CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75143

APPROVAL LETTER

ANDA 75-143

OCT 16 1998

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated June 12, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydroxyurea Capsules USP, 500 mg.

Reference is also made to your amendments dated January 8, March 20, March 31, June 26, and September 15, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Hydroxyurea Capsules USP, 500 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Hydrea® Capsules, 500 mg, of Bristol Myers Squibb Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

10/16/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75143

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
75-143	Gil Kang	September 29, 1998

DRUG PRODUCT:
Hydroxyurea Capsules USP, 500 mg

FIRM:
Barr Laboratories, Inc.

DOSAGE FORM:	STRENGTH:
Capsule	500 mg

cGMP:
EER was found acceptable on October 16, 1997.

BIO:
The Bio study was found acceptable by Dr. J.Chaney on April 27, 1998.

VALIDATION - *(Description of dosage form same as firm's):*
N/A

STABILITY:
The firm has provided 3 months satisfactory accelerated stability data for 500 mg capsule in 175 cc, round, white HDPE bottle for 100 count. The stability data support an expiration period of 24 months.

LABELING:
Labeling was found satisfactory by C. Holquist on April 21, 1998.

STERILIZATION VALIDATION *(If applicable)*:
N/A

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:
The firm has submitted the blank batch record for the intended production batch size of 350 kg for capsules. The size of bio-batch is same as the proposed production batch. The drug substance was manufactured by

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?):*
N/A

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:
Manufacturing process is same.

Signature of chemist:	Signature of supervisor:
/S/	9/29/98

C:\WPFILES\75143NA1.APP

1. CHEMISTRY REVIEW NO.: #3

2. ANDA #: 75-143

3. NAME AND ADDRESS OF APPLICANT:

Barr Laboratories, Inc.
2 Quaker Road
P.O. Box 2900
Pomona, N.Y. 10970-0519

4. LEGAL BASIS FOR SUBMISSION:

Hydrea® Capsules USP, 500 mg
Bristol Laboratories® Oncology Products, A Bristol-Myers Squibb Company.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Hydroxyurea Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

06-12-97 Date of ANDA submission.
12-09-97 NA fax(Major) based on review #1.
12-29-97 Bioequivalency deficiency letter based on review dated 12-22-97.
01-08-98 Response to bio deficiency letter dated 12-29-97.
03-20-98 Response to chemistry deficiency letter dated 12-09-97.
03-31-98 Response to labeling deficiency letter dated 12-09-97.
06-08-98 Bio comments fax based on review dated 4-27-98.
06-26-98 Response to bio comments fax on 06-08-98.
09-09-98 NA facsimile based on review #2.
09-15-98 Response to chemistry deficiency letter dated 09-09-98.

10. PHARMACOLOGICAL CATEGORY: antineoplastic

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):

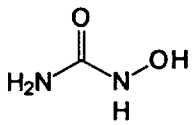
DMF #	TYPE	SUBJECT	HOLDER

13. DOSAGE FORM: Capsules

14. POTENCY: 500 mg

15. CHEMICAL NAME AND STRUCTURE:

Hydroxyurea
Mol.Wt., 76.06



16. RECORDS AND REPORTS:

Memorandum dated August 27, 1997 from Northeast Regional Laboratory(HFR-NE560):

> Northeast Regional Laboratory analyzed hydroxyurea capsules using USP 23 and 2nd Supplement method and the result was satisfactory.

17. COMMENTS: The dissolution test is performed by method instead of the method specified in USP for hydroxyurea capsules.

18. CONCLUSIONS AND RECOMMENDATIONS:

The application is approvable.

19. REVIEWER: Gil Kang DATE COMPLETED: September 28, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75143

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA/AADA #: 75-143 **SPONSOR:** Barr Laboratories, Inc.
DRUG & DOSAGE FORM: Hydroxyurea, USP, Capsules
STRENGTH(s): 500 mg
TYPE OF STUDY: Bioequivalence & dissolution studies
STUDY SITES: **Clinical Study Site:**
Analytical Site:

ASSAY VAIDATION: Acceptable
STUDY SUMMARY: Acceptable

LSMeans and 90% Confidence Intervals For Hydroxyurea in 30 Subjects Following Administration of a Single-Dose of Barr Laboratories' Test Hydroxyurea (4X500 mg Capsules) or Bristol Laboratories' Reference Hydrea® (4X500 mg Capsules) under Fasting Conditions

Parameter	Test	Ref	T/R	90% C.I.
		LSMeans		
AUCI	217.0	218.0	1.00	---
AUCT	209.6	210.6	1.00	---
CMAX	50.35	51.88	0.97	---
		LSMeans Geometric Means		
AUCI	214.5	215.6	0.99	98.2-100.8
AUCT	207.1	208.3	1.00	98.2-100.7
CMAX	48.97	50.87	0.96	89.8-103.2

DISSOLUTION: Acceptable.

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I
INITIAL: JEC **DATE:** 4/17/98

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I
INITIAL: YCH **DATE:** 4/17/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: DPC **DATE:** 4/27/98

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ **DATE:** _____

BIOEQUIVALENCY COMMENTS

ANDA: 75-143 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Hydroxyurea Capsules, 500 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % (Q) of the labeled amount of hydroxyurea in the dosage form is dissolved in 30 minutes.

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,

/S/

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

CC: ANDA 75-143
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-652/ J. Chaney
HFD-652/ Y. Huang
BIO DRUG FILE

HFD-652/ J. Chaney
HFD-652/ Y. Huang YH 4/19/98
HFD-617/ L. Sanchez
HFD-650/ D. Conner DMC 4/27/98

X:\NEW\FIRMSAM\BARR\LTRS&REV\75143A.198
041698

BIOEQUIVALENCY - ACCEPTABLE SUBMISSION DATE: ~~2/6~~ 1/8/98/98

5. **STUDY AMENDMENT** (STA) Strengths: 500 mg Capsule
Outcome: AC

Outcome Decisions: **AC** - Acceptable

OUTCOME DECISIONS: AC - Study Acceptable

WINBIO COMMENTS:

The firm's establishment of stability of the drug product in frozen plasma under the conditions actually used in the bioequivalence study over the period of time exceeding the length of time the bioequivalence study samples were actually stored has been found acceptable by the Division of Bioequivalence. The fasting study is approved.

Hydroxyurea, USP
500 mg Capsules
ANDA #75-143
Reviewer: James Chaney
WP # 75143A.198

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
January 8, 1998

Review of an Amendment to the *in Vivo* Bioequivalence Study Submitted June 12, 1997

Deficiency

Inadequate long term stability data was submitted on the hydroxyurea stored in frozen plasma. The stability of hydroxyurea in plasma during frozen storage was documented over the course of only 29 days. Stability data should be submitted on the hydroxyurea stored in frozen plasma over the period of time corresponding to the time (about 49 days) and temperature at which the frozen samples were actually stored in the bioequivalence studies.

Firm's Response

The stability in frozen plasma was established as shown in Table 1.

Comment

The firm's establishment of stability of hydroxyurea in frozen plasma under the conditions actually used in the bioequivalence study over the period of time exceeding the length of time the bioequivalence study samples were actually stored has been found acceptable by the Division of Bioequivalence.

Recommendations

1. The single-dose, fasting bioequivalence study, conducted by Barr Laboratories, Inc. on its hydroxyurea 500 mg capsule, lot #6R88213 comparing it to Bristol Laboratories' Hydrea® 500 mg capsule, lot #5C06444 has been found acceptable by the Division of Bioequivalence. The study results demonstrate that Barr Laboratories' hydroxyurea 500 mg capsule is bioequivalent under fasting conditions to the reference product, Bristol Laboratories' Hydrea® 500 mg capsule.

2. The following dissolution testing methodology and specifications should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than % (Q) of the labeled amount of hydroxyurea in the dosage form is dissolved in 30 minutes.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 4/19/98

Concur: /S/ Date 4/27/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/041798
X:\NEW\FIRMSAM\BARR\LTRS&REV\75143A.198

Hydroxyurea
Capsules, 500 mg
ANDA #75-143
Reviewer: James Chaney

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
June 12, 1997

REVIEW OF AN *IN VIVO* FASTING BIOEQUIVALENCE STUDY AND *IN VITRO* DISSOLUTION TESTING DATA

I. INTRODUCTION

Hydroxyurea is an antineoplastic drug. It inhibits synthesis of DNA without interfering with synthesis of RNA or proteins. It is indicated, for concomitant use with irradiation therapy, for the control of primary squamous cell carcinoma of the head and neck, excluding the lip. It is manufactured as Hydrea® 500 mg capsules by Bristol-Meyer Squibb.

Following oral administration, hydroxyurea is readily absorbed from the GI tract and serum peak concentration is reached within 2 hours. Data from several animal studies have indicated that metabolism of hydroxyurea occurs *in vivo*. However, none of these conversions have been convincingly demonstrated in humans. This drug distributes rapidly to tissues, and it readily enters the cerebrospinal fluid.

Hydroxyurea drug is rapidly eliminated, and the elimination half life ranges from 3.5-4.5 hours. Principal route of elimination of hydroxyurea is renal excretion; nearly 80% of the dose is recovered in urine within 12 hours after intravenous administration.

