CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-467

APPROVAL LETTER

ANDA 75-467

MAR 28 2001

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

Dear Sir:

This is in reference to your abbreviated new drug application dated September 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Buspirone Hydrochloride Tablets USP, 5 mg, 7.5 mg, 10 mg, and 15 mg.

The inclusion of the 7.5 mg strength of this drug product is based upon an approved ANDA Suitability Petition submitted under Section 505(j)(2)(C) of the Act.

Reference is made to our letters dated December 28, 1999 and May 23, 2000, granting tentative approval to this drug product. Reference is also made to your amendments dated November 9, December 9, and December 18, 1998; February 11, 1999; and March 14, and March 28, 2001.

The listed drug product (RLD) referenced in your application, BuSpar® Tablets of Bristol Myers Squibb Co. Pharmaceutical Research Institute (BMS), is subject to a period of patent protection which expires on November 14, 2008 (U.S. Patent No. 5,015,646 [the '646 patent]). Your application contains a Paragraph IV Certification to the '646 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on this patent or that the patent is otherwise invalid. You have further notified the Agency that Par Pharmaceutical, Inc. (Par) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no legal action regarding the '646 patent was brought against Par within the statutory forty-five day period.

We note that Par also made a Paragraph IV Certification to U.S. Patent No. 6,150,365 (the "365 patent"). However, as a result of recent litigation, Bristol-Myers Squibb Company (BMS), the holder of the NDA for Buspar, requested the agency to remove the '365 patent from the agency's publication entitled Approved Drug

Products with Therapeutic Equivalence Evaluations (Orange Book). In response to this request, as of March 28, 2001, the '365 patent is no longer considered to be listed in the Orange Book. Thus, you are not required to submit a certification to this patent. Your amendment dated March 28, 2001, provides for the withdrawal of your certification to the '365 patent.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the submitted labeling. Please note that because of the unique (split) generic drug exclusivity issues associated with this drug product, the Agency is unable to approve all four strengths of the drug product. **Accordingly, only the 7.5 mg strength of the drug product is approved at this time. The 5 mg, 10 mg, and 15 mg strengths shall remain tentatively approved** and will not receive final approval until the remaining exclusivity issues are satisfactorily resolved. The Division of Bioequivalence has determined your Buspirone Hydrochloride Tablets USP, 7.5 mg, can be expected to have the same therapeutic effect as that of the listed product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

With respect to 180-day generic drug exclusivity and its impact on the approvability of the remaining strengths presented in this application, we note that Par was the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification only for the 7.5 mg strength. Therefore, with this approval Par is eligible for 180-days of market exclusivity for the 7.5 mg strength. Such exclusivity will begin to run from the date Par begins commercial marketing of the 7.5 mg strength. With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of the 7.5 mg strength of this drug product in a prompt manner.

If you have questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

We are unable to grant final approval to the 5 mg, 10 mg, and 15 mg strengths at this time because abbreviated applications for Buspirone Hydrochloride Tablets, USP containing Paragraph IV Certifications for one or more of these strengths were accepted for filing by OGD prior to its receipt of your application. Accordingly, the 5 mg, 10 mg, and 15 mg strengths provided for in your application will be eligible for final approval beginning on the date that is one hundred and eighty days after the date the Agency receives notice of the first commercial marketing of one or more of these strengths, respectively, under the prior applications. We refer you to the Agency's recently issued guidance document "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

Under section 505(A) of the Act, certain changes in the conditions described in this abbreviated application for the 7.5 mg strength require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for the 7.5 mg strength are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of the 7.5 mg strength of Buspirone Hydrochloride Tablets, USP.

We request that you submit, in duplicate, any proposed advertising or promotional copy that 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-240). 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-240) with a completed Form FD-2253 at the time of their initial use.

With respect to the continuation of the tentative approval status of the 5 mg, 10 mg, and 15 mg strengths of this drug product, our decision is based upon information available to the Agency at this time; (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). This

decision is subject to change on the basis of new information that may come to our attention.

