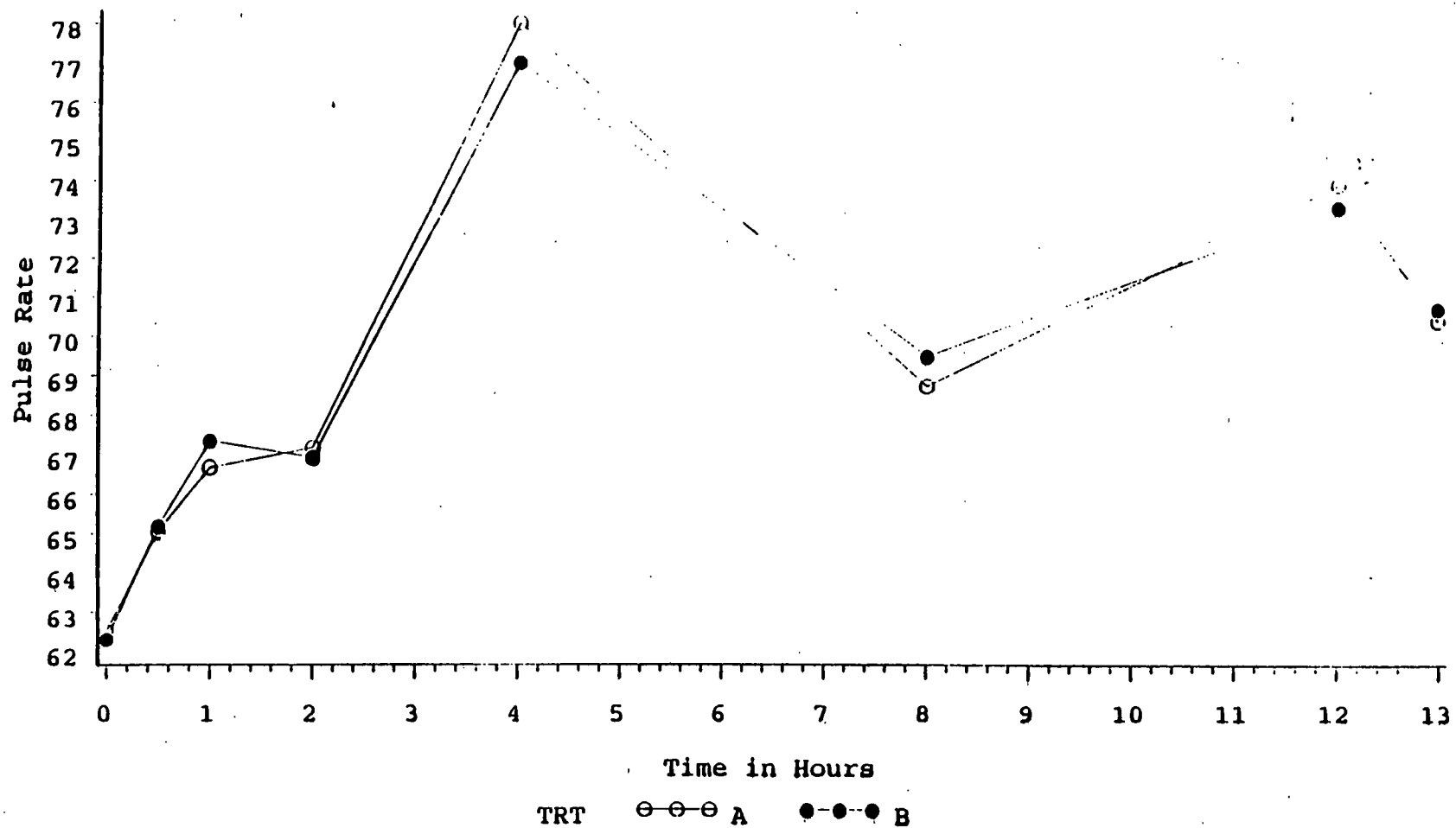
Nitroglycerin (Protocol No. Herc9701)  
Mean Blood Pressure Profiles



## MEAN AND INDIVIDUAL PULSE RATE PROFILES

# Hercon Laboratories, Inc.

Nitroglycerin (Protocol No. Herc9701)  
Mean Pulse Rate Profiles



NOV 24 1995

|                                  |                          |
|----------------------------------|--------------------------|
| Nitroglycerin Transdermal System | Hercon Laboratories, Co. |
| ANDA #89-885; NTS, 0.4 mg/hr     | York, PA                 |
| ANDA #89-884; NTS, 0.2 mg/hr     | Submission Date:         |
| ANDA #89-886; NTS, 0.6 mg/hr     | December 8, 1994         |
| Reviewer: Sikta Pradhan          |                          |
| WP #89885SDW.D94                 |                          |

Review of a Bioequivalence Study, Dissolution Data  
and Waiver Requests

I. INTRODUCTION:

Nitroglycerin is used for the acute relief of angina pectoris. It is used for long term therapy of cardiac insufficiency and cardiac infarction. When given orally, nitroglycerin is extensively metabolized during its first pass, hence alternate routes of administration such as transdermal, are often used. Nitroglycerin transdermal delivery systems are developed in order to control the surface area of application, and the rate of drug delivery, thereby maintaining sustained plasma levels of nitroglycerin over an extended period of time.

This submission is an amendment to the firm's conditionally approved ANDA of Nitroglycerin Transdermal System. The firm has informed the Agency that the product has been reformulated (from a reservoir-type to a face adhesive-type transdermal system) and new manufacturing equipment with different/update controls was used in producing the test product of different formulation. The firm had previously (4/27/93) submitted the results of a bioequivalence study comparing its nitroglycerin transdermal system face adhesive patch 0.4 mg/hr (80 mg NTG/15 cm<sup>2</sup>) with Transderm-Nitro<sup>R</sup> 0.4 mg/hr and Nitro-Dur 0.4 mg/hr. The study had been found unacceptable by the Division of Bioequivalence. The study provided in this amendment is a two-way crossover bioequivalence study conducted on the 10%-reduced-size (13.5 cm<sup>2</sup>) Hercon "face-adhesive" NTS-FA, 0.4 mg/hr patch. The current amendment also contains waiver requests for its 0.2 mg/hr and 0.6 mg/hr products.

Objective:

The objective of this two-way crossover single dose study was to evaluate the bioequivalence of a re-sized (10% reduced) Hercon's Nitroglycerin Transdermal System face adhesive patch (NTS FA) formulation relative to a commercially-available TNG reference patch, Transderm-Nitro<sup>R</sup> of Ciba-Geigy.

In-Vivo Study:

The study was conducted in healthy volunteers. The clinical study

was conducted at ( ) under the supervision of  
Principal Investigator. The analytical  
study was conducted at ( )

Study Dates: April 2, 1994 - May 8, 1994

Study Design:

A randomized 2-way crossover, single dose bioequivalence study including a Hercon nitroglycerin patch formulation and a commercially available nitroglycerin reference patch manufactured by Ciba Geigy was conducted according to protocol # 567794.

Subjects: Forty (40) healthy male and female volunteers (16 males and 24 females) between 18-54 years of age and within  $\pm 15\%$  of their ideal body weight according to Metropolitan Life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Tests (hematology, blood chemistry, urinalysis, etc.) Female subjects tested negative for pregnancy, and were either postmenopausal, surgically sterile, or practiced an acceptable form of birth control (including oral contraceptives) throughout the duration of the study. The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 48 hours before dosing and throughout the period of sample collection.

Treatments:

- A. 1 NTS-FA (Nitroglycerin Transdermal System "face-adhesive" of Hercon) patch (13.5 cm<sup>2</sup>) of 72 mg (0.4 mg/hr) dose, applied for 24 hours; Lot # M0504NG/556; Potency: 97.0%, Lot size: ---- patches Not provided.
- B. 1 Transderm-Nitro<sup>®</sup> (Ciba Geigy) patch (20 cm<sup>2</sup>) of 50 mg (0.4 mg/hr) dose, applied for 24 hours; Lot # C5340; Potency: 99.0%, Expiry date:-----Not provided.

Dose Administration: Each subject received two (2) treatments during the study with a 1-week washout period between them.

Drug Washout Period: One week

Site of Patch Application: The skin at the site of application was clean and dry. Each patch was applied to the chest of each subject approximately halfway between the nipple and medio-clavicular line for 24 hours. The patch including the protective liner was weighed in an analytical balance prior to the application. The protective liner was removed and the patch was applied, and the protective liner was re-weighed. The liner was then transferred into a protective pouch and the pouch was sealed

by folding the top over and securing with tape.

Vital signs: Vital signs such as, heart rate, blood-pressure, respiratory rate, etc. were determined periodically during the study. Times of measurement were: 0 (pre-dose), 0.5, 1, and 6 hours after application of each TNG-patch, and immediately after removal of each patch (24 hours post-dose). All vital sign measurements were taken within 10 minutes before or after the respective blood sampling.

Meal and Food Restrictions: All volunteers fasted for 8 hours prior to and 1 hours after drug administration. Fluids were restricted within one hour of dosing. Standard meal was served. No caffeine-containing food or beverage was served during the study.

Patch Removal:

The patch was removed within 5 minutes after collection of the 24-hour blood sample. Immediately after patch removed, the subject's skin was visually examined and rated for irritation. The patch from each individual subject was transferred into a protective pouch that was properly identified and sealed. Sealed pouches were sent to the sponsor for analysis of residual nitroglycerin content. However, no data on residual contents of nitroglycerin in the used patches were included in the submission.

Blood Sample Collection:

Venous blood samples (5 ml) were collected prior to (0 time) and at 0.5, 1.0, 1.5, 2, 4, 6, 8, 10, 12, 14, 20, 24 hours after patch application. Blood samples were also collected at 24.25, 24.5, 25, and 26 hours after patch removal. Plasma was separated and kept frozen at -70°C until analysis.

Assay Methodology:

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Stability:

Stability was examined by quantitation of quality control samples:

1. Frozen control samples were found to be stable through three freeze/thaw cycles for TNG, 1,2-DNG and 1,3-DNG. The test samples were compared with freshly thawed (once only) samples.

The mean value (n=3) for each level of the quality control has a percent difference from theoretical within  $\pm 15\%$  for TNG, 1,2-DNG and 1,3-DNG for all of the freeze/thaw cycles.

2. Frozen control samples were stable for at least eighteen weeks at  $-70^{\circ}\text{C}$ .
3. TNG, when stored at  $0-4^{\circ}\text{C}$  for 24 hours, was reduced by 24% in concentration at its LOQ level.

### Results:

Forty (40) volunteers (16 males and 24 females) were enrolled in the study. Four subjects withdrew from the study prematurely, and the study was completed by thirty-six (36) subjects. The ANOVA analysis was conducted on 36 subjects. Subjects #123 and 127 voluntarily withdrew from the study after completing Period I and Subjects 126 and 140 withdrew from the study because of an adverse events such as headache, nausea and vomiting. There were no serious adverse events during this study. The adverse events experienced by some subjects have been reported in Table 1 (attached). Mean plasma TNG, 1,2-DNG and 1,3-DNG levels are presented in Tables 2, 3, and 4, respectively. The mean pharmacokinetic parameters derived from the plasma data are presented in Tables 5-7.

Statistics: There were two Groups and two Periods. The dosing of Group 2 in Period 1 was started (4/30/94) a week after the dosing of Group 1 in Period 2 (4/23/94). The firm has indicated that there were no significant Group effects observed for TNG, 1,2-DNG and 1,3-DNG pharmacokinetic parameters, and therefore, the Group term was deleted from the ANOVA model, and the analyses were rerun using the model: ANOVA Model Response = Sequence + Subject (Sequence) + Period + Treatment + Error.

### Comparison of Test and Reference :

For TNG, the differences between the test and reference products in  $\text{AUC}_{0-T}$ ,  $\text{AUC}_{0-14}$ ,  $\text{AUC}_{0-24}$  and  $C_{\text{MAX}}$  were 6% or less and the difference in  $\text{AUC}_{0-\text{inf}}$  was 12%. The 90% confidence intervals (90% CI) for  $\text{LnAUC}_{0-T}$ ,  $\text{LnAUC}_{0-14}$ ,  $\text{LnAUC}_{0-24}$  and  $\text{LnC}_{\text{MAX}}$  of the test product were within the acceptable range of 80-125% (see Table 5). But the 90% confidence interval (90% CI) for  $\text{LnAUC}_{0-\text{inf}}$  was outside the 80-125% limit.

For 1,2-DNG, the differences in  $\text{AUC}_{0-T}$ ,  $\text{AUC}_{0-14}$ ,  $\text{AUC}_{0-24}$ ,  $\text{AUC}_{0-\text{inf}}$  and  $C_{\text{MAX}}$  were 5% or less. The 90% CI for  $\text{LnAUC}_{0-T}$ ,  $\text{LnAUC}_{0-14}$ ,  $\text{LnAUC}_{0-24}$ ,  $\text{LnAUC}_{0-\text{inf}}$  and  $\text{LnC}_{\text{MAX}}$  of the test product were within the acceptable range of 80-125% (see Table 6).

For 1,3-DNG, these differences were 14% or less and the 90%

confidence intervals for  $\text{LnAUC}_{0-T}$ ,  $\text{LnAUC}_{0-14}$ ,  $\text{LnAUC}_{0-24}$  of the test product were outside the acceptable range of 80-125% (see Table 7). The 90% CI for  $\text{LnAUC}_{0-\infty}$  and  $\text{LnC}_{\text{MAX}}$  of the test product were within the acceptable range of 80-125% (see Tables 7).