II. OBJECTIVE

The objective of this study was to evaluate the bioequivalence of Barr Laboratories' hydroxyurea 500 mg capsules with that of Bristol Laboratories' Hydrea®, 500 mg Capsule following a single oral dose (4 x 500 mg capsules) in healthy adult male volunteers under fasting conditions using a randomized, crossover design.

III. INVESTIGATORS AND FACILITIES

Principal Investigator:
Clinical Facility:
Analytical Investigator:

Analytical Facility:

Biostatistician:

IV. STUDY DATES

Thirty subjects were dosed in Period I (3/22/97) and Period II (3/29/97). The analytical portion of Barr Laboratories, Inc. Study No. 9616212B was conducted from April 21, 1997 to May 10, 1997.

V. CLINICAL

Design: Open-label, randomized, single-dose, 2-way crossover study.

Washout Period: Seven days between doses.

Institutional Review Board: The Novum Institutional Review Board approved this study prior to its commencement. Signed, dated and witnessed informed consent forms are on file at Novum.

Subject Selection: The 30 subjects who participated in this study were healthy males, in the age range of 19 to 35 years, non-tobacco users for at least six months prior to dosing and within 15% of their ideal weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination, electrocardiogram and clinical laboratory evaluations. Any laboratory value or vital sign measurement more than 10% outside the normal range was evaluated individually by the Investigator. All were determined to be not clinically significant for those subjects enrolled in the study.

Formulations:

Test (A)	Four (4) 500 mg Hydroxyurea capsules, Barr Laboratories, Inc., Lot #6R88213, Exp. date N/A. The content uniformity is '% %CV, . The potency is %.
Reference (B)	Four (4) 500 mg Hydrea® capsules, Bristol Laboratories Oncology Products, Lot #5C06444, Exp. date 3/1/00. The content uniformity is % . %CV, . The potency is %.

Drug Administration: Thirty subjects received the test and reference after a 10-hour fast in compliance with the randomization schedule. All doses (4 capsules) were administered with 240 mL of water at a rate of two subjects per minute beginning at 0800 hours. All subjects remained under observation sitting upright or standing for 2 hours after each dosing.

Restrictions: Prior to check-in for the study, the subjects were instructed to take no prescribed medications for at least 14 days prior to the initial dosing and throughout the study. No over-the-counter medications were permitted for 72 hours before dosing in each study period. No medications were permitted during confinement except those administered. Subjects were also instructed to abstain from any products containing alcohol or caffeine for 48 hours prior to dosing and throughout each confinement. None of the subjects reported taking any restricted substance within the time frames indicated.

During the confinement periods of the study, water was restricted from one hour before until one hour after dosing except for water administered with the dose. Water was permitted ad lib at all other times. Subjects remained sitting upright or standing for 2 hours after each dosing, except as required for study procedures. No strenuous physical exercise was permitted during confinement.

Monitoring: Urine drug screens were performed at each check-in to test for alcohol, cocaine metabolites, and THC (tetrahydrocannabinol). Blood pressure (sitting), pulse rate, respiratory rate and oral temperature were measured before each dosing. The Investigator considered the measurements of all subjects as clinically acceptable for dosing.

Blood pressure and pulse rate measurements (sitting) were obtained 2 hours after each dose (within ±30 minutes) and prior to release in each study period to monitor the health of the subjects.

A blood sample was collected at the time of the last sample of the study for a hematocrit determination. All hematocrit values were within 10% of the normal range.

Confinement: During the confinement periods of this study, the subjects were housed and fed at the clinical facility. The subjects were released from the clinical facility approximately 24 hours after dosing in each study period.

Meals: Meals were provided on check-in day and completed at least 10 hours prior to scheduled dosing time. No food or beverages (except water) were permitted after 2200 hours on Day -1. During confinement (Days 1-2), standardized, caffeine-free meals or snacks were served at 4, 10, 14, and 24 hours after dosing. The subjects consumed all food and beverages that were required, with the exception of 3 subjects. Subject 03 did not complete lunch on Day 1 of Period 1 and Period II. Subject 13 did not complete lunch on Day 1 Period II. Subject 25 did not complete dinner on Day 1 Period I.

Pharmacokinetic Samples: In each period, blood samples were collected prior to dosing and at the following nominal times after dosing: 10, 20, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 24 hours. Pre-dose samples were collected within one hour before dosing. All other samples were collected at the nominal times except as noted in Table C5 (Volume 1.2, pp 00533-4). The deviations from the nominal collection times were insignificant. Of the 1260 samples drawn the deviations were 1, 2 and 3 minutes for 66, 4 and 3 samples, respectively.

The samples were flash frozen within one hour of collection except for six samples which were frozen within 1.5 hours of collection. The stability validation data indicates stability in plasma at room temperature for 24 hours. All plasma samples were stored frozen at least -67° or lower until shipment to . on 4/1/97.

VI. STATISTICAL ANALYSIS

Analyses of Variance were performed using the General Linear Models (GLM) procedure of SAS with hypothesis testing for treatment effects at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, period and treatment. Sequence effects were tested against the type III mean square term for subjects within sequence. All other main effects were tested against the mean square error term. Least squares means for the treatments (LSMEANS statement) and the differences between adjusted treatment means and the standard errors associated with these differences (ESTIMATE statement) were calculated.

Confidence Intervals (90%) for the comparison of test and

reference area and peak results constructed to test two one-sided hypotheses at the $\alpha = 0.05$ level of significance. The confidence intervals were presented for the ratio of the test-to-reference treatment means, and for the geometric mean ratios (obtained from logarithmic transformation).

Power for pair-wise treatment comparisons for the pharmacokinetic parameters were calculated as the probability ($\alpha = 0.05$) of detecting a difference equal to 20% of the reference treatment mean, or a ratio of 1.25 for the Ln-transformed results.

VII. ANALYTICAL

PRE-STUDY ANALYTICAL VALIDATION

Methods

Linearity

All "r" values obtained were 0.999853 or greater for hydroxyurea over the range of μg/mL.

Intra-day Precision and Accuracy

Intra-day precision and accuracy were evaluated from the results of the QC samples processed on three separate days. The intra-day precision on three separate days was in the range of % and the intra-day accuracy on three separate days was in range of %.

Inter-day Precision and Accuracy

Inter-day precision (%CV) and accuracy were evaluated from the results of the QC samples and back-calculated calibration standard curves for all three days. For calibration curve standards the inter-day precision was in range of % and accuracy was in range of %. For QC samples the inter-day precision was in the range of % and the inter-day accuracy was in range of %.

Precision and Accuracy at the Upper and Lower Limits of Quantitation (ULOQ & LLOQ)

The precision for hydroxyurea at ULOQ was % and at LLOQ it was %. The accuracy at ULOQ was % and at LLOQ it was %.

Recovery

Recovery was based on the comparison of the mean peak areas of extracted plasma QC samples at high μg/mL), medium (30.0 μg/mL) and low μg/mL) levels compared with unextracted water standards. For each concentration, the peak areas of six replicates of extracted and unextracted samples were compared. The mean recovery from plasma was 80.4%.

Selectivity

There was no interfering peak in blank plasma at the retention time of hydroxyurea as seen in the chromatograms.

Stability

Freeze-Thaw Stability

QC samples (9 sets) prepared at high μg/mL), medium (30.0 μg/mL) and low μg/mL) were divided into 3 cycles consisting of 3 sets of QC samples per cycle. Cycle 1 was subjected to 1 freeze and thaw cycle, cycle 2 was subjected to 2 freeze and thaw cycles and cycle 3 was subjected to three freeze and thaw cycles. Each cycle consisted of freezing samples at -20°C for a minimum of 24 hours and thawing at room temperature for 1 hour. The % change for all three cycles was within to %.

Room Temperature Stability

Six sets of plasma QC samples at high μg/mL), medium (30.0 μg/mL) and low μg/mL) were kept at room temperature for 24 hours. The results show that the % change from the nominal values was in range of %, indicating that the plasma samples were stable at room temperature for 24 hours.

In-Process Stability

The stability of hydroxyurea during processing of samples was documented by comparison of the concentrations of extracted replicates to the nominal values. The six sets of extracted plasma QC samples at concentrations of high μg/mL), medium (30.0 μg/mL) and low μg/mL) were allowed to sit next to the HPLC for 48 hours at room temperature after reconstitution and prior to analysis. The mean percent change for hydroxyurea from nominal values was in range of %, showing that hydroxyurea was stable during the maximum time required for sample processing at room temperature.

Stock Solution Stability

Stock solution stability was evaluated for 15 days. The stock solutions diluted to μg/mL concentration were injected in 6 sets and the peak areas of hydroxyurea were compared. The percent change for hydroxyurea was %.

DURING STUDY ANALYTICAL

Study Sample Receipt and Storage

The plasma samples were received frozen and in good condition by The samples were stored at or below -20°C during the analysis period.

Acceptance Criteria

At least one QC sample from each concentration level must be within the above criteria for the run to be accepted. Samples below the lower limit of quantitation were reported as zero.

Calibration Curve Standard Concentrations

All runs had "r" values of 0.998950 or better for the calibration standard curves. For standards, the inter-day precision was % or better and the accuracy ranged from % to %.