To provide for final approval of the 5 mg, 10 mg, and 15 mg strengths, please submit a supplemental application as directed below. Upon request, the Agency will provide written notice of the information needed to determine the earliest possible final approval date of your supplemental application for these three additional strengths under section 505(j)(5)(B)(iv) as soon as such information becomes available. The supplemental application, which must be submitted for prior approval about 60 days prior to the date you believe these strengths will be eligible for final approval, should include updated information such as final-printed labeling, and chemistry, manufacturing and controls data as appropriate. Alternatively, a prior approval supplement should be submitted to request final approval of these strengths and stating that no changes have been made to the application since the date of this letter. Because of the unique circumstances associated with exclusivity for this drug product, the office will entertain your request that the supplemental application be granted "expedited review" status.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the supplemental application will be made.

In addition to, or instead of the supplemental application requesting final approval of the additional strengths, the Agency may at any time prior to final approval, request that you submit an informational document containing the information stated above.

Failure to submit the supplemental application or informational document may result in rescission of the tentative approval determination, or delay in issuance of the final approval letter for the 5 mg, 10 mg, and 15 mg strengths.

The 5 mg, 10 mg, and 15 mg strengths of Buspirone Hydrochloride Tablets, USP may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of these unapproved strengths before the final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, these three additional strengths of the drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book").

Should you have any questions about the approval status of the various strengths of drug product presented in your application, or about the timing or content of the supplemental application to provide for final approval of the remaining strengths, please contact Ms. Elaine Hu, R.Ph., Project Manager, at (301) 827-5848.

Sincerely yours,

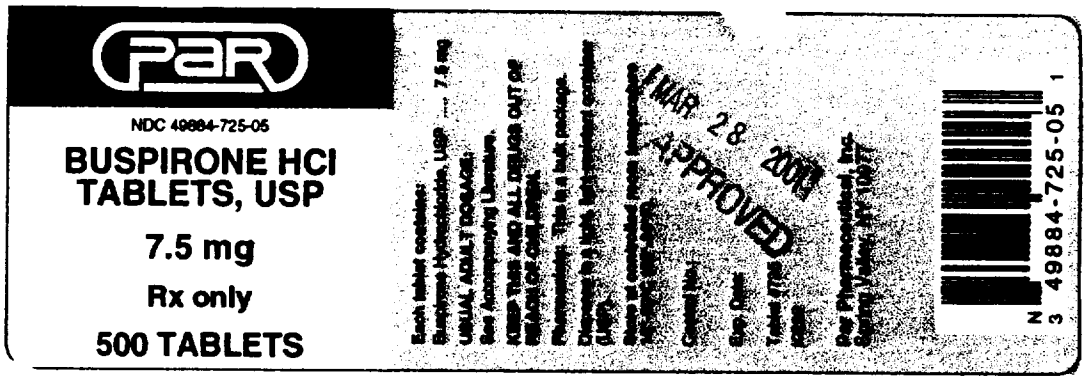
Gary Buehler 3/28/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

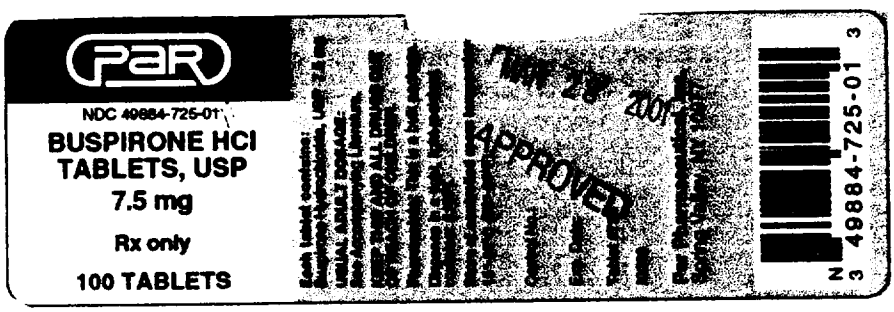
CENTER FOR DRUG EVALUATION AND RESEARCH

75-467

APPLICATION NUMBER:

APPROVED DRAFT LABELING


NDC 49884-725-05
BUSPIRONE HCl
TABLETS, USP
7.5 mg
Rx only
500 TABLETS
MAR 28 2001
APPROVED
N 3 49884-725-05 1


NDC 49884-725-01
BUSPIRONE HCl
TABLETS, USP
7.5 mg
Rx only
100 TABLETS
MAR 28 2001
APPROVED
N 3 49884-725-01 3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-467