Table 2  
Mean Plasma TNG Levels (pg/mL)

| Time (hour) | TEST (A)<br>NST-FA (13.5 cm <sup>2</sup> )<br>of Hercon Lot<br>#M0504NG/556<br>N = 36 | Reference (B)<br>Transderm-Nitro <sup>2</sup><br>Lot #C5340 (Ciba<br>Geigy)<br>N = 36 | Signif.<br>Diff. at<br>p=0.05 |
|-------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------|
| Pre-dose    | 0                                                                                     | 0                                                                                     | NS                            |
| 0.5         | 56.38 (152*)                                                                          | 89.35 (93)                                                                            | NS                            |
| 1.0         | 105.46 (92)                                                                           | 128.54 (76)                                                                           | NS                            |
| 1.5         | 101.96 (112)                                                                          | 129.14 (72)                                                                           | NS                            |
| 2.0         | 121.36 (83)                                                                           | 170.42 (76)                                                                           | S                             |
| 4.0         | 191.64 (80)                                                                           | 203.87 (88)                                                                           | NS                            |
| 6.0         | 246.75 (72)                                                                           | 238.36 (84)                                                                           | NS                            |
| 8.0         | 194.58 (65)                                                                           | 234.98 (80)                                                                           | NS                            |
| 10.0        | 196.22 (86)                                                                           | 198.92 (76)                                                                           | NS                            |
| 12.0        | 220.12 (80)                                                                           | 200.85 (68)                                                                           | NS                            |
| 14.0        | 191.90 (69)                                                                           | 215.80 (83)                                                                           | NS                            |
| 20.0        | 257.74 (83)                                                                           | 229.83 (84)                                                                           | NS                            |
| 24.0        | 233.59 (74)                                                                           | 222.19 (80)                                                                           | NS                            |
| 24.25       | 94.74 (57)                                                                            | 113.60 (94)                                                                           | NS                            |
| 24.50       | 42.43 (105)                                                                           | 38.01 (81)                                                                            | NS                            |
| 25.0        | 11.79 (99)                                                                            | 8.53 (111)                                                                            | NS                            |
| 26.0        | 1.84 (378)                                                                            | 1.42 (290)                                                                            | NS                            |

\* Coefficient of Variation  
N = Total Number of Subjects

Table 3  
Mean Plasma 1,2-DNG Levels (ng/mL)

| Time<br>(hour) | TEST (A)<br>NST-FA (13.5<br>cm <sup>2</sup> ) of Hercon<br>Lot<br>#M0504NG/556<br>N = 36 | Reference (B)<br>Transderm-Nitro <sup>R</sup><br>Lot #C5340 (Ciba<br>Geigy)<br>N = 36 | Signif.<br>Diff. at<br>p=0.05 |
|----------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------|
| Pre-dose       | 0                                                                                        | 0                                                                                     |                               |
| 0.5            | 0.26 (199*)                                                                              | 0.42 (103)                                                                            | S                             |
| 1.0            | 1.05 (109)                                                                               | 1.42 (72)                                                                             | S                             |
| 1.5            | 1.70 (96)                                                                                | 2.13 (64)                                                                             | S                             |
| 2.0            | 1.94 (87)                                                                                | 2.52 (60)                                                                             | S                             |
| 4.0            | 2.81 (67)                                                                                | 3.20 (53)                                                                             | S                             |
| 6.0            | 3.14 (62)                                                                                | 3.38 (50)                                                                             | NS                            |
| 8.0            | 3.50 (66)                                                                                | 3.66 (47)                                                                             | NS                            |
| 10.0           | 3.38 (64)                                                                                | 3.49 (45)                                                                             | NS                            |
| 12.0           | 3.23 (64)                                                                                | 3.41 (45)                                                                             | NS                            |
| 14.0           | 3.24 (63)                                                                                | 3.30 (45)                                                                             | NS                            |
| 20.0           | 3.31 (57)                                                                                | 3.56 (45)                                                                             | NS                            |
| 24.0           | 3.20 (56)                                                                                | 3.63 (43)                                                                             | S                             |
| 24.25          | 3.08 (51)                                                                                | 3.50 (38)                                                                             | S                             |
| 24.50          | 2.37 (53)                                                                                | 2.59 (41)                                                                             | NS                            |
| 25.0           | 1.38 (52)                                                                                | 1.49 (39)                                                                             | NS                            |
| 26.0           | 0.67 (57)                                                                                | 0.68 (48)                                                                             | NS                            |

\* Coefficient of Variation  
N = Total Number of Subjects

**Table 4**  
**Mean Plasma 1,3-DNG Levels (ng/mL)**

| Time .<br>(hour) | TEST (A)<br>NST-FA (13.5 cm <sup>2</sup> )<br>of Hercon Lot<br>#M0504NG/556<br>N = 36 | Reference (B)<br>Transderm-<br>Nitro <sup>2</sup> Lot<br>#C5340 (Ciba<br>Geigy)<br>N = 36 | Signif.<br>Diff. at<br>p=0.05 |
|------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------|
| Pre-dose         | 0                                                                                     | 0                                                                                         | 0                             |
| 0.5              | 0.02 (338 <sup>*</sup> )                                                              | 0.04 (181)                                                                                | --                            |
| 1.0              | 0.13 (136)                                                                            | 0.23 (75)                                                                                 | S                             |
| 1.5              | 0.25 (89)                                                                             | 0.36 (55)                                                                                 | --                            |
| 2.0              | 0.31 (72)                                                                             | 0.44 (52)                                                                                 | S                             |
| 4.0              | 0.42 (59)                                                                             | 0.51 (44)                                                                                 | S                             |
| 6.0              | 0.48 (56)                                                                             | 0.54 (43)                                                                                 | S                             |
| 8.0              | 0.50 (58)                                                                             | 0.56 (41)                                                                                 | NS                            |
| 10.0             | 0.51 (57)                                                                             | 0.56 (41)                                                                                 | NS                            |
| 12.0             | 0.50 (57)                                                                             | 0.55 (41)                                                                                 | NS                            |
| 14.0             | 0.49 (59)                                                                             | 0.53 (40)                                                                                 | NS                            |
| 20.0             | 0.51 (57)                                                                             | 0.57 (43)                                                                                 | S                             |
| 24.0             | 0.48 (55)                                                                             | 0.56 (41)                                                                                 | S                             |
| 24.24            | 0.46 (50)                                                                             | 0.55 (36)                                                                                 | S                             |
| 24.50            | 0.38 (52)                                                                             | 0.44 (38)                                                                                 | S                             |
| 25.0             | 0.26 (50)                                                                             | 0.30 (36)                                                                                 | S                             |
| 26.0             | 0.12 (83)                                                                             | 0.15 (55)                                                                                 | S                             |

\* Coefficient of Variation  
N = Total Number of Subjects

**Table 5**  
**Mean Pharmacokinetic Parameters for Plasma TNG**

| <u>Parameters</u>              | <u>Test(A)</u><br>NST-FA (13.5 cm <sup>2</sup> ) of<br>Hercen Lot<br>#M0504NG/556<br>N = 36 | <u>Reference(B)</u><br>Transderm - Nitro <sup>a</sup><br>Lot #C5340 (Ciba<br>Geigy)<br>N = 36 | Ratio A/B x100 | <u>90% C.I.</u><br>Based on LSM.<br>Subj. = 36 |
|--------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------|------------------------------------------------|
| AUC <sub>0-7</sub> (pg.hr/mL)  | 4977 (62)*                                                                                  | 5067 (68)                                                                                     | 99.3           | 83; 115                                        |
| LnAUC <sub>0-7</sub>           | 7.6596 (8)                                                                                  | 7.7408 (8)                                                                                    | 92.6           | 81; 105                                        |
| Geometric mean                 | 2120.91                                                                                     | 2300.31                                                                                       |                |                                                |
| AUC <sub>0-14</sub> (pg.hr/mL) | 2574 (63)                                                                                   | 2755 (65)                                                                                     | 94.1           | 80; 108                                        |
| LnAUC <sub>0-14</sub>          | 8.3000 (8)                                                                                  | 8.3215 (7)                                                                                    | 98.6           | 87; 112                                        |
| Geometric mean                 | 4023.87                                                                                     | 4111.32                                                                                       |                |                                                |
| AUC <sub>0-24</sub> (pg.hr/mL) | 4906 (62)                                                                                   | 4996 (68)                                                                                     | 99.2           | 83; 115                                        |
| LnAUC <sub>0-24</sub>          | 8.3155 (8)                                                                                  | 8.3361 (7)                                                                                    | 98.7           | 87; 112                                        |
| Geometric mean                 | 4086.73                                                                                     | 4171.79                                                                                       |                |                                                |
| AUC <sub>0-48</sub> (pg.hr/mL) | 6397 (48)                                                                                   | 6769 (56)                                                                                     | 85.2           | 59;112                                         |
| LnAUC <sub>0-48</sub>          | 8.6397 (6)                                                                                  | 8.6874 (6)                                                                                    | 88.4           | 72; 108                                        |
| Geometric mean                 | 5651.63 (N = 22)                                                                            | 5927.75 (N = 18)                                                                              |                |                                                |
| C <sub>MAX</sub> (pg/mL)       | 376 (61)                                                                                    | 353 (63)                                                                                      | 108            | 93; 123                                        |
| LnC <sub>MAX</sub>             | 5.7422 (11)                                                                                 | 5.6846 (11)                                                                                   | 107            | 93; 123                                        |
| Geometric mean                 | 311.75                                                                                      | 294.3                                                                                         | 105.9          |                                                |
| T <sub>max</sub> (hour)        | 12.35 (63)                                                                                  | 11.03 (63)                                                                                    | 111            |                                                |
| t <sub>1/2</sub> (hour)        | 0.413 (73)                                                                                  | 0.373 (51)                                                                                    | 106            |                                                |
| KE (1/hour)                    | 2.187 (40)                                                                                  | 2.358 (47)                                                                                    | 94.2           |                                                |

( ) \* Coefficient of Variation  
N = Total Number of Subjects

**Table 6**

**Mean Pharmacokinetic Parameters for Plasma 1,2-DNG**

| <b>Parameters</b>              | <b>Test(A)<br/>NST-FA (13.5 cm<sup>2</sup>) of<br/>Heron Lot<br/>#M0804NG/556<br/>N=36</b> | <b>Reference(B)<br/>Transderm -Nitro<sup>a</sup><br/>Lot #C5340 (Ciba<br/>Geigy)<br/>N=36</b> | <b>Ratio A/B x100</b> | <b>90% C.I.<br/>Based on LSM.<br/>Subj. = 36</b> |
|--------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------|--------------------------------------------------|
| AUC <sub>0-7</sub> (ng.hr/mL)  | 75.3 (62)*                                                                                 | 81.4 (45)                                                                                     | 92.9                  | 85: 101                                          |
| LnAUC <sub>0-7</sub>           | 3.5089 (16)                                                                                | 3.6416 (13)                                                                                   | 88.0                  | 82: 94                                           |
| Geometric mean                 | 33.41                                                                                      | 38.15                                                                                         |                       |                                                  |
| AUC <sub>0-14</sub> (ng.hr/mL) | 39.3 (67)                                                                                  | 42.7 (48)                                                                                     | 92.3                  | 83: 101                                          |
| LnAUC <sub>0-14</sub>          | 4.1253 (13)                                                                                | 4.2500 (11)                                                                                   | 88.7                  | 83: 95                                           |
| Geometric mean                 | 61.89                                                                                      | 70.10                                                                                         |                       |                                                  |
| AUC <sub>0-24</sub> (ng.hr/mL) | 71.9 (63)                                                                                  | 77.6 (46)                                                                                     | 93                    | 85: 101                                          |
| LnAUC <sub>0-24</sub>          | 4.1736 (13)                                                                                | 4.2988 (11)                                                                                   | 88.6                  | 83: 95                                           |
| Geometric mean                 | 64.95                                                                                      | 73.61                                                                                         |                       |                                                  |
| AUC <sub>0-48</sub> (ng.hr/mL) | 76.2 (62)                                                                                  | 82.2 (45)                                                                                     | 93.1                  | 85: 101                                          |
| LnAUC <sub>0-48</sub>          | 4.1851 (13)                                                                                | 4.3083 (11)                                                                                   | 88.8                  | 83: 95                                           |
| Geometric mean                 | 65.70                                                                                      | 74.31                                                                                         |                       |                                                  |
| C <sub>MAX</sub> (ng/mL)       | 3.78 (59)                                                                                  | 4.00 (42)                                                                                     | 94.9                  | 86: 104                                          |
| LnC <sub>MAX</sub>             | 1.2022 (41)                                                                                | 1.2984 (33)                                                                                   | 91.1                  | 85: 97                                           |
| Geometric mean                 | 3.327                                                                                      | 3.667                                                                                         |                       |                                                  |
| T <sub>max</sub> (hour)        | 15.5 (47)                                                                                  | 16.1 (45)                                                                                     | 95.7                  |                                                  |
| t <sub>1/2</sub> (hour)        | 0.8083 (20)                                                                                | 0.7492 (16)                                                                                   | 108                   |                                                  |
| KE (1/hour)                    | 0.8878 (19)                                                                                | 0.9476 (15)                                                                                   | 93.3                  |                                                  |

( ) \* Coefficient of Variation  
N = Total Number of Subjects

**Table 7**

**Mean Pharmacokinetic Parameters for Plasma 1,3-DNG**

| <u>Parameters</u>              | <u>Test(A)</u><br>NST-FA (13.5 cm <sup>2</sup> ) of<br>Heron Lot<br>#M0504NG/556<br>N = 36 | <u>Reference(B)</u><br>Transderm -Nitro <sup>a</sup><br>Lot #C5340 (Ciba<br>Geigy)<br>N = 36 | Ratio A/B x100<br>Based on LSM | <u>90% C.I.</u><br>Based on LSM.<br>Subj. = 36 |
|--------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------|
| AUC <sub>0-7</sub> (ng.hr/mL)  | 11.4 (58)*                                                                                 | 13.06 (41)                                                                                   | 88.0                           | 81: 94                                         |
| LnAUC <sub>0-7</sub>           | 1.8430 (30)                                                                                | 1.8402 (23)                                                                                  | 82.5                           | 77: 88                                         |
| Geometric mean                 | 5.171                                                                                      | 6.298                                                                                        |                                |                                                |
| AUC <sub>0-14</sub> (ng.hr/mL) | 5.88 (59)                                                                                  | 6.88 (42)                                                                                    | 86.3                           | 79: 94                                         |
| LnAUC <sub>0-14</sub>          | 2.2516 (23)                                                                                | 2.4370 (17)                                                                                  | 83.6                           | 78: 90                                         |
| Geometric mean                 | 9.503                                                                                      | 11.44                                                                                        |                                |                                                |
| AUC <sub>0-24</sub> (ng.hr/mL) | 10.9 (58)                                                                                  | 12.39 (42)                                                                                   | 88.2                           | 82: 95                                         |
| LnAUC <sub>0-24</sub>          | 2.2996 (23)                                                                                | 2.4891 (16)                                                                                  | 83.2                           | 78: 89                                         |
| Geometric mean                 | 9.97                                                                                       | 12.05                                                                                        |                                |                                                |
| AUC <sub>0-48</sub> (ng.hr/mL) | 12.0 (55)                                                                                  | 13.31 (41)                                                                                   | 88.6                           | 82: 95                                         |
| LnAUC <sub>0-48</sub>          | 2.3717 (19)                                                                                | 2.5102                                                                                       | 85.6                           | 81: 91                                         |
| Geometric mean                 | 10.71 (N = 35)                                                                             | 12.31                                                                                        |                                |                                                |
| C <sub>MAX</sub> (ng/mL)       | 0.561 (52)                                                                                 | 0.629 (38)                                                                                   | 89.6                           | 84: 96                                         |
| LnC <sub>MAX</sub>             | -0.6795                                                                                    | -0.5316                                                                                      | 86.7                           | 82: 91                                         |
| Geometric mean                 | 0.5089                                                                                     | 0.5877                                                                                       |                                |                                                |
| T <sub>max</sub> (hour)        | 15.8 (43)                                                                                  | 15.02 (46)                                                                                   | 106                            |                                                |
| t1/2 (hour)                    | 1.09 (25)                                                                                  | 1.023 (24)                                                                                   | 106                            |                                                |
| KE (1/hour)                    | 0.670 (23)                                                                                 | 0.715 (24)                                                                                   | 94.7                           |                                                |