Quality Control Sample Data

For QC samples, the inter-day precision was % or better and the accuracy ranged from %. All but two QC samples for the study were within the SOP control limit of % of the nominal value.

Sample Analysis

The study samples were assayed according to Sample Analysis SOP. For sample analysis, each batch run consisted of standards in singlet and QC samples in duplicate. In run 16, as per SOP an extra set of diluted QC samples was also included due to some over the range samples that were to be diluted. The QC samples were dispersed throughout the run. The study samples including repeats were assayed in sixteen (16) runs. A total of fourteen (14) samples were repeated.

Specificity

No significant interfering peaks were observed at the retention time of hydroxyurea.

Long Term Freezer Stability

The stability of hydroxyurea in plasma during frozen storage was documented over the course of 29 days. The QC samples at μg/mL (high), 30.0 μg/mL (medium) and μg/mL (low), were prepared and stored at -20°C with the study samples. The mean change for hydroxyurea over the storage period of 29 days was -6.2%, -11.2%, and +1.1% for 55.0, 30.0 and 2.00 μg/mL, respectively. The firm mentioned that the long term stability was in process and would be reported at a later date. The duration of time between the first sample draw (3/22/97) and the last assay (5/10/97) was actually 49 days.

VIII. STUDY RESULTS

The mean concentrations of hydroxyurea at each time point for each product are summarized in Table 1. A linear plot of the mean plasma concentration for hydroxyurea as a function of time is shown in Figure 1. The two curves are very similar. A total of 30 subjects were entered into the study and all subjects completed the study.

Table 1. Mean Plasma Concentrations (μg/mL) of Hydroxyurea Following Administration of a Single-Dose of Barr Laboratories' Test Hydroxyurea, (4X500 mg Capsules) or Bristol Laboratories' Reference Hydrea®, (4X500 mg Capsules) under Fasting Conditions

Time	Test	%CV	Reference	%CV	T/R
0	0.00	---	0.00	---	---
0.167	5.239	165.6	2.789	214.1	1.88
0.33	32.75	58.4	33.33	64.9	0.98
0.5	45.14	35.3	47.12	26.1	0.96

(continuation of Table 1)

0.75	41.31	24.2	43.25	16.6	0.96
1	37.17	17.8	38.65	14.7	0.96
1.25	35.25	15.4	35.78	15.5	0.99
1.5	33.08	15.3	33.51	16.4	0.99
1.75	31.61	15.8	31.64	15.6	1.00
2	29.48	15.4	30.00	15.3	0.98
3	24.53	15.6	24.47	16.1	1.00
4	20.31	16.3	20.35	16.9	1.00
5	16.73	18.5	16.77	17.9	1.00
6	13.64	17.9	13.62	16.9	1.00
8	9.10	18.8	9.080	16.2	1.00
10	6.02	18.3	6.020	16.3	1.00
12	3.98	19.0	3.991	17.2	1.00
14	2.74	19.9	2.720	19.7	1.01
16	1.925	21.1	1.913	19.0	1.01
18	1.24	51.2	1.204	50.4	1.03
24	0.039	547.7	0.000	---	---

The pharmacokinetic parameters for hydroxyurea reported by the firm are shown in Tables 2 and 3. Based on the least squares means of the logarithmically transformed variables, the AUC_{0-t} and $AUC_{0-\infty}$ of the Barr formulation were practically identical to the respective means for the Bristol formulation. The test C_{max} value was only 3% lower than that of the reference product. Also, based upon the logarithmic transformations, the 90% confidence intervals about the ratios of test/reference means for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the 80 - 125% limits for bioequivalence when the test product was compared to the reference product (AUC_{0-t}, 98.2-100.7; $AUC_{0-\infty}$, 98.2-100.8; and C_{max}, 89.8-103.2 (Table 3).

Table 2. Comparison of Hydroxyurea Arithmetic and Geometric Mean Pharmacokinetic Results Between Barr Laboratories' Hydroxyurea, 500 Mg Capsule (Test) and Bristol Laboratories' Hydrea®, 500 Mg Capsule (Reference) Administered as 2 G Doses (4x500 Mg) under Fasting Conditions (N=30)

Parameter	Test	%CV	Reference	%CV	T/R
		Arithmetic Means			
AUCI	217.0	16.0	218.0	14.8	1.00
AUCT	209.6	16.4	210.6	15.1	1.00
CMAX	50.35	23.9	51.9	19.9	0.97
KE	0.196	7.7	0.198	8.1	0.99
THALF	3.56	7.6	3.53	7.71	1.01
TMAX	0.639	43.6	0.66	44.6	1.06
		Geometric Means			
AUCI	214.5	----	215.6	----	1.00
AUCT	207.1	----	208.3	----	0.99
CMAX	48.97	----	50.87	----	0.96

Table 3. LSMeans and 90% Confidence Intervals For Hydroxyurea in 30 Subjects Following Administration of a Single-Dose of Barr Laboratories' Test Hydroxyurea (4X500 mg Capsules) or Bristol Laboratories' Reference Hydrea® (4X500 mg Capsules) under Fasting Conditions

Parameter	Test	Ref	T/R	90% C.I.
		LSMeans		
AUCI	217.0	218.0	1.00	---
AUCT	209.6	210.6	1.00	---
CMAX	50.35	51.88	0.97	---
		LSMeans Geometric Means		
AUCI	214.5	215.6	0.99	98.2-100.8
AUCT	207.1	208.3	1.00	98.2-100.7
CMAX	48.97	50.87	0.96	89.8-103.2

In the single-dose bioequivalence study under fasting conditions the firm's data showed that the C_{max} values for 2 out of the 30 subjects (#'s 8 and 24 during the reference treatment) were the first nonzero concentrations. Therefore, data from these 2 subjects were deleted and the statistics were

recalculated by the reviewer. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} remained within the acceptable range of 80-125%. The results are shown in Table 4.

Table 4. Statistical Reanalysis on Hydroxyurea in 28 Subjects (Excluding 2 Subjects Whose C_{max} Was the First Nonzero Concentration) Following a Single-Dose of Hydroxyurea 500 mg Capsules under Fasting Conditions

Parameter	Test	Ref	T/R	90% C.I.
		LSMeans		
AUCI	215.4	216.0	1.00	---
AUCT	208.0	208.7	1.00	---
CMAX	49.80	50.80	0.98	---
		LSMeans Geometric Means		
AUCI	213.0	213.7	1.00	98.4-101.1
(continuation of Table 4)				
AUCT	205.5	206.4	1.00	98.3-100.9
CMAX	48.42	49.88	0.97	90.1-104.6

Individual test/reference ratios of the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for hydroxyurea are shown in Table 5 (appended). Individual $AUC_{0-t}/AUC_{0-\infty}$ ratios for hydroxyurea are shown in Table 6 (appended). Ninety-five percent or more of the $AUC_{0-\infty}$ was measured by AUC_{0-t} for 60 of 60 estimates of $AUC_{0-\infty}$ (Table 6 appended).

Adverse Events: None of the adverse events experienced by the subjects during this study was judged as serious.

IX. FORMULATION

Ingredients	**mg/Capsule**
Hydroxyurea, USP	500.0
Dibasic Sodium Phosphate, USP (Dried)	
Citric Acid, USP Anhydrous (Powder)	
Lactose Monohydrate, NF (Fast-Flo)	
Magnesium Stearate, NF	
# 0, Two Piece Hard Gelatin Capsule (Purple Opaque Cap, Pink Opaque Body)	
Total Capsule Fill Weight (mg)	

Manufacturing Lot # 6R88213 was used in the bioequivalence study. The batch size was capsules.

X. DISSOLUTION TESTING

The firm conducted the dissolution study following the USP dissolution method and tolerance specifications for its product:

Apparatus:	USP Apparatus II (Paddle)
Rotation Speed	50 rpm
Medium:	Water
Volume:	500 mL
Tablets Tested:	12 Test vs. 12 Reference
Tolerance:	Q = NLT % in 30 minutes

The dissolution data obtained using the above method are shown in Table 7. The method and specifications are published in USP 23, Supplement 2.

XI. COMMENTS

1. The firm's single-dose bioequivalence study under fasting conditions demonstrated that the test product, hydroxyurea 500 mg capsule, and the reference listed product, Bristol Laboratories' Hydrea® 500 mg capsule, are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} are within of the acceptable range of %.
2. In the single-dose bioequivalence study under fasting conditions the firm's data showed that the C_{max} values for 2 out of the 30 subjects (#'s 8 and 24 during the reference treatment) were the first nonzero concentrations. Therefore, data from these 2 subjects were deleted by the reviewer and the statistics were recalculated. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} remained within the acceptable range of %.
3. The dissolution testing conducted by the firm on the test product is acceptable.
4. Selection of data points for determination of Kel was satisfactory.
5. The analytical data is acceptable.
6. The assayed potency and the content uniformity of the test and reference products are satisfactory.
7. The test product used for the bioequivalence study and the

dissolution study were from the same batch.

8. The pharmacokinetic parameters and statistics were calculated by the reviewer and were in satisfactory agreement with what the firm reported.