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 5

2. ANDA # 75-467

3. NAME AND ADDRESS OF APPLICANT

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

4. LEGAL BASIS FOR SUBMISSION

The firm certifies in their opinion and to the best of its knowledge, U.S. Patent Numbers 4,215,104 and 4,258,027 held by Bristol-Mayers Squibb will expires on March 26, 1999. Also U.S. Patent number 4,182,763 which claims the listed drug, BuSpar Tablets referred to in this application will expire on May 22, 2000. The firm certifies that U.S. Patent No. 5,015,646 issued on May 14, 1991 and expiring on May 14, 2008 will not infringed upon by the manufacture, use or sale by par of Buspirone Hydrochloride Tablets for which this application is submitted. Added 7.5 mg strength upon suitability petition approved (2/1/99) . Filing under paragraph IV. Court ordered de-listing of the '365 patent on 3/13/01. The 7.5 mg strength can be granted exclusivity.

5. SUPPLEMENT(s)

Original 9/29/98

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Buspirone Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 11/9/98
Amendment 2/11/99 – adds 7.5 mg with paragraph IV certification
Amendment 4/9/99
Amendment 11/19/99
Amendment 3/30/00 – 18 months RT data
Amendment 9/26/00 – 24 months RT data
Amendment 10/31/00 – Labeling (7.5 mg only at this time)
Amendment 3/14/01 – de-listing of the '365 patent by court order

10. PHARMACOLOGICAL CATEGORY

Anti anxiety

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

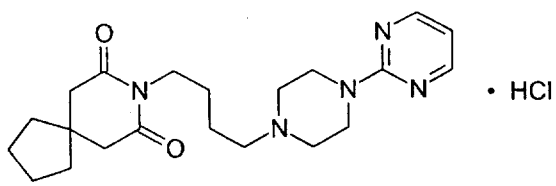
Tablets

14. POTENCY

5, 7.5, 10 , 15 mg

15. CHEMICAL NAME AND STRUCTURE

Buspirone Hydrochloride. 8-Azaspiro[4,5]decane-7,9-dione, 8-[4-[4-(2-primidinyl)-piperazinyl]butyl]-, monohydrochloride. $C_{21}H_{31}N_5O_2 \bullet HCl$. MWt. 421.97. 33386-08-2; 36505-84-7. Tranquilizer . USP 23, page 228.



16. RECORDS AND REPORTS

17. COMMENTS

Tentatively approved 12/28/99. 24 months stability data submitted. No other changes. New BMS patent '365 listed on 11/21/00. Court ordered de-listing on 3/13/01.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable. (7.5 mg at this time; other strengths TA)

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 3/16/01

Supervisor: Paul Schwartz, Ph.D. 3/16/01

cc:

Endorsements:

for 03/16/01

Page(s) 16

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

chem Rev 5

3/16/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-467

BIOEQUIVALENCE

Buspirone Hydrochloride Tablets USP
ANDA #75-467: 7.5 mg, 5 mg, 10 mg & 15 mg
Reviewer: Hoainhon Nguyen
W #75467dw.299

Par Pharmaceutical
Brooklyn, NY
Submission Date:
February 11, 1999

Review of Dissolution Data
and a Waiver Request

I. Background:

The firm has submitted dissolution data for the 7.5 mg strength of the above test product (The strength was approved under Docket No. 98P-0967/CP1, February 1, 1999) in support of the request for waiver of *in vivo* bioequivalence requirements for the 7.5 mg strength. The formulation of the 7.5 mg strength is proportionally similar to that of the 15 mg strength, as shown in the review attachment. The 15 mg strength had previously undergone *in vivo* bioequivalence testing which was found acceptable by the Division of Bioequivalence in the review dated December 15, 1998.

Summary of the dissolution results is given below.