( ) \* Coefficient of Variation  
N = Total Number of Subjects

The dissolution (drug release) testing data are presented in Table 8 below:

| Table 8. In Vitro Dissolution Testing (drug release)                                                                                                                                                                                          |                                                                                            |       |     |                                                                                          |       |     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------|-----|------------------------------------------------------------------------------------------|-------|-----|
| Drug: NTS-FA Transdermal System<br>Dose Strengths: 0.4 mg/hr; Label Claim: 72 mg/13.5 cm. sq.<br>ANDA No.: 89-885<br>Firm: Hercon Lab.<br>Submission Date: December 8, 1994                                                                   |                                                                                            |       |     |                                                                                          |       |     |
| I. Conditions for Dissolution Testing:                                                                                                                                                                                                        |                                                                                            |       |     |                                                                                          |       |     |
| USP XXII Paddle (Apparatus 5) RPM: 50<br>No. Units Tested: 12<br>Medium: Water; Volume: 500 mL<br>Specifications: See in Table 9 below<br>Reference Drug: Transderm-Nitro, (0.4 mg/hr); Label Claim: 50 mg/20 cm. sq.<br>Assay Methodology: ( |                                                                                            |       |     |                                                                                          |       |     |
| The test units were mounted to stainless steel blocks and placed in the dissolution medium.                                                                                                                                                   |                                                                                            |       |     |                                                                                          |       |     |
| II. Results of In Vitro Dissolution Testing:                                                                                                                                                                                                  |                                                                                            |       |     |                                                                                          |       |     |
| Sampling Times (Hour)                                                                                                                                                                                                                         | Test Product: Patch<br>Lot # M0504NG/556<br>Strength 0.4 mg/hr; 72 mg/13.5 cm <sup>2</sup> |       |     | Reference Product: Patch<br>Lot # C5340<br>Strength 0.4 mg/hr ; 50 mg/20 cm <sup>2</sup> |       |     |
|                                                                                                                                                                                                                                               | Mean %                                                                                     | Range | %CV | Mean %                                                                                   | Range | %CV |
| 0.5                                                                                                                                                                                                                                           | 60.1                                                                                       |       | 1.0 | 4.5                                                                                      |       | 3.7 |
| 1                                                                                                                                                                                                                                             | 78.9                                                                                       |       | 0.7 | 5.9                                                                                      |       | 3.7 |
| 1.5                                                                                                                                                                                                                                           | 85.2                                                                                       |       | 0.9 | 7.2                                                                                      |       | 4.1 |
| 2                                                                                                                                                                                                                                             | 87.7                                                                                       |       | 1.0 | 8.4                                                                                      |       | 3.9 |
| 4                                                                                                                                                                                                                                             | 90.1                                                                                       |       | 0.8 | 13.0                                                                                     |       | 5.0 |
| 6                                                                                                                                                                                                                                             | 90.1                                                                                       |       | 1.0 | 17.4                                                                                     |       | 5.7 |
| 8                                                                                                                                                                                                                                             | 89.7                                                                                       |       | 2.7 | 21.8                                                                                     |       | 5.8 |
| 10                                                                                                                                                                                                                                            | 90.0                                                                                       |       | 1.4 | 25.8                                                                                     |       | 5.9 |
| 12                                                                                                                                                                                                                                            | 90.5                                                                                       |       | 1.1 | 29.9                                                                                     |       | 6.1 |
| 14                                                                                                                                                                                                                                            | 90.6                                                                                       |       | 1.9 | 35.6                                                                                     |       | 9.6 |
| 20                                                                                                                                                                                                                                            | 91.2                                                                                       |       | 1.6 | 45.8                                                                                     |       | 5.7 |
| 24                                                                                                                                                                                                                                            | 91.2                                                                                       |       | 2.6 | 53.0                                                                                     |       | 5.7 |

Comparative Dissolution- Patch Size Proportionality has been presented in Table 9 (attached).

Formulations:

The compositions of three proposed strengths of Hercon's Nitroglycerin Transdermal System are presented below:

| <u>Components</u>       | <u>Strengths</u>            |                            |                             |
|-------------------------|-----------------------------|----------------------------|-----------------------------|
|                         | <u>0.2 mg/hr</u>            | <u>0.4 mg/hr</u>           | <u>0.6 mg/hr</u>            |
| Patch size              | 6.75 cm <sup>2</sup>        | 13.5 cm <sup>2</sup>       | 20.2 cm <sup>2</sup>        |
| Nitroglycerin           | 36.0 mg                     | 72.0 mg                    | 108.0 mg                    |
| Adhesive Polymer        | 12.6 mg                     | 25.3 mg                    | 37.9 mg                     |
| Adhesive Polymer        | 15.4 mg                     | 30.9 mg                    | 46.3 mg                     |
| Backing Film            | <u>6.750 cm<sup>2</sup></u> | <u>13.5 cm<sup>2</sup></u> | <u>20.25 cm<sup>2</sup></u> |
| Coated Reservoir Weight | 64.1 mg                     | 128 mg                     | 192.71 mg                   |

Comments:

1. For nitroglycerin (TNG) of test product, the 90% confidence interval for  $\text{LnAUC}_{0-7}$ ,  $\text{LnAUC}_{0-14}$ ,  $\text{LnAUC}_{0-24}$ , and  $\text{LnC}_{\text{MAX}}$  were within the 80% to 125% limit. However, the 90% confidence intervals for  $\text{LnAUC}_{0-12}$  remained outside the 80-125% limit.
2. For 1,2-dinitroglycerin of test product, the 90% confidence intervals (CI) for  $\text{LnAUC}_{0-7}$ ,  $\text{LnAUC}_{0-14}$ ,  $\text{LnAUC}_{0-24}$ ,  $\text{LnAUC}_{0-12}$  and  $\text{LnC}_{\text{MAX}}$  were within the acceptable range of 80-125%. However, for 1,3-dinitroglycerin of test product, the 90% confidence intervals (CI) for  $\text{LnAUC}_{0-7}$ ,  $\text{LnAUC}_{0-14}$  and  $\text{LnAUC}_{0-24}$  were outside the acceptable range of 80-125%.
3. The dosing of Group 2 in Period 1 was started (4/30/94) a week after the dosing of Group 1 in Period 2 (4/23/94). In order to establish the fact that the difference between the products are not significant in both groups, the firm should be advised to conduct the analysis using the following statistical model:

Model Y = Seq Group Seq\*Group Subj(Seq Group) Per(Group) Trt  
Trt\*Group.

If Trt\*Group is not significant ( $p > 0.10$ ), Trt\*Group could be dropped from the model. Then the following model could be used:

Model Y = Seq Group Seq\*Group Subj(Seq Group) Per(Group) Trt;

or, Model Y = Seq Subj(Seq) Per(Group) Trt.

In either case, the period effect should be modeled as Per(Group), and not just Per. It would be to the benefit of the firm to try these analyses, since their own analysis did not meet the 90% C.I. criterion.

4. The firm has conducted the in vivo bio-study in 36 subjects, but has reported "40 subjects" in all headings of Tables and Figures.
5. The firm has determined the residual content of nitroglycerin in the used patches. However, the data were not included in the submission.
6. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.4 mg/ml, Lot #M0504NG/556 comparing it to Transderm-Nitro<sup>R</sup>, 0.4 mg/hr, Lot #C5340 manufactured by Ciba-Geigy is incomplete. The first time point in the release rate data submitted to the Agency is a 30-minute time point, however, firm's proposed drug release specifications contain a 15-minute time point. The firm should be advised to establish the appropriate specifications for the release rate of its test product from the data obtained in the drug release study.
7. The drug release data were derived from 6 dosage units of 0.2 mg/hr and 0.6 mg/hr patches. The firm should be advised that in vitro dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range and coefficient of variation data.

#### Recommendations:

1. The in vivo bioequivalence study conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch (72 mg /13.5 cm<sup>2</sup>) of 0.4 mg/hr, Lot #M0504NG/556 comparing it to Transderm-Nitro<sup>R</sup> patch (50 mg /20 cm<sup>2</sup>) of 0.4 mg/hr, Lot #C5340 manufactured by Ciba Geigy is incomplete for reasons cited in comments #1-7 above.

2. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch (13.5 cm<sup>2</sup>), 0.4 mg/ml, Lot #M0504NG/556, comparing it to Transderm-Nitro<sup>2</sup> (Ciba Geigy), 0.4 mg/hr, Lot #C5340 is incomplete due to the reason cited in comment #7 above.
3. The drug release testing conducted on 0.2 mg/hr and 0.6 mg/hr patches is not acceptable for reasons cited in comments #6 & #7 above.
4. The request for waiver of in vivo testing will not be considered until an acceptable in vivo bioequivalence study is conducted by the firm on this drug product.
5. The firm should be advised of the Comments (#1 - #7) and Recommendations, above.

*/S/*  
Sikta Pradhan, Ph. D.  
Division of Bioequivalence  
Review Branch I

RD INITIALED YCHUANG  
FT INITIALED YCHUANG

*/S/*  
Concur: -----  
Keith K. Chan, Ph. D.  
Director, Division of Bioequivalence

Date: *11/24/95*

cc: ANDA # 89-885 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/06-16-95/X:\wpfile\Pradhan\89885SDW.D94

Table 1  
Summary and Frequency of Adverse Events For Each Treatment

| Adverse Event                    | NTS-FA-13.5<br>No. of Events | Transderm-Nitro<br>No. of Events |
|----------------------------------|------------------------------|----------------------------------|
| Headache                         | 33                           | 33                               |
| Nausea                           | 7                            | 8                                |
| Vasovagal Episode                | 1                            | 5                                |
| Vomiting                         | 2                            | 2                                |
| Dizziness                        | 1                            | 1                                |
| Itching at Patch Site            | 2                            | -                                |
| Sore Throat                      | -                            | 1                                |
| Tiredness                        | -                            | 2                                |
| Lightheadedness                  | 1                            | -                                |
| Nosebleed                        | 1                            | -                                |
| Stinging Sensation at Patch Site | 1                            | -                                |
| Anxiety                          | -                            | 1                                |
| Dyspepsia                        | -                            | 1                                |
| Throat Abrasion                  | -                            | 1                                |
| Warm Sensation                   | -                            | 1                                |

Table 9

**NITROGLYCERIN TRANSDERMAL FACE ADHESIVE PRODUCT (NTS-FA)**

**COMPARATIVE DISSOLUTION- PATCH SIZE PROPORTIONALITY**

| Patch Size<br>(sq. cm.) | Nitroglycerin<br>Content (mg) | Lot #<br>Tested | Nitroglycerin released (mg)<br>(average of 6 units) |         |         | Nitroglycerin released (% label claim)<br>(average of 6 units) |         |         |
|-------------------------|-------------------------------|-----------------|-----------------------------------------------------|---------|---------|----------------------------------------------------------------|---------|---------|
|                         |                               |                 | 15 min.                                             | 30 min. | 60 min. | 15 min.                                                        | 30 min. | 60 min. |
| 6.75                    | 36                            | L0974NG/560     | 14.1                                                | 22.7    | 29.8    | 39.2                                                           | 63.1    | 82.8    |
| 13.5                    | 72                            | M0504NG/556     | 27.8                                                | 44.6    | 58.0    | 38.6                                                           | 61.9    | 80.6    |
| 20.25                   | 108                           | L0974NG/561     | 43.0                                                | 69.0    | 89.7    | 39.8                                                           | 63.9    | 83.1    |

Dissolution Specifications: 15 min: ☒ % of label claim  
 30 min: ☒ % of label claim  
 60 min: ☒ % of label claim