DEFICIENCY

Inadequate long term stability data was submitted on the hydroxyurea stored in the frozen plasma. The stability of hydroxyurea in plasma during frozen storage was documented over the course of only 29 days. Stability data should be submitted on the hydroxyurea stored in frozen plasma over the period of time corresponding to the time (about 49 days) and temperature at which the frozen samples were actually stored in the bioequivalence studies.

RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study, conducted by Barr Laboratories, Inc. on its hydroxyurea 500 mg capsule, lot #6R88213 comparing it to Bristol Laboratories' Hydrea® 500 mg capsule, lot #5C06444 has been found incomplete by the Division of Bioequivalence due to the above deficiency.

2. The following dissolution testing methodology and specifications should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than % (Q) of the labeled amount of hydroxyurea in the dosage form is dissolved in 30 minutes.

The firm should be advised of the recommendations.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 12/20/97

Concur: /S/ Date 12/22/97
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/121997
X:\NEW\FIRMSAM\BARR\LTRS&REV\75143SD.697

Table 5. Individual Hydroxyurea Test/Reference Ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} Following Oral Dosing of Barr's Test Hydroxyurea (4X500 mg Capsules) and Bristol Laboratories' Reference Hydrea® (4X500 mg Capsules) Under Fasting Conditions

Subj #	AUCT	AUCI	CMAX
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
Mean	1.00	1.00	0.99
Minimum			
Maximum			
N	30	30	30

Table 6. Individual Hydroxyurea AUC_{0-t} to AUC_{0-inf} Ratios Following Oral Dosing of Barr's Test Hydroxyurea (4X500 mg Capsules) and Bristol Laboratories' Reference Hydrea® (4X500 mg Capsules) Under Fasting Conditions

Subj	Test	Reference
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
Mean	0.96	0.97
Minimum		
Maximum		
N	30	30

Table 7. *In Vitro* Dissolution Testing

Drug (Generic Name): Hydroxyurea
Dose Strength: 500 mg.
ANDA No.: 75-143
Firm: Barr Labs, Inc.
Submission Dates: 6/12/97
File Name: 75143sd.697

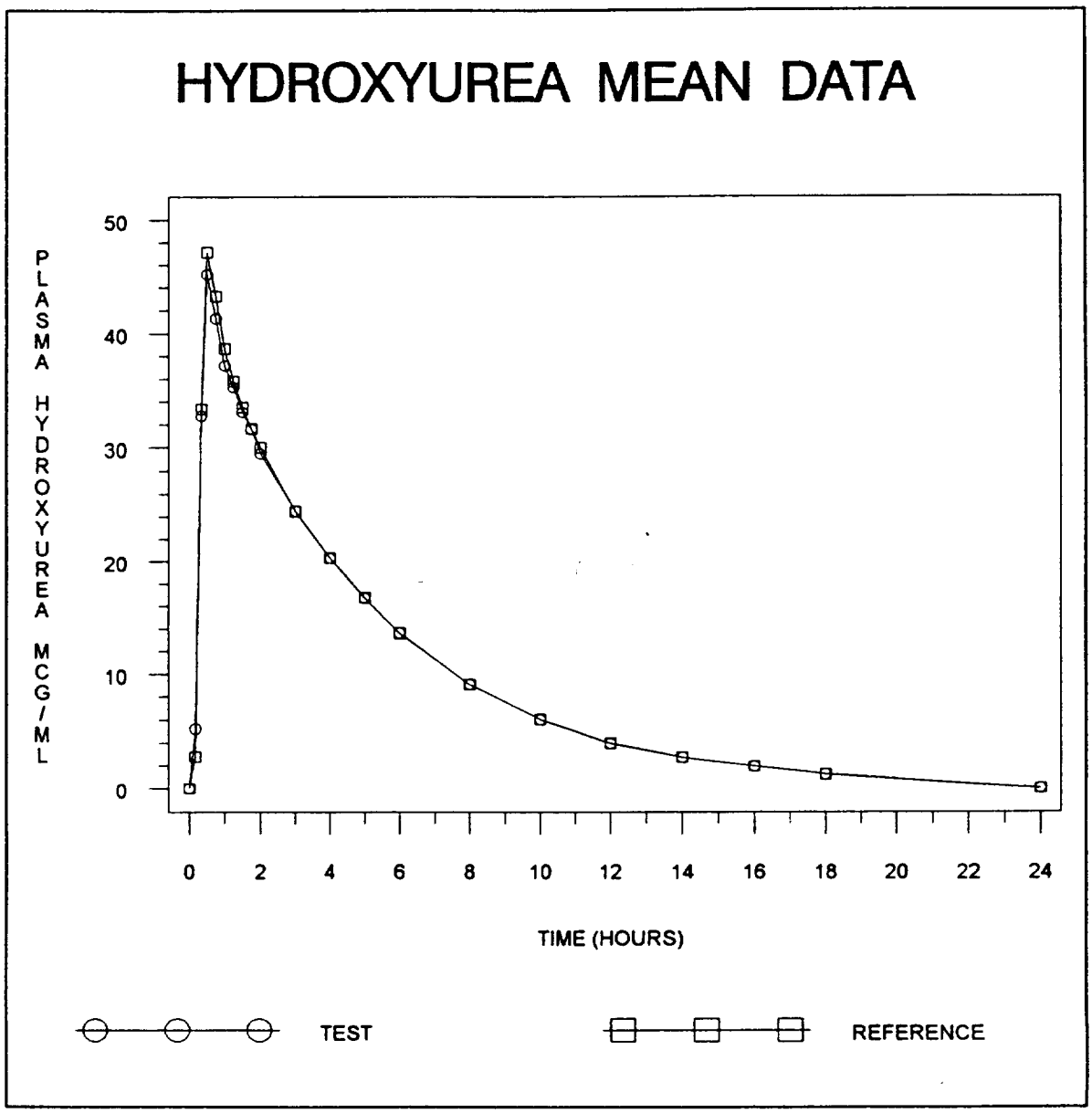
I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:X RPM: 50
No. Units Tested: 12
Medium: Water Volume: 500 mL
Specifications (FDA): NLT % (Q) in 30 min
Reference Drug: Hydrea®, manufactured Bristol-Meyer
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot#6R88213 Strength(mg) 500			Reference Product Lot #5C06444, Expir. 3/1/00 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
10	88		1.3	84		2.9
20	96		1.4	96		1
30	100		1.3	101		1.7
60	105		2.2	105		2.4

Figure 1: Linear Plot of Mean Plasma Hydroxyurea Concentrations *vs* Time



BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-143 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Hydroxyurea Capsules, 500 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Inadequate long term stability data was submitted on the hydroxyurea stored in frozen plasma. The stability of hydroxyurea in plasma during frozen storage was documented over the course of 29 days. Stability data should be submitted on the hydroxyurea stored in frozen plasma over the period of time corresponding to the time (about 49 days) and temperature at which the frozen samples were actually stored in the bioequivalence studies.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75143

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

September 15, 1998

ORIG AMENDMENT

N/FA

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

FACSIMILE AMENDMENT

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Hydroxyurea Capsules, USP 500 mg**.

Reference is also made to your letter dated September 9, 1998 in which the following is stated:

The Deficiencies presented below represent FACSIMILE deficiencies.

COMMENT #1:

Please explain how you can accurately integrate the hydroxylamine peak from the 1.52 minute peak. The chromatogram on page 15-00076 indicates that two peaks are not separated enough to integrate accurately. In addition, please provide related chromatograms and their integration data with your response.

RECEIVED

SEP 16 1998

GENERIC DRUGS

... Continued

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 MG

RESPONSE:

In response to comment number one, Barr conducted a thorough literature review on hydroxylamine as well as any potential degradation products of hydroxyurea. There is not much information in the literature concerning the degradation of hydroxyurea. However, there is data that documents the potential degradation reactions and reaction mechanisms for urea. This information may be extrapolated to outline the potential degradation compounds for hydroxyurea.

In general, urea is quite stable at room temperature. Urea can be converted to nitrogen and carbon dioxide, which can further react to form sodium carbonate. Urea can also react with hydrogen peroxide to yield a white crystalline powder, urea peroxide (Hyperbol®).

The manufacturer of hydroxyurea, has provided data that supports the literature data for urea. For example, the following reactions occur under severe base and acid hydrolysis:

Basic Hydrolysis:

$$HONH\text{-}CO\text{-}NH_2 + 2\,H_2O + 2\,NaOH \rightarrow 2\,NH_4OH + Na_2CO_3$$

Acidic Hydrolysis:

$$2\,HONH\text{-}CO\text{-}NH_2 + 2\,H_2O + 4\,HCl \rightarrow 2\,NH_4Cl + 2CO_2$$

As the balance molecular equations indicate, the potential degradation products of hydroxyurea are either harmless volatile compounds (ammonia and carbon dioxide) or harmless inorganic salts. The technical data package provided by the vendor, documenting the forced degradation studies, demonstrates that hydroxylamine is not formed.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 MG

In addition to the studies performed by Barr performed forced degradation studies on its finished product. The studies are discussed and concluded in Method Validation Report No. RD97-029A. (ANDA pages 16-00093 through 16-00182.) These studies were conducted under oxidation, acid/base hydrolysis, thermal, and UV light conditions. Hydroxylamine was not indicated as a degradation product at the conclusion of the studies.