II. Dissolution Testing: USP's method

Drug (Generic Name): Buspirone Hydrochloride Tablets Firm: Par Pharm..
Dose Strength: 15 mg, 10 mg, 7.5 mg & 5 mg ANDA# 75-467
Submission Date: February 11, 1999

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: 0.01N HCl Volume: 500 ml
Reference Drug: (Manuf.) BuSpar Tablets (Bristol-Myers)
Assay Methodology
Specifications· in 30 minutes

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product (Par's) Lot # 18547 Strength (mg) 7.5 Mean % Dissolved(CV%)	Range	Reference Product (Par's) Lot # 20388 Strength (mg) 15 Mean % Dissolved(CV%)	Range
10	81.2(9.4)		79.2(14.3)	
20	90.7(5.8)		96.2(3.9)	
30	95.9(3.7)		99.4(2.2)	
45	99.1(2.4)		101.2(1.2)	

Similar Factor F2 between the 7.5 and 15 mg strengths of the ... ...is 71.56.

Sampling Times (Min.)	Reference Product (Buspar®) Lot # C8J238A Strength (mg) 15 Mean % Dissolved(CV%)	Range
10	89.3(5.4)	
20	94.5(3.8)	
30	96.4(3.4)	
45	98.0(3.1)	

III. Comments:

1. The in vitro dissolution data for the test and reference products are acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.01 N HCl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than [redacted] the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

2. The formulation of the 7.5 mg strength of the test product is proportionally similar to that of the 15 mg which underwent the bio studies (See comparative

formulations attached).

IV. Recommendations:

1. The in-vitro dissolution testing conducted by Par on its Buspirone Hydrochloride Tablets, 7.5 mg and 15 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.01 N HCl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

2. The firm has demonstrated that the formulation of its Buspirone Hydrochloride Tablets, 7.5 mg, is proportionally similar to that of the 15 mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 7.5 mg tablets is granted.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 3/12/99

Concur: Date: 3/12/99
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Buspirone HCl Tablets, USP
5 mg, 10 mg & 15 mg
ANDA # 75-467
Reviewer: Hoainhon Nguyen
W #75467a.d98

Par Pharmaceutical
Spring Valley, NY
Submission Date:
December 18, 1998

Review of a Study Amendment

The firm has amended the original bioequivalence study report (submitted September 29, 1998) with minor corrections of the clinical data. The corrections were for the total number of adverse events reported in the Study Project No. 980563 (The number of "dizziness" events was changed by one less.), and for a number of events dosing dates reported in the Study Project No. ("JUL" instead of "AUG" for 10 events, and "AUG" instead of "SEP" for 1 event.)

These corrections are judged as having no impact on the study results and the review recommendations made previously (See review dated December 15, 1998). The Division of Bioequivalence has no comments or questions for the firm concerning this amendment. No further action is required.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 1/22/99

Concur: Dale P. Conner Date: 2/11/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

a),

Attachment: 0 page

Buspirone Hydrochloride Tablets USP
ANDA #75-467: 5 mg, 10 mg & 15 mg
Reviewer: Hoainhon Nguyen
WP #75467sdw.998

Par Pharmaceutical
Brooklyn, NY
Submission Date:
September 29, 1998
December 9, 1998*
*Telephone Amendment

Review of Two Bioequivalence Studies, Dissolution Data and a Waiver Request

I. Background:

Buspirone hydrochloride is a non-benzodiazepine anxiolytic drug indicated in the management of anxiety disorders or the short term relief of the symptoms of anxiety. A member of the class of compounds known as azaspirodecanediones, it is both pharmacologically and neurochemically distinct from the benzodiazepine anxiolytics; from a safety standpoint, the drug shows significantly less sedation and psychomotor impairment. Although the exact mechanism of action remains unknown, it appears to affect a variety of dopamine mediated biochemical and behavioral events but is free of cataleptic activity. The drug has an affinity for brain D_2-dopamine receptors, where it acts as both an antagonist and agonist and for the 5-HT1A (serotonin) receptors, where it acts as an agonist.

Buspirone HCl is highly protein bound (greater than 95%) and interacts with both albumin and alpha-acid glycoprotein. It is rapidly and completely absorbed following oral administration and undergoes extensive first pass metabolism. Consequently, the mean bioavailability is approximately 4%. The primary route of elimination appears to be oxidative metabolism; in humans, less than 0.1% of an oral dose is excreted in the urine as unchanged drug. This oxidative process yields several hydroxylated derivatives and the pharmacologically active metabolite 1-pyrimidinylpiperazine (1-PP), which is present in greater levels than the parent drug. Following oral administration, plasma concentrations of unchanged buspirone are very low and variable between subjects. Peak plasma levels of 1 to 6 ng/mL have been observed 40 to 90 minutes after single oral doses of 20 mg. The single-dose bioavailability of unchanged buspirone when taken as a tablet is on the average about 90% of an equivalent dose of solution, but there is large

bioavailability.