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FIGURE I

COMPARATIVE DISSOLUTION PROFILES OF HERCON NTS-FA  
VERSUS TRANSDERM-NITRO

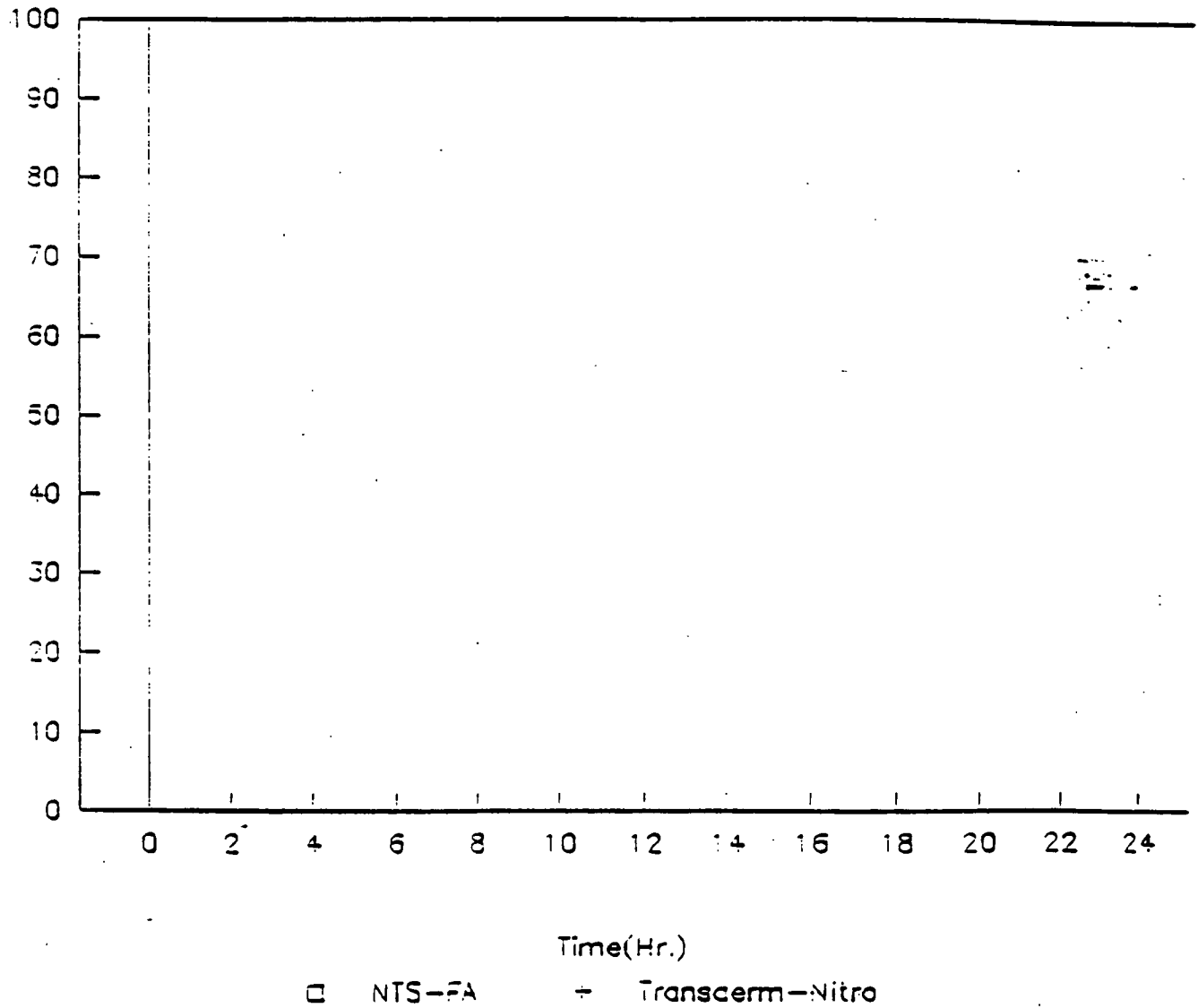
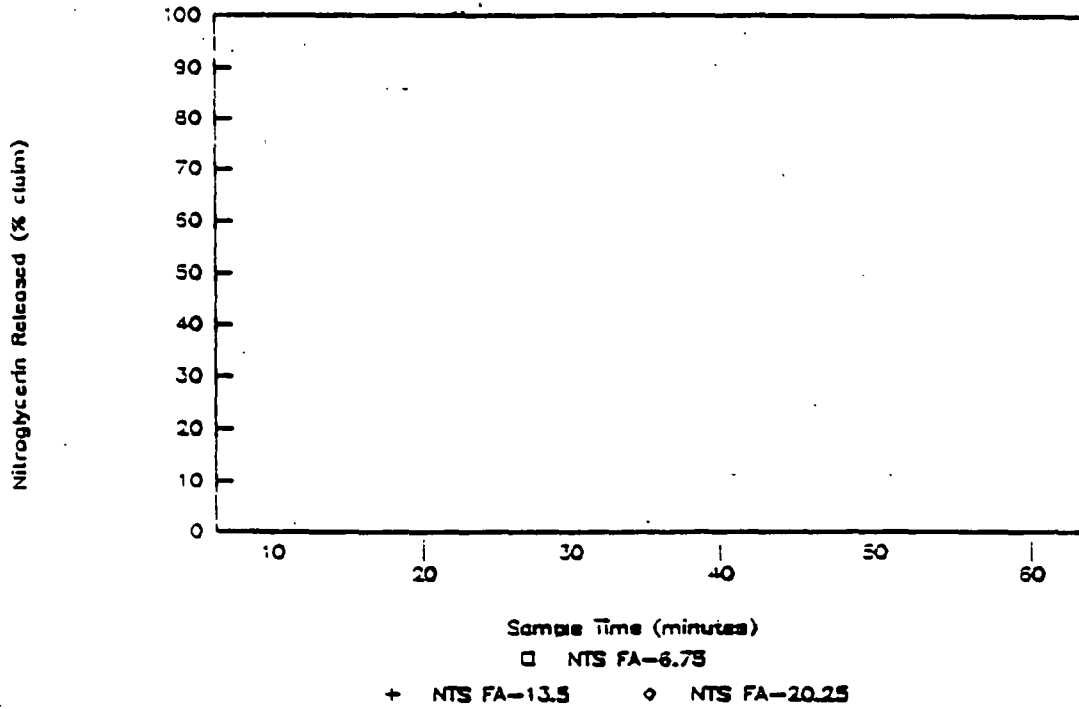


Fig. 2.

# NTS FA COMPARATIVE DISSOLUTION

Patch Size Proportionality



# NTS FA COMPARATIVE DISSOLUTION

Patch Size Proportionality

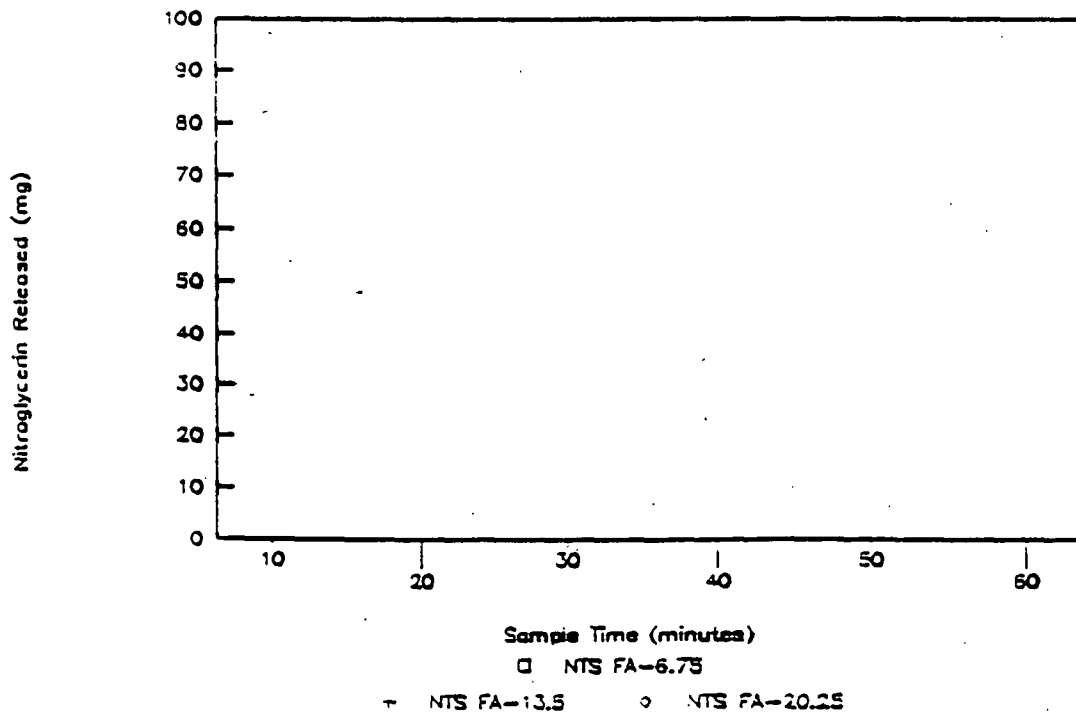
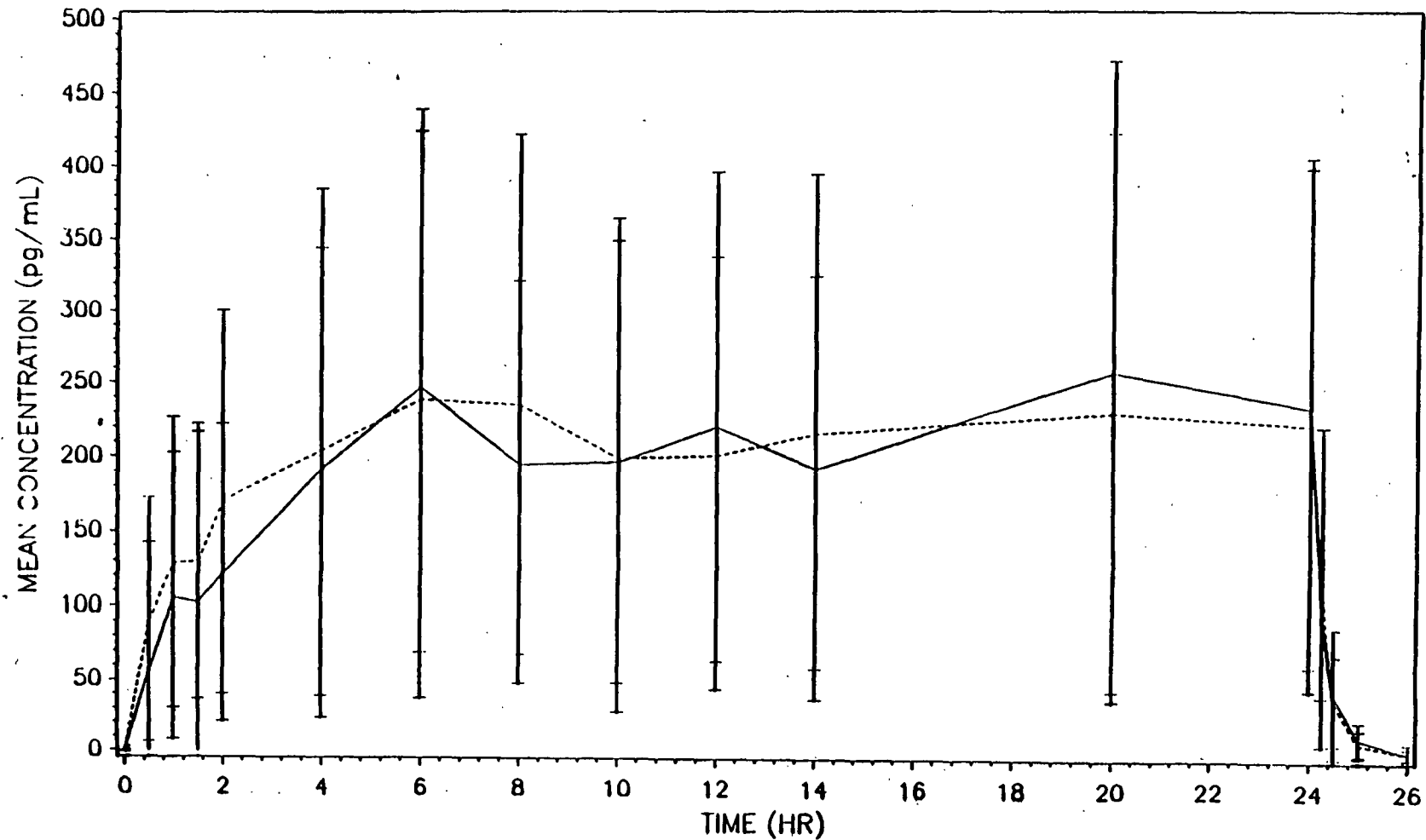


FIGURE # 3

HERCON LABORATORIES CORPORATION  
BIOEQUIVALENCE EVALUATION OF TWO NITROGLYCERIN PATCHES IN 40 HEALTHY VOLUNTEERS  
TRINITROGLYCERIN ANALYSIS: MEAN (+/- SD) PLASMA CONCENTRATION VS. TIME



TREATMENT: — A: NTS FA-13.5      - - - B: TRANSDERM-NITRO

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FIGURE 4

HERCON LABORATORIES CORPORATION  
BIOEQUIVALENCE EVALUATION OF TWO NITROGLYCERIN PATCHES IN 40 HEALTHY VOLUNTEERS  
1,2-DINITROGLYCERIN ANALYSIS: MEAN (+/- SD) PLASMA CONCENTRATION VS. TIME