The chromatogram, noted on page 15-00076 of ANDA 75-143, is a representative sample chromatogram from the Impurities/Degradation Products Test. Hydroxylamine is not added to the sample solution but is added to Hydroxyurea standard to create a resolution solution. The resolution solution is injected once at the beginning of the chromatographic run as part of system suitability. (The resolution between Hydroxylamine and Hydroxyurea is not less than 1.0.) Therefore, the name for the hydroxylamine peak appears in every chromatogram at the retention time established when the resolution solution was injected. In this particular example, the named peak from the resolution solution remained in the table of names and printed out at the retention time established by the resolution solution. The name would appear in this case although no hydroxylamine would be present. The two peaks eluting between 1.5 and 2.0 minutes in the referenced chromatogram are placebo peaks. A representative chromatogram of the placebo can be found on page 16-000130 of the original ANDA.

Based on the literature, the vendor's studies, and studies conducted at Barr Laboratories, there is no indication that hydroxylamine would be found in the finished product or would form during stability storage of finished product. Further, hydroxylamine is not added to the impurities/degradation sample solution. Therefore, there is no need to be able to resolve hydroxylamine from either placebo peaks or diluent peaks.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 MG

COMMENT #2:

Please tighten further the limits of individual impurity (NMT %) and total impurities (NMT %) at release of drug product based on your quality control specification test result (page 15-00063) of the original application.

RESPONSE:

The active raw material used to manufacture Hydroxyurea Capsules, USP 500 mg is Hydroxyurea, USP manufactured by . Hydroxyurea, USP meets all compendial specifications as noted in USP 23 and its Supplements. The USP specification for the raw material allows for the presence of Urea at NMT % as well as a secondary related compound at the same level, NMT %.

At the present time Barr has only evaluated one finished product batch on stability, submission batch 6R88213. Based upon the data available, Barr has updated and tightened the individual impurity/degradation product limit for release of its finished product from NMT % to NMT %, the same limit set by the USP for the presence of an individual related compound in the raw material. Barr has also updated the total impurities limit from NMT % to NMT %. The updated limit is only % above the total limit allowed by the USP for the total of Urea and Related Compounds in the raw material.

Enclosed on Pages 1 through 2, please find the updated finished product specification sheet with the tightened individual impurity/degradation products limit of NMT % and the total impurities/degradation products limit of NMT %.

COMMENT #3:

Please revise method Your revision should include the statement that system suitability requirements, a check standard, and response factor of bracketed samples be carried out for every chromatographic sequence.

... Continued

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 MG

RESPONSE:

In order to ensure that chromatographic methods of analysis are performed on a uniform basis throughout the various laboratory departments of Barr Laboratories as well as Barr's Contract Testing Laboratories, Barr has established a Standard Operating Procedure for conducting chromatography, SOP# 16.0.12. The SOP for Chromatographic Analysis provides the set of requirements that are to be followed when conducting any chromatographic analysis. The requirements outlined in SOP 16.0.12 include, but are not limited to, the following: system suitability, check standards, and standards injected throughout a chromatographic run.

Section 2 of SOP 16.0.12 states that system suitability checks must be performed immediately preceding all chromatographic analyses to ensure system suitability as recommended by USP, or Barr Method.

Section 2.3 further establishes the sequence of injections to be performed when check standards are required. The same section also includes the criteria for the acceptance of calibration and check standards. If the check standard injections are not consistent with the calibration standard injections, the standard injections used to establish system suitability, section 2.3.4 indicates the appropriate steps for the testing analyst to follow.

Finally, section 3 of SOP 16.0.12 includes the injection sequence and requirements for standards injected throughout the course of all chromatographic runs to ensure the system remains suitable for sample injection and calculation. This section also contains reference to a table that indicates the maximum number of sample injections that may take place between standards. The number of injections of sample is dependent on the type of analysis being performed for example, the maximum number of sample injections between standards is 10 for a content uniformity test whereas it is only 3 for a Related Compounds/Chromatographic Purity Test.

... Continued

Any additional requirements, particular to a specific test method, are outlined in the individual test method. SOP 16.0.12, Standard Operating Procedure for Chromatographic Analysis, ensures that all chromatographic runs are performed consistently. Therefore, Barr does not find it necessary to update to include a statement containing the general chromatographic requirements already outlined in SOP 16.0.12.

COMMENT #4:

An official method (967.07) is for the determination of urea. Please provide the proof that the optimum p-dimethylaminobenzaldehyde concentration for the colorimetric method used for urea is same as that for hydroxyurea. The range of concentration used for the robustness study is too narrow to reach any conclusion.

RESPONSE:

According to Barr's colorimetric procedure to determine dissolved hydroxyurea, the p-dimethylaminobenzaldehyde reagent solution is used to develop the colored complex for both the standard and sample solutions. Since the final concentrations of Hydroxyurea and p-dimethylaminobenzaldehyde, in the reaction vessel, are about 0.0033 molar and 0.053 molar, respectively and based on the reaction stoichiometry, the p-dimethylaminobenzaldehyde reagent is well in excess. This assumes a worst case scenario of 100% dissolved for Hydroxyurea. The final concentrations represent about a 15-fold excess of p-dimethylaminobenzaldehyde; thus, demonstrating that Hydroxyurea is the limiting reagent.

Barr determined that the reaction time is the more critical parameter with regard to the colormetric method of analysis. Barr validated the method to ensure that the absorbance values generated were found in the most linear region of the spectrophotometer. This region is between 0.5 and 0.6 absorbance units. Therefore, the more critical parameter, reaction time, as it relates to absorbance, was validated to cover a range of 10 to 70 minutes.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 MG

COMMENT #5:

The stability result on page 47 of this amendment indicates that the maximum amount of individual impurity and total impurity are 0.2% and 0.49%, respectively. Please tighten the limits based on your stability study result.

RESPONSE:

The same method of analysis is used for both release and stability purposes. Therefore, Barr is responding to observations 2 and 5 in the same manner. As indicated in response number 2, Barr has updated and tightened the individual impurities/degradation products limit from NMT % to NMT % for QC release purposes. Barr has also tightened the stability specification to NMT % individual and NMT % total. The individual specification is at the same level allowed in the USP for a related compound in the active raw material. The tightened total impurities/degradation products limit of NMT % is only % higher than the allowable USP Urea and Related Compounds limit for the raw material of NMT %.

Attached on Pages 3 through 4, please find the updated Marketed Stability Specification Record with the tightened Individual Impurities/Degradation Test specification of NMT % and the updated Total Impurities/Degradation Products specification of NMT %.

COMMENT #6:

Please respond to the comments 1 and 2 of the deficiency letter dated December 9, 1997.

RESPONSE:

Barr acknowledges the following two comments noted on page four of FDA's December 9, 1997 Major Amendment Letter:

... Continued

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 MG

1. **USP methods are the regulatory methods and will prevail in the event of a dispute.**

2. **Firms referenced in the ANDA should be in compliance with current good manufacturing practices at the time of approval.**

Barr agrees that in the event of a dispute the USP methods are the regulatory methods and will prevail. In addition, Barr acknowledges comment number 2 and has provided cGMP statements verifying compliance in section ten of the ANDA (pages 10-00007 through 10-00009).

An identical copy of this Facsimile Amendment has been provided to the New York District Office. A document certification is attached.

This completes the present Facsimile Amendment and response to FDA letter dated September 9, 1998. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Janice Barrett for
Christine Mundkur
Regulatory Counsel and Director of
Regulatory Affairs

CM/krg
Enc.

cc: New York District Field Office

This Submission is comprised of **Pages 1 through 4.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

June 26, 1998

ORIG AMENDMENT
N/AB
BIOAVAILABILITY

RECEIVED
JUN 29 1998
GENERIC DRUGS

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

FACSIMILE AMENDMENT

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 MG

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Hydroxyurea Capsules, USP 500 mg.**

Reference is also made to your facsimile letter dated June 8, 1998 in which the following is stated:

BIOEQUIVALENCY COMMENT:

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution should be conducted in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than [redacted] % (Q) of the labeled amount of hydroxyurea in the dosage form is dissolved in 30 minutes.

... Continued

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 MG

RESPONSE:

Barr acknowledges FDA's comment and has incorporated the following dissolution test method into its stability and quality control program: Conduct in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product will meet the following specifications:

> **Not less than % (Q) of the labeled amount of hydroxyurea in the dosage form is dissolved in 30 minutes.**

In-Process and Finished Product Test Methods, ' (6/5/96) and ' (12/3/96) which contained the above dissolution method were submitted to the Agency in Original Application dated 6/12/97, Section XV. Please note that the above method is the official USP compendial dissolution method.

This completes the present Facsimile Amendment and response to FDA facsimile letter dated June 8, 1998. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Regulatory Counsel and Director of
Regulatory Affairs

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 31, 1998

ORIG AMENDMENT
MAF FPL
FPL Submitted

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

AMMENDMENT TO MAJOR AMENDMENT

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 mg

Reference is made to our Abbreviated New Drug Application (ANDA) dated June 12, 1997, submitted pursuant to 21 CFR 314.120 regarding **Hydroxyurea Capsules, USP 500 mg**.