Administration of buspirone HCl with food increases the bioavailability of the drug (both AUC and CMAX). Since absorption is not markedly altered, it is thought that this increased bioavailability is due to a decrease in the extent of first-pass metabolism.

A multiple-dose study conducted in 15 subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher blood levels of unchanged buspirone than would be predicted from results of single-dose studies.

In a single-dose study using 14C-labeled buspirone, 29% to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18% to 38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10 to 40 mg is about 2 to 3 hours.

Buspirone is supplied as tablets for oral administration containing 5 mg, 10 mg or 15 mg of buspirone hydrochloride.

The usual dosing regimen is 7.5 mg administered twice daily; this may be increased in 5 mg increments at intervals of 2 - 3 days. The maximum daily dosage should not exceed 60 mg per day.

The most common adverse events associated with buspirone include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

The firm has submitted the results of a fasting, single-dose bioequivalence study and a post-prandial bioequivalence study comparing its Buspirone Hydrochloride Tablets USP, 15 mg, with Bristol-Myers Squibb's BuSpar® 15 mg Buspirone Hydrochloride Tablets. Comparative dissolution data for the test and RLD products of the 5 mg, 10 mg and 15 mg strengths are also submitted in support of the *in vivo* bioequivalence study waiver requests for the 5 mg and 10 mg strengths.

II. Bioequivalence Studies:

A. FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL "[redacted]" "Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Par and Bristol-Myers Squibb (Buspar®) 15 mg Buspirone HCl Tablets in Healthy Adult Males under Fasting Conditions Following Administration of a 30 mg Dose"

Study Objective: Bioequivalency of Par and Bristol-Myers Squibb (Buspar®) 15 mg Buspirone HCl Tablets under fasting conditions following a 30 mg dose.

Study Facilities/Dates/Investigators:

Clinical: Phoenix International Life Sciences, Quebec, Canada; June 30 and July 7, 1998; Samuel Serfaty, M.D..

Analytical: The Analytical Division at Phoenix International, Quebec, Canada; between July 9 and 19, 1998; Claude Amestoy.

Study Design: 2-treatment, 2-period, randomized crossover

Demographics: 49 normal, healthy non-smoking male volunteers; 19-45 years of age; mean height 174 cm; mean weight 70 kgs participated in the study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Pages 202-3, Vol. 1.1. The subjects especially did not receive MAO inhibitors.

Restrictions:

No prescription and OTC medications for at least 14 days prior to the study and no concomitant medications during the study sessions.

No alcoholic beverages and no , grapefruit- or xanthine-containing beverages or

food for 48 hours prior to and during the study period.

No food for 10 hours overnight prior to and for 4 hours postdose.

Washout: 7 days.

Confinement: at least one evening pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

Treatment A(Test Product): Two of Par's Buspirone Hydrochloride 15 mg tablets, lot # 012155 (Batch size of units, potency of 98.8%); manuf. April 27, 1998.

Treatment B(Reference Product): Two of Bristol-Myers' BuSpar® 15 mg buspirone hydrochloride tablets, lot # C8J238A (Potency: 97.2%); exp. 2/2001.

Blood samples collected: predose, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 10, 12, 16 and 24 hours postdose. Plasma samples were stored at -12^{0}C pending assay.

Assay Methodology: by Phoenix analytical laboratory.

Assay procedure:

Assay Specificity: acceptable for both buspirone and 1-PP (metabolite 1-Pyrimidinylpiperazine)

Linearity: Buspirone: 50.3 to 10,070 pg/mL; 1-PP: 199.9-24,992 pg/mL

Reproducibility:

Buspirone:

Interday CV = 7.8% at 151.6 pg/mL (n=51), 5.4% at 4044 pg/mL(n=52),

and 4.5% at 8088pg/mL(n=52).