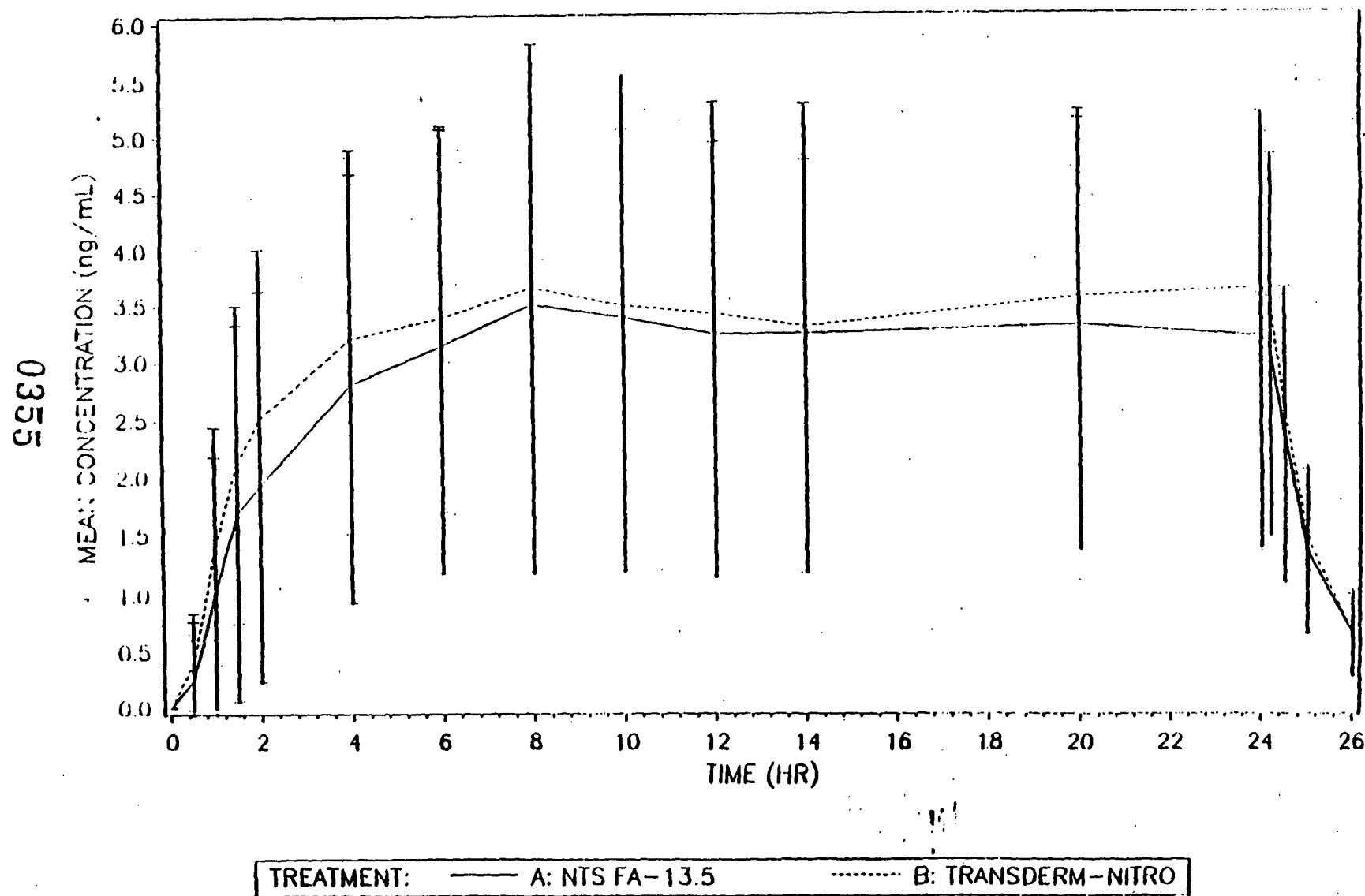
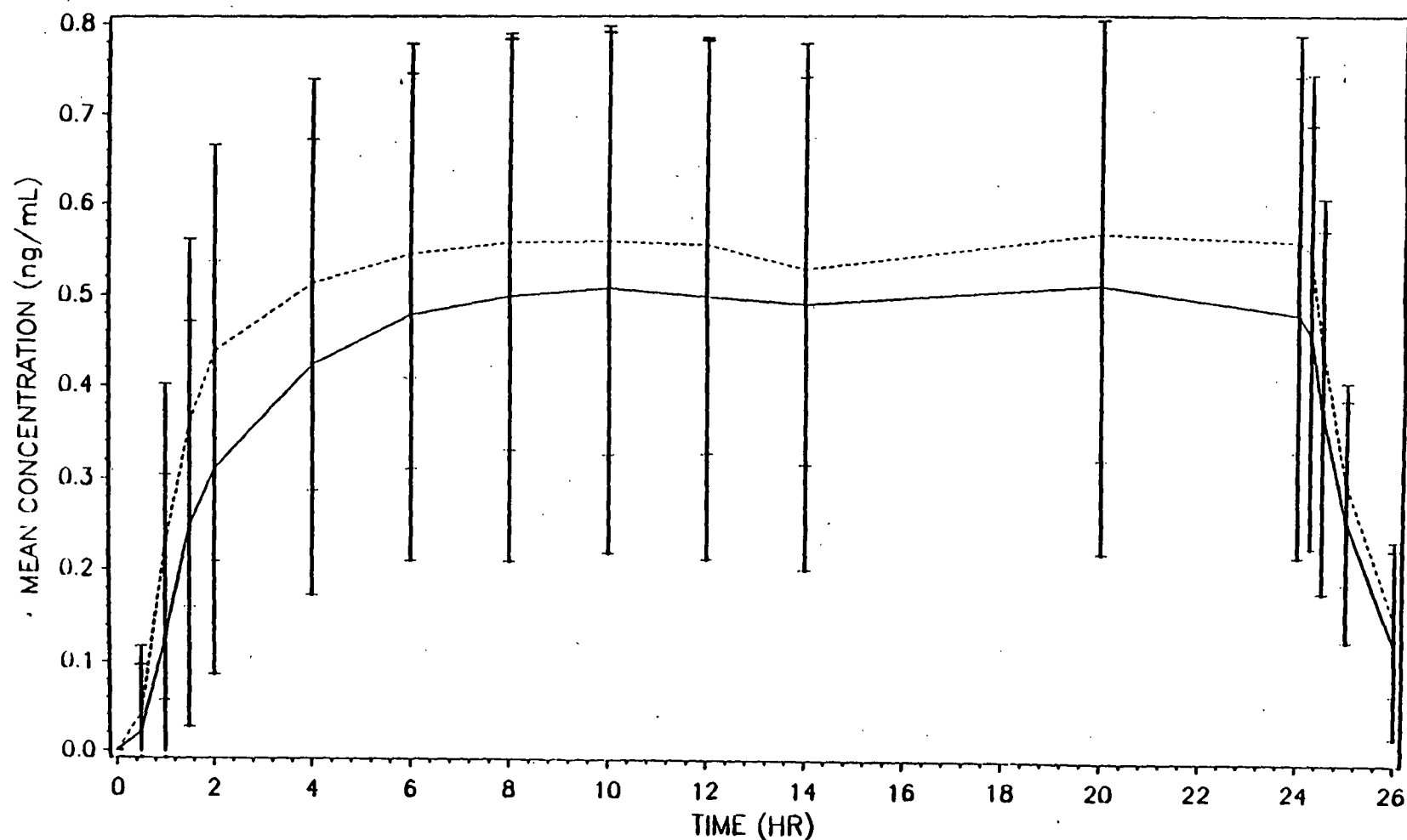


FIGURE 5

HERCON LABORATORIES CORPORATION  
BIOEQUIVALENCE EVALUATION OF TWO NITROGLYCERIN PATCHES IN 40 HEALTHY VOLUNTEERS  
1,3-DINITROGLYCERIN ANALYSIS: MEAN (+/- SD) PLASMA CONCENTRATION VS. TIME



TREATMENT: — A: NTS FA-13.5      - - - B: TRANSDERM-NITRO

MAY 8 1994

3.1

Nitroglycerin Transdermal System  
0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr  
ANDA #89-884, 89-885, 89-886  
Reviewer: YC Huang  
89885S.493

Hercon Laboratories  
York, PA  
Submission date:  
April 27, 1993

**Review of A Bioequivalence Study**

(a repeated insult patch test and waiver request)

**Introduction** The submission is an amendment to the firm's conditionally-approved ANDA of this drug product (December 8, 1987). The firm has stated that the product has been reformulated and that the formulation, methods, and controls differ substantially from those for the previous formulation. The firm has also stated that all materials previously submitted to this application are replaced by this amendment and that all previously submitted information should be disregarded.

The submission contains the results of two in vivo studies: (1) Bioequivalence Evaluation of Three Glyceryl Trinitrate patches in 36 Healthy Volunteers, and (2) Adhesive Wear Properties and Repeated Insult Patch Test (RIPT) to Three Transdermal Nitroglycerin Patches. Waiver requests for the 0.2 mg/hr and 0.6 mg/hr strengths of the test product have also been made.

**I. Bioequivalence study**

**Objective**

The objective of the bioequivalence study was to compare the bioavailability of nitroglycerin (NTG) and its 1,2- and 1,3-dinitroglycerin metabolites (1,2-DNG and 1,3-DNG) following a new NTG patch with two commercially available NTG patches.

**Products tested**

- |                  |                                                                                                                                                                                  |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Test (A)         | Nitroglycerin Transdermal System, containing 80 mg of NTG, delivering NTG at 0.4 mg/hour (10 mg/24 hours), manufactured by Hercon. (Lot #Y0632NG/487). Batch size was not given. |
| Reference I (B)  | Transderm Nitro®, containing 50 mg of NTG, delivering NTG at 0.4 mg/hour (10 mg/24 hours), manufactured by Ciba Geigy. (Lot #1M149250)                                           |
| Reference II (C) | Nitro-Dur®, containing 80 mg of NTG, delivering NTG at 0.4 mg/hour (10 mg/24 hours), manufactured by Key Pharmaceuticals. (Lot#D2212411)                                         |

**Study design** The study was conducted following a three-treatment, three-period, six-sequence crossover design. The washout period was at least three days.

| <u>Sequence</u> | <u>Subject Number</u>  |
|-----------------|------------------------|
| A B C           | 5, 6, 12, 23, 25, 34   |
| B C A           | 1, 7, 8, 24, 29, 31    |
| C A B           | 3, 10, 15, 19, 27, 32  |
| A C B           | 18, 21, 22, 28, 35, 36 |
| C B A           | 2, 4, 9, 13, 16, 30    |
| B A C           | 11, 14, 17, 20, 26, 33 |

[Reviewer's Note: Subjects were divided into three groups.]

The dosing times for each group are as follows:

| <u>Group No.</u> | <u>Subject No.</u>          | <u>Dosing Time</u>       |
|------------------|-----------------------------|--------------------------|
| 1                | 1 - 9 (N=9)                 | 6/18/92, 6/25/92, 7/2/92 |
| 2                | 10, 12-18, 20-22, 24 (N=12) | 6/20/92, 6/27/92, 7/4/92 |
| 3                | 11, 19, 23, 25-36 (N=15)    | 6/23/92, 6/30/92, 7/7/92 |

Site of patch application Each patch was applied to the subject's chest in the mid-clavicular line over the fifth intercostal space, on either the left or right side of the thorax for 24 hours. The whole patch (i.e., including the protective liner) was weighed using an analytical balance prior to the application and the weight was recorded.

#### Study sites and investigators

Investigators were:  
(Data analysis), and

(Assay)

#### Subject Selection

##### 1. Pre-study health screening

The pre-study screening was performed within 14 days prior to the study. The screening consisted of an interview, physical examination, EKG, and laboratory tests, including a urinary drug screen.

##### 2. Pre-Study NTG screening (test-treatment)

All subjects satisfying health screening criteria underwent an 8-hour clinical test-treatment with one of the study's two reference NTG patches. The purpose of this test was to try to identify and screen out those subjects unable to tolerate NTG treatment. This test-treatment was conducted during the 14-day period between health screening and start of the first formal NTG treatment. No blood samples were taken during this test-treatment.

Forty-three subjects entered the study and seven were dropped during the test-treatment. Of the 36 subjects who received formal treatment, five subjects (#8, #20, #29, #30, and #36) dropped after the first period, one subject (#19) dropped after the second period, and 30 subjects completed all three treatments. The demographics for subjects who received formal treatment were as follows: mean age 30.4 years (range, 18-46 years), mean height 69.8 inches (range, 64.5-76 inches), and mean weight 160.3 pounds (range, 124-223 pounds). The weights were within  $\pm 15\%$  of the ideal weight.

Confinement and restriction Subjects were confined in the clinical facility from the evening prior to dosing until after the collection of 26-hour blood sample, for a total of 38 hours. Subjects were abstained from any caffeine-containing foods or beverages for 48 hours prior to each patch application. Subjects were told not to engage in strenuous exercise or lie down flat until at least five hours after patch application.

Blood samples Venous blood samples (8 mL each) were collected at the following times: 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 9, 12, 16, 20, 24, 24.25, 25, and 26 hours after dosing. Blood tubes were placed into an ice-water-bath at 4 degrees C within 5 seconds of blood withdrawals and centrifugation was completed in a cooled centrifuge within 15 minutes of blood withdrawals. Plasma samples were frozen at -70 degrees C until analysis.

#### Assay

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

ASSAY

Stability: The firm did not submit the stability data of the study samples.

Vital signs Vital signs (heart rate, blood pressure, and respiratory rate) were measured at the following times: 0 (pre-dose), 0.5, 1, 4, and 12 hours after patch application, and immediately after removal of each patch (24 hours post-dose). At each vital sign assessment period, subjects were interviewed to elicit information on possible side effects.

Patch removal The patch was removed within 5 minutes after collection of the 24-hour blood sample. Immediately after patch removal, the subject's skin at the application site was visually examined and assigned a score for irritation. The site of application was wiped twice with an individual alcohol swab. Patch and swab were transferred into separate protective pouches. The used patches were analyzed for the residual NTG contents.

Waiver request To support the waiver request, the firm has submitted the in vitro drug release data and formulation information of the test products.

Formulation of the test product

| <u>Component</u> | 0.2 mg/hr           | 0.4 mg/hr            | 0.6 mg/hr            |
|------------------|---------------------|----------------------|----------------------|
|                  | theory qty.         | theory qty.          | theory qty.          |
|                  | <u>per patch</u>    | <u>per patch</u>     | <u>per patch</u>     |
| --- Patch size-- | 7.5 cm <sup>2</sup> | 15.0 cm <sup>2</sup> | 22.5 cm <sup>2</sup> |
| Nitroglycerin    |                     |                      |                      |
| Adhesive Polymer |                     |                      |                      |
| Adhesive Polymer |                     |                      |                      |
| Coated Reservoir | 71.16 mg            | 142.3 mg             | 213.5 mg             |
| Weight           |                     |                      |                      |

Drug release study The dissolution (drug release) testing was conducted using the following conditions:

USP Apparatus II (paddle) at 50 rpm  
 Medium: 500 mL of deionized water at 32° C ( $\pm$  0.5° C)  
 Sampling times: 15, 30, and 60 minutes  
 Analytical method: (

The test units were mounted to stainless steel weights and placed in the dissolution medium.

The results were reported as follows: (N = 6)

| Key                           | Content Claim |       | In-Vitro release |      |              |      |              |      |
|-------------------------------|---------------|-------|------------------|------|--------------|------|--------------|------|
|                               | (mg)          | mg/hr | 15 min<br>mg     | %    | 30 min<br>mg | %    | 60 min<br>mg | %    |
| (Lot #:D2212411)              | 80            | 0.4   | 23.5             | 29.4 | 37.4         | 46.8 | 52.2         | 65.2 |
| Ciba<br>(Lot #:1M149250)      | 50            | 0.4   | 1.76             | 3.52 | 2.25         | 4.50 | 3.02         | 6.04 |
| Hercon<br>(Lot #:E0692NG/488) | 40            | 0.2   | 15.6             | 39.0 | 26.3         | 65.8 | 35.6         | 89.0 |
| Hercon<br>(Lot #:Y0632NG/487) | 80            | 0.4   | 33.0             | 41.2 | 52.8         | 66.0 | 68.7         | 85.9 |
| Hercon<br>(Lot #:E0762NG/489) | 120           | 0.6   | 45.4             | 37.8 | 73.9         | 61.6 | 96.0         | 80.0 |

Data analysis The following pharmacokinetic parameters were derived from the plasma concentration-time data:

Cmax and Tmax

Cmin: the lowest concentration during steady-state (where the steady-state interval was determined statistically)

Cav: the average concentration during steady-state

DF (degree of fluctuation):  $100\% \times (C_{max} - C_{min}) / C_{av}$

AUC(0-24), AUC(0-last), AUC(0- $\infty$ ): areas under the curve were calculated based on linear and/or log-linear trapezoidal rules.