Reference is also made to Barr's Major Amendment response dated March 20, 1998. Barr inadvertently omitted the response to the labeling observations made in your letter dated December 9, 1997 in which the following comments are made:

COMMENT:

Labeling Deficiencies:

1. Container (100's)
   Satisfactory in draft.

RECEIVED
APR 0 1 1998
GENERIC DRUGS

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 mg

COMMENT:

2. Insert

   a. Description

      i. Revise the first two sentences of paragraph one to read as follows:

         Hydroxyurea, an antineoplastic agent, occurs as an essentially tasteless, white crystalline powder.

      ii. Revise paragraph two to read as follows:

         Each capsule, for oral administration contains 500 mg hydroxyurea. In addition, each capsule contains the following inactive ingredients: citric acid…

   b. Actions

      Revise this section heading to read:

      Clinical Pharmacology

   c. Adverse Reactions

      Delete from the fifth sentence of paragraph one.

   d. Dosage and Administration

      i. Paragraph one – Revise the superscript to read "1-7" rather than

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 mg

ii. "Solid Tumors" and "Resistant Chronic Myelocytic Leukemia" are subsection headings under Dosage and Administration. Therefore, decrease their prominence. These headings should have the same prominence as other subsection headings that appear throughout the text of the insert.

iii. Resistant Chronic Myelocytic Leukemia, paragraph two – Delete from the fifth sentence.

e. References

i. Correct the alignment of references 3 through 7. They are indented further than 1 and 2.

ii. Revise reference number two to read as follows:

...1985; 253(11) : 1590-1592

RESPONSE:

Barr has revised its insert labeling, as instructed above. In accordance with 21 CFR 314.94(a) (8) (iv), Barr has attached a side-by-side comparison of the proposed labeling.

Enclosed on **Page 1**, please find 12 final printed package brochures which have been revised according to the Agency's recommendation.

Enclosed on **Pages 2 and 3**, please find 1 copy of a comparison between Barr's last submitted label and Barr's proposed label, and 12 final printed proposed package labels, respectively.

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 mg

Enclosed on **Pages 4 through 14**, please find a side by side comparison of Barr's proposed package brochures with Barr's last submitted package brochure.

Barr has also enclosed an expanded scale version of the brochure on **Pages 15 through 18**.

Please be advised that an identical copy of this amendment to the Major Amendment has been provided to the New York District Offices. A document certification is attached.

This completes the present response to the Agency's letter dated December 9, 1997. If you have any questions, please contact me directly by telephone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Regulatory Counsel and Director of
Regulatory Affairs

CM/jb

This amendment is comprised of **Pages 1 through 18 .**

Barr Laboratories, Inc.

Document Certification

Barr Laboratories, Inc. hereby certifies that a field copy of this amendment to the Major Amendment for the Pending Hydroxyurea Capsules, USP 500 mg Application has been submitted to the New York district office of the FDA. Barr Laboratories, Inc. further certifies that the field copy is a true copy of the material submitted to the Agency, in accordance with 21 CFR 314.71 (b).

Christine Mundkur

March 30, 1998

Christine Mundkur
Regulatory Counsel and Director of Regulatory Affairs

Date

Barr Laboratories, Inc.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 20, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MAJOR AMENDMENT

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 mg

Reference is made to our Abbreviated New Drug Application (ANDA) dated June 12, 1997, submitted pursuant to 21 CFR 314.120 regarding **Hydroxyurea Capsules, USP 500 mg**.

Reference is also made to your letter dated December 9, 1997 in which the following comments are made:

COMMENT:

A. Deficiencies:

Barr QC Raw Material Specification (section III)

Drug Substance:

1. Microbial limits tests on your COA are missing. Please submit.

 ... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

RESPONSE:

According to the hydroxyurea drug substance monograph specified in USP 23 and the current supplements, there is no microbial limit test required. Furthermore, neither the drug substance nor the drug product claims to be a sterile product. Therefore, microbial testing is not required for Hydroxyurea, USP drug substance.

Whereas, the manufacturer of Hydroxyurea, USP, performs microbial testing in accordance with the FU 9, Farmacopea Ufficiale Italiana Nona Edizione (9th Edition of the Italian Pharmacopoeia). This testing is not required for USP material. Therefore, has removed the reference to this testing from the drug substance Certificates of Analysis sent to Barr. Barr is providing the revised Certificate of Analysis for lot H-639 (lot number 95M16) of Hydroxyurea, USP that was used in the manufacture of the submission batch. (See page 1)

COMMENT:

2. Figures I, II and III (representative chromatograms of the resolution, standard and sample solutions from the assay test, page 08-00041, 08-00042 and 08-00043) need integration data.

RESPONSE:

On page seven of thirteen (ANDA page 08-00038) of Barr's Hydroxyurea, USP raw material test method, two notes refer to representative chromatograms I, II, and III (ANDA pages 08-00041 through 08-00043, respectively). As indicated in both notes, the purpose of the representative chromatograms is to illustrate for the chemist, the approximate retention time(s), and peak shape of the analyte, internal standard, and the resolution compound, hydroxylamine. Figures I, II, and III (representative chromatograms of the resolution, standard, and sample solutions from the assay test) contained in Barr's Acceptance Tests for Raw Materials, are for illustrative purposes only. The integration data is not necessary for this purpose.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

COMMENT:

3. Chromatograms should present the lower scale of the Y axis (including zero counts).

RESPONSE:

The data system automatically scales the largest peak in the chromatogram to full-scale; therefore, the numbers on the y-axis are an arbitrary scale. Like any data system, the millivolt output of the detector is converted to a digital number via an A/D converter and stored in memory. The resulting digitized peak is integrated and the peak area stored in memory. The net stored peak area can be determined from the scaled figure by subtracting the lower area count from the upper area count. The result would represent the net peak area for the largest peak. For example, the peak area of hydroxyurea contained in Figure 1 is 284,622 – 4621 = 280,001 (ANDA page 08-00041). The peak would appear small if absolute scaling (y- axis 0 counts) were used. Additional advantages to relative scaling, which enlarges the peak, are to ensure consistent integration and to show more clearly the baseline of the chromatogram.

COMMENT:

4. The revised specification shows the change of "the limit of % hydroxyurea retained on a sieve" to NMT %. But your data (page 08-00054) indicated that screen retained only % hydroxyurea. Please explain the high limit.

RESPONSE:

The data reported on page 08-00054 was obtained from one lot of Hydroxyurea, USP drug substance, H639, the lot of material used to manufacture the bio-batch, 6R88213. Whereas, the particle size specifications for Hydroxyurea, USP, established in test method were determined by studying multiple lots of Hydroxyurea, USP drug substance with varying particle size distributions.

... Continued

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

The initial particle size test for Hydroxyurea, USP, outlined in was written to obtain a significant body of data in order to establish scientifically based specifications to ensure the quality of the finished product. As noted on the Raw Material Specification Test Record (ANDA page 08-00013) for , the limit for the particle size was "Report Results". Barr then established the particle size specification as provided in by evaluating six lots of raw material used in the manufacture of trial batches of Hydroxyurea Capsules, USP 500 mg. The particle size distributions of the raw material lots were compared to the dissolution profiles of the batches manufactured with the six lots of material. The percent retained on the mesh screen for the six lots ranged from about %. The dissolution profiles of the trial batches manufactured from these lots as well as the processing performance of these batches were comparable. (See page 2 for the data on the effect of particle size on finished product dissolution profile.) Therefore, the particle size specification for the screen was set at "NMT % retained," using a one-sided % confidence interval based on the data obtained from the six lots of raw material.

COMMENT:

Other ingredients:

5. Please explain why microbial limits tests for *Pseudomonas aeruginosa* and *Staphylococcus aureus* are not performed for the gelatin capsule.

RESPONSE:

Although there is no USP monograph for gelatin capsules, the "Handbook of Pharmaceutical Excipients" refers to the monograph for Gelatin, USP for the testing of capsules. The Gelatin, USP monograph requires microbial testing for the following: *Salmonella*, *E. Coli*, and Total Aerobic Microbial Count (see pages 3 through 6). In addition, the FCC requires the same microbial testing (see pages 7 through 8). Neither monograph requires testing of *Staphylococcus aureus*, or *Pseudomonas aeruginosa*. Barr currently performs microbial testing for *Salmonella*, *E. Coli*, and Total Aerobic Microbial Count on every shipment of capsules received in accordance with the Gelatin, USP monograph.

... Continued

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

COMMENT:

Biobatch Validation Report (section XII)

6. The formula of encapsulated waste and rejects, converted to blend (formula, D÷E×H in Step item "o", page 12-00013) should be corrected since the ratio D/E (average actual fill weight/average gross capsule weight) of acceptable capsules is not same as the ratio of encapsulated waste and rejects.

RESPONSE:

Barr acknowledges your comment; however, this calculation is consistent with other FDA approved encapsulated products manufactured by Barr. In addition, the calculation proposed by the agency would have a negligible effect on the final accountability of the batch.