1-PP:

Interday CV = 9.1% at 600.2 pg/mL (n=52), 5.3% at 8003 pg/mL(n=51), and 4.6% at 20,007 pg/mL(n=52).

Sensitivity: **Buspirone:** 50.3 pg/mL (back-calculated standard CV=9.0%(n=26); prestudy QC CV=19.4%(n=6)); 1-PP: 200 pg/mL (back-calculated standard CV=10.4%(n=24); prestudy QC CV=9.1%(n=8)).

Accuracy:

Buspirone:

Recovery=100.7% at 151.6pg/mL(n=51), 101.8% at 4044 pg/mL(n=52), and 99.3% at 8088 pg/mL(n=52).

1-PP:

Recovery=95.3% at 600.2 pg/mL(n=52), 103.5% at 8003 pg/mL(n=51), and 99.5% at 20,007 pg/mL(n=52).

Stability Studies: acceptable

Buspirone:

Long-term: 204 days @ -22 C (percent change was -7.8%(148 pg/mL), and -11.2%(3966 pg/mL)

Short-term: 6 hours at room temperature (unprocessed samples) and 26.2 hours at room temperature (processed samples).

Freeze-thaw: 3 cycles

1-PP:

Long-term: 204 days @ -22 C (percent change was -8.0%(600 pg/mL), and -4.3%(20,000 pg/mL)

Short-term: 6 hours at room temperature (unprocessed samples) and 24.5 hours at room temperature (processed samples).

Freeze-thaw: 3 cycles

Pharmacokinetic Results:

For pharmacokinetics and statistical analysis methods, see pp. 147-8, Vol. 1.1. There was no deviation from the standard methods.

Results:

Forty-seven of 49 enrolled volunteers completed the clinical portion of the study. Subject #34 was withdrawn from the study for medical reasons (vomited). Subject #5 withdrew from the study after completion of Period 1 for personal reasons.

Buspirone:

There was no significant difference (alpha=0.05) between treatments for LAUC(0-T), LAUC(0-Inf) or LCMAX. For Subject #9 (Period 1, Treatment A, buspirone) and Subject #43 (Period 2, Treatment B, buspirone), the first time point was CMAX. These subjects' CMAX data for these treatments were not included in the analyses. The results are summarized in the tables below:

Table I
Buspirone Comparative Pharmacokinetic Parameters
Dose=30 mg; n=47
Fasting Study

Parameters	Test Mean(CV%)	Reference Mean(CV%)	90% C.I.	Ratio T/R
AUC (0-T) pg.hr/mL	4496*	4212*	[0.97;1.18]	1.07
AUC(0-Inf) pg.hr/mL	4953*	4695*	[0.96;1.16]	1.06
CMAX** pg/mL	1722*	1646*	[0.93;1.18]	1.05
TMAX (hrs)	0.930(81)	0.939(68)		
KEL (1/hrs)	0.321(29)	0.296(29)		
T1/2 (hrs)	2.42(45)	2.56(32)		

*Geometric LSMeans
**Recalculated with Subjects #9(Treatment A) and 43(Treatment B) data excluded

Table II
Comparative Mean Plasma Levels of Buspirone
Dose=30 mg; n=47
pg/ml(CV%)
Fasting Study

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B
0	0.00 (0.0)	0.00 (0.0)
0.25	466.33 (179.7)	696.19 (380.0)
0.33	1219.40 (133.2)	1258.86 (207.4)
0.5	2127.38 (127.7)	2452.67 (135.3)
0.75	2115.86 (111.2)	2257.00 (115.6)
1	1669.30 (99.9)	1825.76 (109.0)
1.5	1347.28 (95.8)	1550.28 (131.7)
2	1270.19 (97.6)	1274.99 (116.6)
2.5	1080.73 (89.2)	1106.08 (110.6)
3	920.71 (96.5)	892.67 (107.2)
4	662.99 (84.7)	673.35 (107.9)
6	321.39 (91.5)	290.43 (92.5)
7	236.97 (92.7)	218.96 (90.8)
8	144.89 (104.2)	135.46 (107.7)
10	67.30 (127.9)	64.18 (139.8)
12	40.72 (159.8)	41.00 (193.8)
16	20.81 (226.9)	24.87 (230.7)
24	3.00 (489.1)	1.77 (685.6))