## Results

1. Thirty-six (36) subjects received formal treatment. Five subjects (#8, 20, 29, 30, and 36) dropped after the first period and one subject, (#19) dropped after the second period. That is to say 32 subjects received treatment A (Hercon), 33 subjects received treatment B (Transderm-Nitro) and 32 received treatment C (Nitro-Dur). Among them, 30 subjects received both treatments A and B and 31 subjects received both

treatments A and C. The firm reported only 30 sets of data for treatment C, stating that there were no samples between hour 9-24 (5 time points, see page 257) for subject #3 after treatment C.

2. The mean Cp-t profiles and summaries of pharmacokinetic parameters for NTG, 1,2- and 1,3-DNG as reported in the submission (pages 306-308) are shown in Tables 1-3. The corresponding figure is shown in Figure 1 (page 310). The results of Cmax, Cmin, Cav, and DF are summarized in Tables 4-6. The results of 90% confidence intervals are summarized in Tables 7-9.
3. For NTG, the 90% confidence intervals for both Cmax and AUC were outside the acceptable range of 80-125% (for both Hercon versus Transderm-Nitro and Hercon versus Key, see Table 7). The reported Cmax value of Hercon's patch was 27% higher than those of Transderm-Nitro and Nitro-Dur and the AUC(0-24) value of Hercon's patch was 12% and 18% higher than those of Transdermal Nitro and Nitro-dur, respectively. Comparison between Hercon's NTG patch and Transderm-Nitro: For 1,2-DNG, the Cmax and AUC(0-24) values of Hercon's patch were 11% and 14% higher than those of Transderm-Nitro, respectively. The 90% confidence intervals for these two parameters were within the range of 80-125%. For 1,3-DNG, the Cmax and AUCs values of Hercon's patch were 2 to 5% higher than those of Transderm-Nitro and the 90% confidence intervals were within the range of 80-125%. Comparison between Hercon's NTG patch and Nitro-Dur: For 1,2-DNG, the Cmax and AUC(0-24) values of Hercon's patch were 15% and 19% higher than those of Nitro-Dur. While the 90% confidence interval for Cmax value is within the range of 80-125%, the value of AUC(0-24) was outside the 80-125% range (i.e., %, Table 8). For 1,3-DNG, the Cmax and AUC values were 8% to 13% higher than those of Nitro-Dur. The 90% confidence intervals for both Cmax and AUC are within the range of 80-125%.
4. The summary of adverse events was reported on page 87 in the submission. The adverse events included headache, nausea, dizziness, lightheadedness and the reactions to the patch site included erythema, stinging/burning, irritation/redness, and itching. The incidences of the adverse events and the reactions to the patch application sites were comparable among the test and the reference products.

Table 1: Mean NTG data

| Time (hr)                | Hercon |     |    | Transderm Nitro |     |    | Nitro-Dur |     |    |
|--------------------------|--------|-----|----|-----------------|-----|----|-----------|-----|----|
|                          | Mean   | %CV | N  | Mean            | %CV | N  | Mean      | %CV | N  |
| 0                        | 0      |     |    | 0               |     |    | 0         |     |    |
| 0.5                      | 0.134  | 125 | 18 | 0.117           | 73  | 16 | 0.110     | 70  | 20 |
| 1.0                      | 0.241  | 155 | 25 | 0.179           | 128 | 26 | 0.130     | 79  | 27 |
| 1.5                      | 0.224  | 117 | 31 | 0.160           | 110 | 30 | 0.133     | 73  | 29 |
| 2.0                      | 0.199  | 101 | 32 | 0.176           | 122 | 31 | 0.121     | 65  | 30 |
| 4.0                      | 0.223  | 89  | 32 | 0.213           | 69  | 32 | 0.180     | 79  | 30 |
| 6.0                      | 0.249  | 94  | 32 | 0.274           | 102 | 32 | 0.150     | 74  | 31 |
| 9.0                      | 0.269  | 90  | 32 | 0.264           | 93  | 32 | 0.207     | 83  | 31 |
| 12.0                     | 0.268  | 102 | 32 | 0.212           | 99  | 32 | 0.193     | 90  | 31 |
| 16.0                     | 0.239  | 87  | 32 | 0.255           | 115 | 32 | 0.262     | 82  | 31 |
| 20.0                     | 0.265  | 92  | 32 | 0.286           | 83  | 32 | 0.336     | 89  | 30 |
| 24.0                     | 0.334  | 119 | 32 | 0.246           | 122 | 32 | 0.198     | 90  | 31 |
| 24.25                    | 0.168  | 102 | 30 | 0.118           | 82  | 32 | 0.148     | 65  | 29 |
| 24.50                    | 0.143  | 164 | 24 | 0.0819          | 80  | 24 | 0.073     | 48  | 22 |
| 25.0                     | 0.102  | 133 | 12 | 0.0539          | 45  | 16 | 0.0537    | 71  | 10 |
| 26.0                     | 0.131  | 190 | 10 | 0.0442          | 35  | 8  | 0.0639    | 43  | 3  |
| C <sub>max</sub> (ng/mL) | 0.555  | 80  | 31 | 0.416           | 81  | 30 | 0.417     | 70  | 30 |
| AUC(0-24) (hr-ng/mL)     | 5.96   | 75  | 31 | 5.59            | 92  | 30 | 5.01      | 69  | 30 |
| AUC(0-last)              | 6.11   | 75  | 31 | 5.68            | 93  | 30 | 5.09      | 68  | 30 |
| AUC(0-∞)                 | 7.63   | 70  | 21 | 7.33            | 82  | 19 | 6.38      | 54  | 21 |
| T <sub>max</sub> (hr)    | 13.36  | 60  | 31 | 12.94           | 60  | 30 | 16.02     | 39  | 30 |
| K (hr <sup>-1</sup> )    | 1.795  | 75  | 21 | 1.675           | 79  | 19 | 1.957     | 68  | 21 |
| T <sub>1/2</sub> (hr)    | 0.80   | 138 | 21 | 1.43            | 244 | 19 | 0.73      | 128 | 21 |

Table 2: Mean 1,2-DNG data

| Time<br>(hr)                | Hercon |     |    | Transderm Nitro |     |    | Nitro-Dur |     |    |
|-----------------------------|--------|-----|----|-----------------|-----|----|-----------|-----|----|
|                             | Mean   | %CV | N  | Mean            | %CV | N  | Mean      | %CV | N  |
| 0                           | 0      |     |    | 0               |     |    | 0         |     |    |
| 0.5                         | 0.527  | 72  | 10 | 0.316           | 60  | 12 | 0.339     | 63  | 15 |
| 1.0                         | 0.949  | 76  | 28 | 0.861           | 66  | 31 | 0.733     | 55  | 30 |
| 1.5                         | 1.546  | 70  | 32 | 1.334           | 53  | 32 | 1.073     | 48  | 32 |
| 2.0                         | 2.009  | 61  | 32 | 1.635           | 47  | 33 | 1.346     | 43  | 32 |
| 4.0                         | 2.695  | 42  | 32 | 2.351           | 38  | 33 | 1.936     | 42  | 32 |
| 6.0                         | 2.960  | 40  | 32 | 2.592           | 34  | 33 | 2.198     | 39  | 32 |
| 9.0                         | 3.205  | 37  | 32 | 2.727           | 33  | 32 | 2.530     | 39  | 31 |
| 12.0                        | 3.180  | 36  | 32 | 2.613           | 37  | 32 | 2.755     | 42  | 31 |
| 16.0                        | 3.165  | 35  | 32 | 2.607           | 30  | 32 | 2.694     | 36  | 31 |
| 20.0                        | 3.041  | 38  | 32 | 2.851           | 31  | 32 | 2.925     | 35  | 31 |
| 24.0                        | 3.333  | 38  | 32 | 2.900           | 31  | 32 | 2.778     | 34  | 31 |
| 24.25                       | 3.163  | 34  | 32 | 2.736           | 26  | 33 | 2.742     | 40  | 31 |
| 24.50                       | 2.551  | 36  | 32 | 2.2829          | 32  | 33 | 2.119     | 40  | 32 |
| 25.0                        | 1.727  | 37  | 32 | 1.3829          | 36  | 33 | 1.358     | 45  | 32 |
| 26.0                        | 0.878  | 52  | 32 | 0.569           | 35  | 33 | 0.595     | 54  | 32 |
| C <sub>max</sub><br>(ng/mL) | 3.732  | 34  | 31 | 3.247           | 28  | 30 | 3.215     | 35  | 30 |
| AUC(0-24)<br>(hr-ng/mL)     | 69.17  | 37  | 31 | 59.13           | 31  | 30 | 57.05     | 36  | 30 |
| AUC(0-last)                 | 73.01  | 37  | 31 | 62.21           | 31  | 30 | 60.18     | 36  | 30 |
| AUC(0-∞)                    | 75.76  | 35  | 30 | 62.91           | 31  | 30 | 61.02     | 36  | 30 |
| T <sub>max</sub> (hr)       | 18.02  | 35  | 31 | 16.62           | 42  | 30 | 18.53     | 27  | 30 |
| K (hr <sup>-1</sup> )       | 0.708  | 25  | 30 | 0.845           | 14  | 30 | 0.814     | 20  | 30 |
| T <sub>½</sub> (hr)         | 1.08   | 46  | 30 | 0.84            | 15  | 30 | 0.88      | 21  | 30 |

Table 3: Mean 1,3-DNG data

| Time<br>(hr)                | Hercon |     |    | Transderm Nitro |     |    | Nitro-Dur |     |    |
|-----------------------------|--------|-----|----|-----------------|-----|----|-----------|-----|----|
|                             | Mean   | %CV | N  | Mean            | %CV | N  | Mean      | %CV | N  |
| 0                           | 0      |     |    | 0               |     |    | 0         |     |    |
| 0.5                         | 0.174  | 51  | 4  | 0.151           | 18  | 2  | 0.122     | 12  | 4  |
| 1.0                         | 0.291  | 95  | 17 | 0.241           | 59  | 20 | 0.247     | 63  | 15 |
| 1.5                         | 0.312  | 84  | 29 | 0.325           | 60  | 29 | 0.283     | 57  | 26 |
| 2.0                         | 0.371  | 59  | 31 | 0.413           | 58  | 30 | 0.314     | 57  | 31 |
| 4.0                         | 0.493  | 60  | 32 | 0.553           | 50  | 32 | 0.440     | 69  | 32 |
| 6.0                         | 0.555  | 67  | 32 | 0.553           | 56  | 33 | 0.480     | 61  | 32 |
| 9.0                         | 0.577  | 72  | 32 | 0.571           | 56  | 32 | 0.532     | 63  | 31 |
| 12.0                        | 0.572  | 62  | 32 | 0.528           | 57  | 32 | 0.579     | 67  | 31 |
| 16.0                        | 0.610  | 68  | 32 | 0.579           | 63  | 32 | 0.573     | 77  | 31 |
| 20.0                        | 0.582  | 72  | 32 | 0.587           | 51  | 32 | 0.614     | 62  | 31 |
| 24.0                        | 0.607  | 59  | 32 | 0.633           | 60  | 32 | 0.560     | 65  | 31 |
| 24.25                       | 0.573  | 61  | 32 | 0.555           | 56  | 33 | 0.587     | 61  | 31 |
| 24.50                       | 0.491  | 64  | 32 | 0.507           | 55  | 33 | 0.455     | 66  | 32 |
| 25.0                        | 0.367  | 51  | 32 | 0.351           | 59  | 33 | 0.3227    | 62  | 32 |
| 26.0                        | 0.276  | 68  | 29 | 0.214           | 58  | 28 | 0.219     | 55  | 23 |
| C <sub>max</sub><br>(ng/mL) | 0.754  | 56  | 31 | 0.728           | 54  | 30 | 0.683     | 64  | 30 |
| AUC(0-24)<br>(hr-ng/mL)     | 12.96  | 64  | 31 | 12.43           | 56  | 30 | 12.10     | 66  | 30 |
| AUC(0-last)                 | 13.75  | 63  | 31 | 13.14           | 56  | 30 | 12.79     | 66  | 30 |
| AUC(0-∞)                    | 15.01  | 61  | 29 | 13.61           | 55  | 30 | 13.31     | 64  | 30 |
| T <sub>max</sub> (hr)       | 17.21  | 42  | 31 | 16.45           | 48  | 30 | 19.49     | 26  | 30 |
| K (hr <sup>-1</sup> )       | 0.469  | 47  | 29 | 0.570           | 29  | 30 | 0.553     | 42  | 30 |
| T <sub>1/2</sub> (hr)       | 2.22   | 110 | 29 | 1.48            | 86  | 30 | 1.55      | 61  | 30 |

**Table 4. The Mean Values of Cmin, Cmax, Cav, and DF for NTG at the Steady State**

| Parameter          | Treatment A<br>Mean (%CV) | Treatment B<br>Mean (%CV) | Treatment C<br>Mean (%CV) |
|--------------------|---------------------------|---------------------------|---------------------------|
| Cmin (9-24), ng/mL | 0.135 (107)               | 0.146 (110)               | 0.113 (81)                |
| Cmax (9-24), ng/mL | 0.504 ( 82)               | 0.393 ( 87)               | 0.401 (76)                |
| Cav (9-24), ng/mL  | 0.266 ( 74)               | 0.247 ( 95)               | 0.246 (73)                |
| DF (9-24), %       | 129.0 ( 55)               | 104.1 ( 46)               | 110.7 (50)                |

Treatment A = Hercon's NTG patch, 0.4 mg/hr

Treatment B = Transderm-Nitro, 0.4 mg/hr

Treatment C = Nitro-Dur, 0.4 mg/hr

For both treatments A and B, N=31. For treatment C, N=30.

The steady state was determined to be between hour 9-24.

**Table 5. The Mean Values of Cmin, Cmax, Cav, and DF for 1,2-DNG at the Steady State**

| Parameter          | Treatment A<br>Mean (%CV) | Treatment B<br>Mean (%CV) | Treatment C<br>Mean (%CV) |
|--------------------|---------------------------|---------------------------|---------------------------|
| Cmin (9-24), ng/mL | 2.703 ( 39)               | 2.285 ( 30)               | 2.354 (39)                |
| Cmax (9-24), ng/mL | 3.712 ( 35)               | 3.148 ( 31)               | 3.154 (35)                |
| Cav (9-24), ng/mL  | 3.170 ( 35)               | 2.708 ( 30)               | 2.749 (35)                |
| DF (9-24), %       | 32.5 ( 69)                | 32.3 ( 46)                | 30.2 (46)                 |

For treatment A, N=31. For both treatments B and C, N=30.