By utilizing 1) the average fill weight (D), 2) the average gross capsule weight (E), and 3) the encapsulated waste and rejects (H) (capsules and powder) to calculate the theoretical amount of blend in the encapsulated waste and rejects (O), Barr is providing an accurate and reasonable representation of the batch accountability. From the actual average fill weight of the capsules, Barr determines the theoretical number of filled capsules that the blend should have yielded. Therefore, Barr incorporates the actual powder weight used in the calculation for accountability.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

Differentiating between the types of waste generated during encapsulation (i.e., empty capsules, over-filled capsules, under-filled capsules, and powder) will not significantly effect the final yield and accountability of the batch. For example, an empty capsule has an average weight of mg; it is only % of the total weight of a filled capsule. Based on the batch record, an average filled capsule weighs mg. Even if Barr sorted the waste (powder versus capsules) to obtain the most accurate quantities of powder waste, Barr would need to further manually sort the capsule waste between empties, partial filled, target and overfills. This is not a common practice within the industry. The classification of waste to this level provides no useful information concerning the quality of the batch. For the above-discussed reasons, Barr does not find it necessary to adjust the calculation in the manufacturing master.

COMMENT:

Container (section XIV)

7. The light transmission test result (page 14-00027) in the analytical report prepared by states that the result did not meet the specification for percent light transmission for closure-sealed container. Please explain why it did not meet the specification.

RESPONSE:

The contract laboratory analytical report is incorrect. The actual analytical data reported in the report is correct; however, the statement that the results did not meet specification is inaccurate. As presented in the analytical report on page 14-00027, the raw date reported in the table demonstrates that Barr's container meets the specification for percent light transmission. In fact, none of the percent transmission for any wavelength exceeds %. The highest value obtained was % (Trial 2) at 450 nm. Enclosed please find on pages 9 through 11 a revised report from reflecting that the Barr container conforms to the USP specification.

... Continued

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 mg

COMMENT:

8. data sheet is not readable, and should be replaced.

RESPONSE:

Please see pages 12 through 13 for a new copy of the Material Safety Data Sheet.

COMMENT:

Biobatch Process Validation Report (section XV)

9. Figures I - VII (chromatograms, page 15-00013 to 15-00019) need integration data. Chromatograms should show the lower scale of the Y axis (from 0 counts).

RESPONSE:

See response three under "Barr QC Raw Material Specification (section III)".

COMMENT:

10. Figure IV (representative chromatogram of the standard solution from the impurities/degradation products test, page 15-00057) shows 1.52 min peak. Please explain. The preparation of the impurities/degradation products standard solution (page 15-00047) contains only hydroxyurea reference standard solution.

RESPONSE:

The peak at 1.52 minutes (ANDA page 15-00057) was not only detected in the sample representative chromatogram but also in the diluent chromatogram (see pages 14 through 15). For all impurity tests run by , it is Barr's policy to inject a blank (diluent) specifically for this reason. The peak in this representative chromatogram can be attributed to the diluent.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

COMMENT:

11. The limit of individual impurity (NMT %) and total impurities NMT %) at release of drug product are not justified by your data. Please tighten these limits.

RESPONSE:

Barr has revised its release and stability specifications for individual and total impurities as follows:

Individual Impurities: NMT %

Total Impurities: NMT %

Please see pages 16 through 40 for the following revised documents:

- **Quality Control Analytical Specification Test Record for Hydroxyurea Capsules, USP 500 mg, Revision 3**
- **Acceptance Tests for In-Process & Finished Products for Hydroxyurea Capsules, USP 500 mg,**

  Please note that the finished product test method references the 250 mg strength. The 250 mg strength is currently under development. Barr is not interested in seeking approval for this strength at this time.

- **Marketed Product Stability Specification Sheet/Test Record for Hydroxyurea Capsules, USP 500 mg, Revision 1**

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

COMMENT:

Method Validation Report RD97-029A (section XVI)

12. You asked to remove the use of an internal standard as the method in a method. This is not acceptable unless you provide the statement that the calibration curve with relative standard deviation will be carried out routinely in the method for the assay and blend content uniformity in test method

RESPONSE:

The advantages of employing an internal standardization calibration technique are that the quantities injected need not be accurately measured and the detector response need not be known or remain constant since any change in response will not alter the peak area ratio. The disadvantages are that the internal standard or its degradation compounds can potentially interfere with the analyte peak. Typically, internal standards were employed when performing manual injections, since these tended to not be reproducible. Barr Laboratories is equipped with very precise autosampling systems, which undergo a rigorous IQ/OQ/PQ program and are calibrated every six months. In addition, Barr's test conduct is of a rigorous design to ensure the reproducibility of the detector response throughout the chromatographic sequence. For example, every chromatographic sequence must conform to all System Suitability requirements contained in the test method. Once System Suitability is established, a check standard is injected whose response factor must agree within ± 2.0% of the average of the system suitability. Following the check standard injection, all the samples are bracketed throughout the chromatographic sequence by a procedural control standard (PCS), whose response factor must be within ± 2X RSD as specified in the individual method as well. This will ensure that the detector response is stable throughout the chromatographic sequence.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

In most chromatographic analyses, Barr employs single-point standardization instead of a calibration curve. This is justified based on an acceptable linearity validation experiment. For Hydroxyurea, a linearity experiment was performed and is documented in Barr's method validation report RD97-029A, pages 6-8 (ANDA pages 16-00098 through 16-00100) which demonstrates that suitable linearity is achieved from % (mg/mL) of the working concentration (mg/mL). The correlation coefficient, R, was determined to 0.99993 with a y-intercept of %. The relative response factors (relative to the % linearity solution) were found to be in a range %. The mean of the relative response factors at all concentration levels was found to be % with a relative standard deviation of %. Further evidence of goodness-of-fit is the plot of residuals (actual peak areas – fitted peak areas) vs. concentrations showed a random distribution of residuals.

An equivalency study was also performed between the Barr method (no internal standard) and the USP 23 method (with an internal standard) and the results documented in Barr's Method Validation Report RD97-029A on pages 10-11 (ANDA pages 16-00102 through 16-00103). The data summarized in the validation report in Table 8 demonstrates the equivalency of the two methods.

In conclusion, based on the use of precise, qualified autosampling equipment, the linearity and equivalency studies conducted, the use of an external standard employing single-point standardization is justified.

COMMENT:

Method Validation Report RD96-054A (section XVI)

13. This validation report needs more detailed information to find the optimum p-dimethylaminobenzaldehyde concentration for the colorimetric method and should provide evidence that the maximum absorbance is constant with different concentrations of hydroxyurea studied.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

RESPONSE:

This colorimetric assay is based on an Official AOAC method (967.07) procedure for the determination of Urea in animal feeds (see page 41). Therefore, the optimum concentration of colorimetric reagent, p-dimethylaminobenzaldehyde, has been previously determined for the colorimetric complex. Furthermore, robustness data is contained in Table 17 in the method validation report on page 15 (ANDA page number 16-00198) that further supports the method concentration of p-dimethylaminobenzaldehyde. These method validation experiments were performed varying the concentration of the derivatizing reagent, p-dimethylaminobenzaldehyde. The results of these analyses demonstrate that colorimetric complex has a stable maximum wavelength and a consistent absorbance and extinction coefficient independent of the reagent concentration. Additionally, the concentration of reagent employed provides a complex concentration whose absorbance falls in the most linear, stable region of the UV-Vis spectrophotometer, i.e., 0.1 – 0.5 absorbance units.

According to Barr's internal Standard Operating Procedures, only the spectrum for the blank, standard, check standard and one sample were scanned. However, if the wavelength was shifting as a function of hydroxyurea concentration, the extinction coefficients would vary resulting in poor linearity. The linearity study conducted at Barr contained in method validation report RD96-054A page 7 (ANDA page number 16-00190) demonstrates suitable linearity. Specifically, linearity was observed in the range of about mg/mL (representing a range of about % of the working concentration mg/mL). This is based on a correlation coefficient, R, of 0.99994. In addition, the relative response factors (relative to the % linearity solution) were determined to be in the range of %. The mean of all relative response factors was found to be % with a relative standard deviation Further evidence of goodness-of-fit is the a plot of residuals (actual peak areas – fitted peak areas) vs. concentrations showed a random distribution of residuals.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

It is noteworthy that this product is an immediate release product (Q is % at thirty minutes) whose typical dissolution profile exceeds % in the first 10 minutes (ANDA page number 12-00162) and is between % at the Q timepoint (30 minutes). Therefore, both for routine quality control testing and dissolution profile testing, the linearity study is not an issue, since the dissolution sample concentration range over the dissolution experiment, typically mg/mL, are comparable to the standard concentration of about mg/mL.

COMMENT:

Stability of Finished Dosage Form (section XVII)

14. Stability summary report (Table 1) indicates that tests at 3 months under controlled room temperature were not performed. Please explain.

RESPONSE:

As explained in the Introduction Section of the submitted stability report, #RD97-020A, (ANDA page 17-00029), Barr was having difficulty demonstrating the Assay method was stability-indicating, since the hydroxyurea molecule ultimately degrades to carbon dioxide and ammonia, which will not be detected by conventional analysis employing detection. Barr would not test the stability sample until these studies were completed and the analytical method demonstrated stability indicating properties. Samples of hydroxyurea degraded under varying conditions were sent out for The report documents that under all exposed conditions, acid hydrolysis, base hydrolysis, and hydrogen peroxide oxidation/reduction. 55°C, white light and UV light, the peak integrity of Hydroxyurea remains intact, i.e., the peak is homogenous. Once the method was proven to be stability indicating, the remaining stability timepoints were tested. All results generated through 18 months CRT stability storage are well within specification. Please see pages 42 through 52 for an updated stability report containing data through 18 month CRT (25°C/60% RH) storage.

... Continued

REFERENCE: ANDA 75-143
HYDROXYUREA CAPSULES, USP 500 mg

COMMENT:

15. Stability summary report (Table 2) indicates that the total impurities under accelerated conditions and controlled room temperature conditions are less than %. Please justify your total impurities limit, NMT %.

RESPONSE:

As stated in Barr's response to comment 11, Barr revised the stability individual impurity and total impurities specifications. Please see the response to comment 11.

COMMENT:

16. Based on stability summary report on moisture (Table 4), NMT % is too high. Please tighten the limit.

RESPONSE:

Based on the stability data (3 months accelerated and 18 months CRT 25°C/60% RH) generated to date for the moisture test, Barr revised the stability moisture specification to NMT %. Please see pages 18 through 40 for the following revised documents:

- **Acceptance Tests for In-Process and finished products for Hydroxyurea Capsules, USP 500**

  Please note that the finished product test method references the 250 mg strength. The 250 mg strength is currently under development. Barr is not interested in seeking approval for this strength at this time.

- **Marketed Product Stability Specification Sheet/Test Record, for Hydroxyurea Capsules, USP 500 mg, Revision 1**

Note: see Exhibit for copies of the ANDA pages referenced in Barr's responses.

... Continued

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, USP 500 mg

Please be advised that an identical copy of this Major Amendment has been provided to the New York District Offices. A document certification is attached.

This completes the present response to the Agency's letter dated December 9, 1997. If you have any questions, please contact me directly by telephone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Regulatory Counsel and Director of
Regulatory Affairs

CM/rl

This submission is comprised of **pages 1 through 52** and **ANDA page Exhibits.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 8, 1998

N/AB

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT

BIOEQUIVALENCE AMENDMENT

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, 500 MG

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Hydroxyurea Capsules, 500 mg.**

Reference is also made to your letter dated December 29, 1997 in which the following is stated:

COMMENT:

THE DIVISION OF BIOEQUIVALENCE HAS COMPLETED ITS REVIEW OF YOUR SUBMISSION(S) ACKNOWLEDGED ON THE COVER SHEET. THE FOLLOWING DEFICIENCY HAS BEEN IDENTIFIED:

INADEQUATE LONG TERM STABILITY DATA WAS SUBMITTED ON THE HYDROXYUREA STORED IN FROZEN PLASMA. THE STABILITY OF HYDROXYUREA IN PLASMA DURING FROZEN STORAGE WAS DOCUMENTED OVER THE COURSE OF 29 DAYS. STABILITY DATA SHOULD BE SUBMITTED ON THE HYDROXYUREA STORED IN FROZEN PLASMA OVER THE PERIOD OF TIME CORRESPONDING TO THE TIME (ABOUT 49 DAYS) AND TEMPERATURE AT WHICH THE HUMAN SAMPLES WERE ACTUALLY STORED IN THE BIOEQUIVALENCE STUDIES.

RECEIVED
JAN 12 1998
GENERIC DRUGS

Continued

REFERENCE: **ANDA 75-143**
HYDROXYUREA CAPSULES, 500 MG

RESPONSE:

On June 11, 1997 issued an addendum to the analytical method validation report providing the long-term freezer stability data for hydroxyurea in plasma stored at -20°C for 55 days. The addendum to the validation report containing this data is provided on pages 1 and 2.

This completes the present Bioequivalence Amendment and response to FDA letter dated December 29, 1997. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Regulatory Counsel and Director of
Regulatory Affairs

CM/krg
Enc.

This Submission is comprised of **Pages 1 and 2.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

June 12, 1997

505(j)(2)(a)(ii)
Anna Marie H. Weikel
7/1/97

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

labeling received
completed
8-20

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydroxyurea Capsules, USP 500 mg.

The application is provided both as an archival copy and a review copy. The archival copy of the application is contained in blue binders and consists of 5 volumes. The review copy is divided into two parts. The chemistry, manufacturing, and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 3 volumes.

The format of this application is in accordance with the recent FDA/CDER Guidance for Industry, Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application, April 1997. The contents of this application have been complied in accordance the October 14, 1994 communication from Dr. Janet Woodcock, Director (CDER) and Mr. Ronald Chesemore (ORA). Numerous SOPs are no longer submitted in the application; however, these procedures are kept current and are available for inspection by the FDA District Field Investigators.

In accordance with the Generic Drug Enforcement Act of 1992, a Debarment Certification Statement with a List of Convictions Statement is provided in this application. In addition, in accordance with the FDA's Final Rule (Federal Register, Vol. 58, No. 172, September 8, 1993), a "Field Copy" of this application has been forwarded to the New York District Office.

Regarding Barr Laboratories' **Bio-IND** for Hydroxyurea Capsules, USP 500 mg, Barr is providing the following responses to the agency's comments set forth in the March 14, 1997 letter from the review of the Chemistry, Manufacturing and Controls portions of our Bio-IND:

> Please submit a copy of the label and labeling to be provided to each investigator for the clinical trials pursuant to 21 CFR 312.23 (a) (7) (iv) (d). The labeling must also fulfill the requirements of 21 CFR 312.6.

RESPONSE:

Section V. Labeling 3. Barr's Proposed Drug Product Labeling of this Abbreviated New Dug contains copies of the draft container label and draft package insert. (See pages 05-00015 to 05-00022.

The Division of Bioequivalence study comparing Barr Labs, Inc., Hydroxyurea 500 mg Capsules (test product) is acceptable provided comments 1-6 are incorporate in the final report:

COMMENT:

1. Please provide in detail the methodology for the isolation of drug from the plasma and it's subsequent analysis using a validated method.

RESPONSE:

The Method Validation of Hydroxyurea in Human Plasma, provides in detail the methodology for the isolation of drug from the plasma and it's subsequent analysis using a validated method. Please refer to pages 6-00201 to 6-00240.

COMMENT:

2. The test drug product used in the *in vivo* bioequivalence study and *in vitro* dissolution testing should be from the same production batch. Batch size of the test drug and actual yield should be provided.

RESPONSE:

The test drug product, Barr's Hydroxyurea Capsules, USP 500 mg, used in the *in vivo* bioequivalence study and *in vitro* dissolution testing was from the same production batch, #6R88213. The batch size of Barr's bioequivalence batch, 6R82213, was capsules. The actual net yield was capsules. The net % yield was %. Please refer to Section VI, page 6-01241 and Section XII, pages 12-00003 to 12-00013.

COMMENT:

3. The in vitro dissolution data for the test and reference products was provided, however, the lots of test and reference products employed in the *in vitro* dissolution test should be identical to those employed in the *in vivo* bioequivalence study.

RESPONSE:

The lots of test product, Barr Lot #6R88213, and reference product, Hydrea® Capsules Lot #5C06444 employed in the *in vitro* dissolution test were identical to those employed in the *in vivo* bioequivalence study. Please refer to Section VI, pages 6-00489 to 6-00498 for the *in vivo* bioequivalence study. Please refer to Section VI, pages 6-01241 to 6-01247 for the *in vitro* Comparative Study Report.

COMMENT:

4. All the side effects should be reported with the Final report.

RESPONSE:

Any adverse effects are included in the *In Vivo* Bioequivalence Final Report. There is a Clinical Case Report Form for both Period 1 and Period 2 for each individual subject. If a subject should have any adverse effect, it is documented on that subjects Clinical Case Report Form. Please refer to pages 6-00540 to 6-01240 for individual Clinical Case Report Forms.

COMMENT:

5. The *in vivo* fasting bioequivalence study should be conducted on a minimum batch of units of test capsules. Potency and content uniformity of the test and reference products should be submitted. The potency of the lot of the test product should be within % of that for the reference product. Expiry dates of the batch should be provided.

RESPONSE:

The theoretical batch size of Barr's bioequivalence test batch, 6R82213, was capsules with an actual net yield of capsules. Barr has provided an *In Vitro* Comparative Study Report in the ANDA on pages 6-01241 to 6-01247. The *In Vitro* Comparative Study Report compares the dissolution profiles, assay and content uniformity of Barr's bioequivalence batch #6R82213 to the reference product, Hydrea® Capsules Lot #5C06444 (expiry March 1, 2000). The potency of the Barr's bioequivalence test batch %) is within % of that for the reference product %). The Barr bioequivalence test does not have an approved expiration date; Barr has provided in the ANDA proposed 24 month expiry period.

COMMENT:

6. A 3.5 diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analysis should be submitted. The files should be configured as follows:

   (a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{ei} and $t_{1/2}$ /...

   (b) subj seq per trt C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

RESPONSE:

Barr acknowledges the above comment. Barr has provided in the ANDA on the first page of Section VI a 3.5 diskette in ASCII format containing the pharmacokinetic data and the model codes used in the statistical analysis and is configured as requested in the comment.

Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur for
Claire M. Lathers, Ph.D., F.C.P.
Chief Scientific Officer

CML:mm
Enclosures