The steady state was determined to be between hour 9-24.

**Table 6. The Mean Values of Cmin, Cmax, Cav, and DF for 1,3-DNG at the Steady State**

| Parameter          | Treatment A<br>Mean (%CV) | Treatment B<br>Mean (%CV) | Treatment C<br>Mean (%CV) |
|--------------------|---------------------------|---------------------------|---------------------------|
| Cmin (4-24), ng/mL | 0.442 ( 69)               | 0.425 ( 60)               | 0.409 (74)                |
| Cmax (4-24), ng/mL | 0.735 ( 59)               | 0.721 ( 55)               | 0.668 (65)                |
| Cav (4-24), ng/mL  | 0.588 ( 64)               | 0.559 ( 56)               | 0.555 (66)                |
| DF (4-24), %       | 50.9 ( 49)                | 55.9 ( 67)                | 48.4 (34)                 |

For treatment A, N=31. For both treatments B and C, N=30.

The steady state was determined to be between hour 4-24.

**Table 7. Results of 90% Confidence Intervals of NTG**

| Parameter      | Treatment A | Treatment B | Treatment C | A/B Ratio | A/C Ratio | 90% C.I.                             |
|----------------|-------------|-------------|-------------|-----------|-----------|--------------------------------------|
| LN(Cmax)       | -0.869      | -1.127      | -1.123      | 1.27      | 1.27      | A/B: 1.06 - 1.52<br>A/C: 1.06 - 1.52 |
| Geometric mean | 0.4195      | 0.3241      | 0.3254      |           |           |                                      |
| LNAUC(0-24)    | 1.557       | 1.431       | 1.380       | 1.12      | 1.18      | A/B: 0.97 - 1.30<br>A/C: 1.01 - 1.37 |
| Geometric mean | 4.745       | 4.183       | 3.975       |           |           |                                      |
| LNAUC(0-last)  | 1.579       | 1.446       | 1.397       | 1.13      | 1.18      | A/B: 0.97 - 1.31<br>A/C: 1.02 - 1.37 |
| Geometric mean | 4.850       | 4.246       | 4.043       |           |           |                                      |
| LNAUC(0-∞)     | 1.820       | 1.746       | 1.701       | 1.12      | 1.11      | A/B: 0.93 - 1.34<br>A/C: 0.93 - 1.30 |
| Geometric mean | 6.1722      | 5.7355      | 5.4802      |           |           |                                      |
| Tmax (hr)      | 13.36       | 12.94       | 16.02       | 1.03      | 0.83      |                                      |
| DF(9-24), %    | 129.0       | 104.1       | 110.7       | 1.24      | 1.16      |                                      |

Calculation of 90% confidence intervals was based on log-transformed data.

Treatment A = Hercon's NTG patch, 0.4 mg/hr

Treatment B = Transderm-Nitro, 0.4 mg/hr

Treatment C = Nitro-Dur, 0.4 mg/hr

The unit for Cmax is ng/mL and for AUC is hr-ng/mL

For treatment A, N= 31 [except AUC(0-∞), N=21].

For treatment B, N= 30 [except AUC(0-∞), N=19].

For treatment C, N= 30 [except AUC(0-∞), N=19].

**Table 8. Results of 90% Confidence Intervals of 1,2-DNG**

| Parameter      | Treatment A | Treatment B | Treatment C | A/B Ratio | A/C Ratio | 90% C.I.                             |
|----------------|-------------|-------------|-------------|-----------|-----------|--------------------------------------|
| LN(Cmax)       | 1.2514      | 1.1373      | 1.1049      | 1.11      | 1.15      | A/B: 1.03 - 1.20<br>A/C: 1.06 - 1.24 |
| Geometric mean | 3.4952      | 3.1183      | 3.0189      |           |           |                                      |
| LNAUC(0-24)    | 4.1623      | 4.0273      | 3.9780      | 1.14      | 1.19      | A/B: 1.05 - 1.23<br>A/C: 1.11 - 1.29 |
| Geometric mean | 64.2191     | 56.1092     | 53.4101     |           |           |                                      |
| LNAUC(0-last)  | 4.2175      | 4.0798      | 4.0318      | 1.14      | 1.19      | A/B: 1.05 - 1.24<br>A/C: 1.10 - 1.29 |
| Geometric mean | 67.8636     | 59.1336     | 56.3622     |           |           |                                      |
| LNAUC(0-∞)     | 4.2585      | 4.0911      | 4.0456      | 1.16      | 1.20      | A/B: 1.06 - 1.26<br>A/C: 1.11 - 1.31 |
| Geometric mean | 70.7038     | 59.8056     | 57.1455     |           |           |                                      |
| Tmax (hr)      | 18.02       | 16.62       | 18.53       | 1.08      | 0.97      |                                      |
| DF(9-24), %    | 32.5        | 32.3        | 30.3        | 1.01      | 1.08      |                                      |

The unit for Cmax is ng/mL and for AUC is hr-ng/mL

For treatment A, N= 31. For treatment B, N= 30.

For treatment C, N= 30.

**Table 9. Results of 90% Confidence Intervals of 1,3-DNG**

| Parameter      | Treatment A | Treatment B | Treatment C | A/B Ratio | A/C Ratio | 90% C.I.                             |
|----------------|-------------|-------------|-------------|-----------|-----------|--------------------------------------|
| LN(Cmax)       | -0.401      | -0.4339     | -0.5345     | 1.02      | 1.13      | A/B: 0.93 - 1.12<br>A/C: 1.03 - 1.25 |
| Geometric mean | 0.6696      | 0.6480      | 0.5860      |           |           |                                      |
| LNAUC(0-24)    | 2.4240      | 2.3990      | 2.3342      | 1.02      | 1.08      | A/B: 0.93 - 1.12<br>A/C: 0.99 - 1.19 |
| Geometric mean | 11.2909     | 11.0122     | 10.3212     |           |           |                                      |
| LNAUC(0-inf)   | 2.4860      | 2.4548      | 2.3983      | 1.02      | 1.09      | A/B: 0.93 - 1.12<br>A/C: 0.99 - 1.19 |
| Geometric mean | 12.0131     | 11.6441     | 10.9168     |           |           |                                      |
| LNAUC(0-∞)     | 2.5784      | 2.4949      | 2.4356      | 1.05      | 1.11      | A/B: 0.95 - 1.16<br>A/C: 1.01 - 1.23 |
| Geometric mean | 13.1760     | 12.1205     | 11.4227     |           |           |                                      |
| Tmax (hr)      | 17.21       | 16.45       | 19.49       | 1.05      | 0.88      |                                      |
| DF(4-24), %    | 50.9        | 55.9        | 48.4        | 0.92      | 1.05      |                                      |

Treatment A = Hercon's NTG patch, 0.4 mg/hr

Treatment B = Transderm-Nitro, 0.4 mg/hr

Treatment C = Nitro-Dur, 0.4 mg/hr

The unit for Cmax is ng/mL and for AUC is hr-ng/mL

For treatment A, N= 31 [except AUC(0-∞), N=29].

For treatment B, N= 30.

For treatment C, N= 30.

## **II. Wear and repeated insult patch test**

**Title**        Adhesive wear properties and repeated insult patch test (RIPT) of three transdermal nitroglycerin patches

### **Objectives**

To determine and compare the wear characteristics, irritation potential and/or allergic contact sensitization potential of three transdermal adhesive patch test articles (an "active" test article, a placebo control article, and an "active" control article) after repetitive 24-hour applications to the skin of human subjects. The active control article was studied for its wear characteristics only.

### **Formulations tested**

1. Active test article: Hercon's NTS (FA-7.5), 0.2 mg/hr (Lot #E0692NG/488)
2. Placebo control article: Hercon's placebo patch (Lot #61102NBG/496)
3. Active control article: Key's Nitro-Dur®, 0.2 mg/hr (Lot #D1Y04211)

### **Study site and investigators**

Principal investigator:  
Medical investigator:

**IRB approval**    The study protocol and the informed consent form were reviewed and approved by the Institutional Review Board at the

**Subjects**        One hundred twenty (120) subjects, 29 males and 91 females, participated in the study. The subjects met the inclusion/exclusion criteria specified in the study protocol and had the ages between 18 and 65 years. The test facility made every effort to enroll subjects who were considered "tolerant" to the major expected side effects of nitroglycerin (i.e., headache, nausea, etc.). Subjects wore the patches under conditions of normal daily activity (work, recreation, shower, bathing, sleeping, etc.). They were instructed not to reaffix any patch should "loosening" be observed, and to note and record the date, time and circumstances under which any of the patches fell off.

**Study dates**     The study was initiated on September 14, 1992 (Subjects #1-104) and September 21, 1992 (Subjects #105-120) and completed on October 23 (Subjects #1-104) and October 30, 1992 (Subjects #105-120).

## Study design (induction phase and challenge phase)

Duration of the study The duration of the study was approximately six weeks. Each subject participated in a three-week induction period, followed by a resting period of approximately two weeks. Challenge patch applications were made and scored during the final (6th) week of the study.

Induction phase (Hercon's active and placebo patches): three times a week for three weeks

Twenty-four hour patch applications were made on a Monday, Wednesday, Friday schedule. Twenty-four hour rest periods followed the patch removals on Tuesday and Thursday, and a 48-hour rest period followed the patch removal on Saturday. The application sites were scored by a trained examiner just prior to the next patch application (Reviewer's note: From the data presented, it appeared that the firm had also scored the sites right after the removal of the patch, i.e., score at 24-hour, in addition to the score at 48-hour). This procedure was repeated until 9 induction applications of the active test article and of the placebo were made to one site each. The active control patch (i.e., Nitro-Dur® patch) was not applied during the induction phase.

Challenge phase (either Hercon's active/Hercon's placebo or Nitro-Dur®/Hercon's placebo)

Approximately two weeks after application of the last induction patches, challenge patches (the active test article and placebo or the active control and placebo) were applied to previously unpatched (virgin) sites, adjacent to the original induction patch sites. The patches were removed after 24 hours. The application sites were scored immediately post-removal and again 24 hours later. The subjects were asked to report any delayed reactions which might occur after the final patch readings (any?). For the protection of the test subjects at challenge, only one active patch and the placebo patch were applied during one 24 hour period (Reviewer's note: It is interesting to note that the nominal dosage for the active test article was 0.2 mg/hr and the dosage for the patches used in the bioequivalence study was 0.4 mg/hr.) The test scheme was as follows:

| <u>† Remaining</u><br><u>Subjects</u> | <u>Monday</u><br>(virgin sites) | <u>Tuesday</u> | <u>Wednesday</u><br>(new virgin sites) | <u>Thursday</u> | <u>Friday</u> |
|---------------------------------------|---------------------------------|----------------|----------------------------------------|-----------------|---------------|
| 25†                                   | A & B                           | Remove/Read    | B & C                                  | Remove/Read     | Final Read    |
| 25†                                   | B & A                           | Remove/Read    | C & B                                  | Remove/Read     | Final Read    |
| 25†                                   | C & B                           | Remove/Read    | B & A                                  | Remove/Read     | Final Read    |
| 25†                                   | B & C                           | Remove/Read    | A & B                                  | Remove/Read     | Final Read    |

NOTE: Final readings were also performed on Wednesday for Monday patches prior to new application.

A = Hercon patch, B = Placebo patch, C = Nitro-Dur® patch

Using the above scheme, all subjects were applied all three articles, but only one nitroglycerin patch at a time.

[Reviewer's note: Initial readings were made 24 hours post application, i.e., immediately after patch removal. Final readings were made 24 hours after patch removal.]

Site and duration of patch application All application sites were washed with a residue-free soap (e.g., Ivory®) and water, and dried completely prior to application of any patches. Each patch was applied for 24 hours. The patch was applied to the inner aspect of both the upper arms of each subject. Following 24 hours of wear, the subjects returned to the clinic to have their patches evaluated for quality of wear. After removal of the patches, the sites were scored for residual adhesive and irritation.

#### Data analysis (Chi-square Analyses of Frequency)

Quality of wear (for overall condition and quality of adherence to the skin)

- 0 = Patch not present
- 1 = Practically falling off
- 2 = Approximately 3/4 of adhesive area loose
- 3 = Approximately 1/2 of adhesive area loose
- 4 = Approximately 1/4 of adhesive area loose
- 5 = Full adhesion observed

Residual adhesive (for any residual adhesive material that may or may not still be adhering to the skin following patch removal)

- 0 = None
- 1 = Slight
- 2 = Moderate
- 3 = Extensive

Skin Irritation (skin response/edema)

- 0 = No evidence of any effect
- + = (Barely perceptible) Minimal, faint, uniform or sporty erythema
- 1 = (Mild) Pink, uniform erythema covering all or most of the contact site
- 2 = (Moderate) Pink-red erythema uniform in the entire contact site
- 3 = (Marked) Bright-red erythema with/without petechiae or papules
- 4 = (Severe) Deep-red erythema with vesiculation or weeping

Edema at the test site was described according to the following scale:

- 0 = No edema
- 1 = (Barely perceptible) Very slight edema
- 2 = (Slight) Edges of area well defined by define raising
- 3 = (Moderate) Raised approximately 1 mm.
- 4 = (Severe) Raised more than 1 mm and extending beyond the area of exposure

## Results

### I. Induction phase

One hundred twenty (120) subjects enrolled in the study and 86 completed the study. The firm reported that thirty-four subjects discontinued due to either intolerable side effects or personal reasons unrelated to the conduct of the study.

Skin irritation scores (24-hour)      The frequency of peak 24-hour erythema scores observed: (N=86)

| <u>Test Article</u> | <u>Induction Phase</u><br><u>Peak Erythema Scores (24-hour)</u> |          |          |          |          |          | <u>N</u> |
|---------------------|-----------------------------------------------------------------|----------|----------|----------|----------|----------|----------|
|                     | <u>0</u>                                                        | <u>+</u> | <u>1</u> | <u>2</u> | <u>3</u> | <u>4</u> |          |
| Hercon NTS          | 2                                                               | 6        | 43       | 34       | 1        | 0        | 86       |
| Hercon Placebo      | 29                                                              | 29       | 24       | 3        | 1        | 0        | 86       |

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher scores ( $P < 0.001$ ) than Hercon's placebo patch.

Skin irritation scores (48-hour)      The frequency of peak 24-hour erythema scores observed: (N=86)

| <u>Test Article</u> | <u>Induction Phase</u><br><u>Peak Erythema Scores (48-hour)</u> |          |          |          |          |          | <u>N</u> |
|---------------------|-----------------------------------------------------------------|----------|----------|----------|----------|----------|----------|
|                     | <u>0</u>                                                        | <u>+</u> | <u>1</u> | <u>2</u> | <u>3</u> | <u>4</u> |          |
| Hercon NTS          | 23                                                              | 16       | 39       | 8        | 0        | 0        | 86       |
| Hercon Placebo      | 52                                                              | 13       | 18       | 3        | 0        | 0        | 86       |

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher scores ( $P < 0.001$ ) than Hercon's placebo patch.

Quality of Wear Scores (24-hour)      The frequency of quality of wear scores recorded: (Data from discontinued subjects were used up to their point of discontinuation.)

| <u>Test Article</u> | <u>Induction Phase</u><br><u>Quality of Wear Scores (24-hour)</u> |          |          |          |          |                        |                        | <u>N</u> |
|---------------------|-------------------------------------------------------------------|----------|----------|----------|----------|------------------------|------------------------|----------|
|                     | <u>5</u>                                                          | <u>4</u> | <u>3</u> | <u>2</u> | <u>1</u> | <u>(F)</u><br><u>0</u> | <u>(R)</u><br><u>0</u> |          |
| Hercon NTS          | 598                                                               | 52       | 11       | 8        | 5        | 40                     | 46                     | 760      |
| Hercon Placebo      | 439                                                               | 115      | 52       | 31       | 41       | 96                     | 22                     | 796      |

- (F) = Panelist reported patch fell off  
 (R) = Panelist reported removal of the patch

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly better quality of wear ( $P < 0.001$ ) than Hercon's placebo patch.

Residual Adhesive Scores (24-hour) The frequency of residual adhesive scores recorded. Data from discontinued subjects were used up to their point of discontinuation.

| <u>Test Article</u> | <u>Induction Phase</u><br><u>Residual Adhesive Scores (24-hour)</u> |          |          |          | <u>N</u> |
|---------------------|---------------------------------------------------------------------|----------|----------|----------|----------|
|                     | <u>0</u>                                                            | <u>1</u> | <u>2</u> | <u>3</u> |          |
| Hercon NTS          | 184                                                                 | 542      | 58       | 8        | 792      |
| Hercon Placebo      | 583                                                                 | 213      | 2        | 0        | 798      |

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher residual adhesive ( $P < 0.001$ ) than Hercon's placebo patch.

Residual Adhesive Scores (48-hour) The frequency of residual adhesive scores recorded. Data from discontinued subjects were used up to their point of discontinuation.

| <u>Test Article</u> | <u>Induction Phase</u><br><u>Residual Adhesive Scores (24-hour)</u> |          |          |          | <u>N</u> |
|---------------------|---------------------------------------------------------------------|----------|----------|----------|----------|
|                     | <u>0</u>                                                            | <u>1</u> | <u>2</u> | <u>3</u> |          |
| Hercon NTS          | 397                                                                 | 361      | 11       | 3        | 772      |
| Hercon Placebo      | 723                                                                 | 53       | 0        | 0        | 776      |

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher residual adhesive ( $P < 0.001$ ) than Hercon's placebo patch.

## II. Challenge Phase

A total of 86 subjects completed the challenge phase of the study. Observations of skin reaction were made at 24 and 48 hours post-application.

The following table summarizes the frequency of skin reactions observed at the 24-hour and 48-hour.

| <u>Test Article</u> | <u>Challenge Phase</u><br><u>Erythema Scores (24-hour)</u> |          |          |          |          |          | <u>N</u> |
|---------------------|------------------------------------------------------------|----------|----------|----------|----------|----------|----------|
|                     | <u>0</u>                                                   | <u>+</u> | <u>1</u> | <u>2</u> | <u>3</u> | <u>4</u> |          |
| Hercon NTS          | 29                                                         | 34       | 21       | 0        | 0        | 0        | 84       |
| Hercon Placebo      | 77                                                         | 5        | 2        | 0        | 0        | 0        | 84       |
| Nitro-Dur®          | 20                                                         | 46       | 17       | 2        | 0        | 0        | 85       |
| Hercon Placebo      | 74                                                         | 4        | 7        | 0        | 0        | 0        | 85       |

Both Hercon NTS and Nitro-Dur® patch exhibited significantly higher erythema scores than Hercon placebo patch ( $P < 0.001$ ). There was no significant difference between Hercon NTS and Nitro-Dur® patch.

| <u>Test Article</u> | <u>Challenge Phase</u><br><u>Erythema Scores (48-hour)</u> |          |          |          |          |          | <u>N</u> |
|---------------------|------------------------------------------------------------|----------|----------|----------|----------|----------|----------|
|                     | <u>0</u>                                                   | <u>+</u> | <u>1</u> | <u>2</u> | <u>3</u> | <u>4</u> |          |
| Hercon NTS          | 80                                                         | 2        | 3        | 0        | 0        | 0        | 85       |
| Hercon Placebo      | 81                                                         | 3        | 1        | 0        | 0        | 0        | 85       |
| Nitro-Dur®          | 83                                                         | 2        | 0        | 1        | 0        | 0        | 86       |
| Hercon Placebo      | 81                                                         | 3        | 2        | 0        | 0        | 0        | 86       |

There were no significant differences among the three test articles at the 48-hour reading.

#### Quality of Wear Scores (24-hour)

The following table summarizes the frequency of quality of wear scores recorded during the challenge phase of the study.

| <u>Test Article</u> | <u>Challenge Phase</u><br><u>Quality of Wear Scores (24-hour)</u> |          |          |          |          |                        |                        | <u>N</u> |
|---------------------|-------------------------------------------------------------------|----------|----------|----------|----------|------------------------|------------------------|----------|
|                     | <u>5</u>                                                          | <u>4</u> | <u>3</u> | <u>2</u> | <u>1</u> | <u>(F)</u><br><u>0</u> | <u>(R)</u><br><u>0</u> |          |
| Hercon NTS          | 57                                                                | 7        | 5        | 2        | 2        | 5                      | 6                      | 84       |
| Hercon Placebo      | 30                                                                | 11       | 7        | 6        | 5        | 24                     | 1                      | 84       |
| Nitro-Dur®          | 58                                                                | 9        | 2        | 2        | 0        | 9                      | 5                      | 85       |
| Hercon Placebo      | 24                                                                | 9        | 6        | 9        | 12       | 24                     | 1                      | 85       |

(F) = Panelist reported patch fell off

(R) = Panelist reported removal of the patch

Both Hercon NTS and Nitro-Dur® patch exhibited significantly better 24-hour quality of wear scores than the placebo patch ( $P < 0.001$ ). There was no significant difference between Hercon NTS and Nitro-Dur® patch.

#### Residual Adhesive Scores (24-hour and 48-hour)

| <u>Test Article</u> | <u>Challenge Phase</u><br><u>Residual Adhesive Scores (24-hour)</u> |          |          |          | <u>N</u> |
|---------------------|---------------------------------------------------------------------|----------|----------|----------|----------|
|                     | <u>0</u>                                                            | <u>1</u> | <u>2</u> | <u>3</u> |          |
| Hercon NTS          | 19                                                                  | 61       | 4        | 0        | 84       |
| Hercon Placebo      | 69                                                                  | 15       | 0        | 0        | 84       |
| Nitro-Dur®          | 17                                                                  | 64       | 4        | 0        | 85       |
| Hercon Placebo      | 65                                                                  | 20       | 0        | 0        | 85       |

| <u>Test Article</u> | <u>Challenge Phase</u>                    |          |          |          |          |
|---------------------|-------------------------------------------|----------|----------|----------|----------|
|                     | <u>Residual Adhesive Scores (48-hour)</u> |          |          |          |          |
|                     | <u>0</u>                                  | <u>1</u> | <u>2</u> | <u>3</u> | <u>N</u> |
| Hercon NTS          | 47                                        | 37       | 1        | 0        | 85       |
| Hercon Placebo      | 80                                        | 5        | 0        | 0        | 85       |
| Nitro-Dur®          | 39                                        | 44       | 3        | 0        | 86       |
| Hercon Placebo      | 70                                        | 14       | 1        | 1        | 86       |

The placebo patch exhibited significantly less ( $P < 0.001$ ) residual adhesive than Hercon NTS and Nitro-Dur® patch at both 24-hour and 48-hour readings. There were no significant differences between Hercon NTS and Nitro-Dur® patch at either 24-hour or 48-hour readings.

Side effects The major reported side effects that were considered test article related included: headache (360 cases: 170 mild, 114 moderate, and 76 severe), nausea/upset stomach (25 cases), dizziness/light-headed (13 cases), vomiting (4 cases), and sting/burning at the patch site (4 cases). The firm did not report the comparative frequency of the side effects among the test articles.

### Conclusion

The data observed in the challenge phase indicated that there were no significant differences in the erythema scores, in the quality of wear as defined in the study, and in the residual adhesive scores between Hercon's 0.2 mg/hr patch and Nitro-Dur 0.2 mg/hr.

The firm also concluded that under the conditions of a repeated insult patch test, the test article (Hercon's 0.2 mg/hr patch, Lot #E0692NG/488) was a low-grade irritant to human skin and was significantly more irritating than the placebo patch (Lot #G1102NGB/496)

### Comments (to the bioequivalence study)

1. For nitroglycerin, the 90% confidence intervals for both Cmax and AUC were outside the acceptable range of 80-125%. [Hercon versus Transderm-Nitro: LN(Cmax), 106% -152% and LN(AUC0-24), 97%-130%, Hercon versus Key: LN(Cmax), 106%-152% and LN(AUC0-24), 101%-137%.] The AUC values for 1,2-dinitroglycerin, Hercon versus Key, were also outside the acceptable range of 80-125%.
2. There is a discrepancy in the number of data set reported in the mean data and the data used in the statistical analysis (ANOVA). Apparently, the firm used the data from all the subjects received each respective treatment in the mean data calculation (i.e., 32 received treatment A, 33 received treatment B, and 32 received treatment C). While in fact, only

30 subjects completed both treatments A and B, and 30 subjects completed both treatments A and C. The final statistical report showed 31 data sets for treatment A, apparently due to the inclusion of data from both subjects #3 and #19 (Note: Subject #19 did not receive treatment B and data from subject #3 after treatment C were stated as not evaluable due to the missing of samples between hr 9-24). In the future submission, the firm should be advised to report the results only from subjects who completed both test and reference products.

3. The data reported in the mean data calculation and in the variance analysis (ANOVA) are inconsistent. In the mean data calculation (see pages 306-308), the firm apparently treated those samples with assayed values less than the limit of quantitation (LOQ) as "missing" (see the count, N, in the mean data). While in the procedure of ANOVA, those samples with assayed values less than LOQ were reported as "zero". In the future submission, the firm should be advised to be consistent in the data presentation and to report those values less than LOQ as zero.
4. The firm described (on page 351) how the time to steady state was determined. Criterion 1 (requires no significant differences among the concentrations observed at each time point prior to the steady state time) appears to be in error. How would this affect the values of C<sub>max</sub>, C<sub>min</sub>, C<sub>av</sub>, and the value of degree of fluctuation (DF) is not clear. For now, the determination of time to steady state would not affect the conclusion of the study.
5. The batch size of the test product was not reported.
6. The firm has determined the residual content of nitroglycerin in the used patches. The data, however, were not submitted.
7. It should be noted that each test patch was applied for 24 hours, which is different from the dosing schedule (i.e., to include a daily patch-off period of 10-12 hours) specified in the labeling of this drug product. In the future submission, the firm should be advised to apply the patch for 12-14 hours. The firm should be advised that an IND may be required for outside labeling use.
8. The drug release data were derived from 6 dosage units. The firm should be advised that in vitro dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range, and coefficient of variation data.

Comments (to the wear and repeated insult patch test)

9. Eighty-six (86) subjects completed the induction phase of the study. According to the study protocol, each subject received 24-hour patch applications three times a week (on Monday, Wednesday, and Friday) for three weeks and for each patch application the sites were scored at 24-hour and 48-hour. The irritation scores at 24-hour and 48-hour showed a total number of 86. It is not clear whether the scores reported were mean values. The firm should be advised to clarify. And if those were mean values, the firm should be advised to report the mean, range, and coefficient of variation of the data as well.
10. There is a discrepancy in the number of data set (i.e., N) reported in the challenged phase. The firm should be advised to clarify why N for the 48-hour score is more than that for the 24-hour score.
11. The firm has conducted the bioequivalence study on 0.4 mg/hr patch. While the wear and repeated insult patch study was conducted on 0.2 mg/hr patch. The firm should be advised that the observation made on the wear properties and the irritation potential of this study pertains only to the 0.2 mg/hr patch and the study does not establish that the larger patches have acceptable skin irritation characteristics.

#### Recommendation

The in vivo bioequivalence study conducted by Hercon Laboratories on its nitroglycerin transdermal patch, 0.4 mg/hr, Lot #Y0632NG/487, comparing it to Ciba's Transderm-Nitro®, 0.4 mg/hr, Lot #1M149250 and to Key's Nitro-Dur®, 0.4 mg/hr, Lot #D2212411 has been found unacceptable by the Division of Bioequivalence for the reason cited in comment #1.

The dissolution (drug release) testing conducted by Hercon Laboratories on its nitroglycerin transdermal patches, 0.2 mg/hr, Lot #E0692NG/488, 0.4 mg/hr, Lot #Y0632NG/487, and 0.6 mg/hr, Lot #E0762NG/489, is not acceptable for the reason cited in comment #8. Furthermore, the request for waiver of in vivo testing will not be considered until an acceptable in vivo bioequivalence study is conducted by the firm on this drug product.

The firm should be informed of the recommendation and comments #1-#11.

  
Yin-Chain Huang, Ph.D.  
Division of Bioequivalence  
Review Branch III

RD INITIALED MPark  
FT INITIALED MPark

/S/

CONCUR

/S/

Date

5/8/94

Ramakant M. Mhatre, Ph.D.  
Acting Director  
Division of Bioequivalence

cc: ANDA #89-885 (original, duplicate), HFD-600 (Hare), HFD-630,  
HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Park,  
Huang), Drug File, Division File.

# Nitroglycerin and Metabolite Mean Concentrations Over Time