AUCT [pg.hr/mL]	6576.3 (93.8)	6827.8 (118.3)
AUCI [pg.hr/mL]	6950.1 (90.6)	7636.7 (109.2)
Cmax [pg/mL]	2657.68 (104.3)	2669.57 (107.4)

1-PP:

There was no significant difference (alpha=0.05) between treatments for LAUC(0-T), LAUC(0-Inf) or LCMAX. The results are summarized in the tables below:

Table III
1-PP Comparative Pharmacokinetic Parameters
Dose=30 mg; n=47
Fasting Study

Parameters	Test Mean(CV%)	Reference Mean(CV%)	90% C.I.	Ratio T/R
AUC (0-T) pg.hr/mL	87,527*	87,643*	[0.96;1.04]	1.00
AUC(0-Inf) pg.hr/mL	92,559*	92,558*	[0.96;1.04]	1.00
CMAX pg/mL	12,868*	12,961*	[0.93;1.06]	0.99
TMAX (hrs)	1.300(67)	1.320(68)		
KEL (1/hrs)	0.162(28)	0.160(28)		
T1/2 (hrs)	4.748(39)	4.767(36)		

*Geometric LSMeans

Table IV
Comparative Mean Plasma Levels of 1-PP
Dose=30 mg; n=47
pg/ml(CV%)
Fasting Study

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.000	(0.0)	0.000	(0.0)
0.25	1794.76	(136.5)	1440.51	(124.7)
0.33	4383.27	(98.8)	3996.04	(105.0)
0.5	8648.60	(64.9)	9026.89	(66.4)
0.75	11104.87	(40.3)	11341.33	(41.6)
1	10926.84	(30.9)	10749.54	(34.5)
1.5	10727.21	(33.9)	10514.40	(31.5)
2	10336.07	(29.9)	10077.30	(30.8)
3	9410.10	(32.8)	9366.62	(31.1)
4	8475.65	(38.2)	8398.16	(36.6)
6	7119.47	(47.6)	6903.02	(45.7)
7	6080.90	(53.3)	6062.56	(50.8)
8	5346.26	(58.4)	5389.50	(57.4)
10	3903.50	(72.3)	3898.62	(68.0)
12	3076.61	(86.9)	3038.66	(81.2)
16	1955.50	(117.6)	1941.56	(103.1)
24	692.45	(161.6)	692.56	(152.3)
AUCT [pg.hr/mL]	100364.5	(56.9)	99447.1	(53.4)
AUCI [pg.hr/mL]	108872.6	(66.0)	107492.6	(62.0)
Cmax [pg/mL]	13414.34	(27.8)	13725.82	(34.3)

Adverse Effects:

There was no serious adverse event reported. Twenty-three and thirty mild to moderate adverse reactions were reported during the test and reference treatment, respectively. The probably and possibly drug-related reactions included dizziness, nausea, back pain, fatigue, hot flashes, light headache, numbness, sweating, tingling

sensation, blurred vision, feeling cold, weakness, heartburn and vomiting.

B. FED/FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL "Comparative, Randomized, 3-Way Crossover Bioavailability Study of Par and Bristol-Myers Squibb (Buspar®) 15 mg Buspirone HCl Tablets Following Administration of a 30 mg Dose in Healthy Adult Males under Fed and Fasting Conditions"

Study Objective: Bioequivalency of Par and Bristol-Myers Squibb (Buspar®) 15 mg Buspirone HCl Tablets under fed and fasting conditions following a 30 mg dose.

Study Facilities/Dates/Investigators:

Clinical: Phoenix International Life Sciences, Quebec, Canada; July 21, 28 and August 4, 1998; Samuel Serfaty, M.D..

Analytical: The Analytical Division at Phoenix International, Quebec, Canada; between August 9 and September 16, 1998; Claude Amestoy.

Study Design: 3-treatment, 3-period, randomized crossover

Demographics:

21 normal, healthy non-smoking male volunteers; 19-42 years of age; mean height 175 cm; mean weight 72 kgs participated in the study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Same as in Fasting Study

Restrictions/Washout/Confinement/Fasted Conditions: See the fasting study above.

Fed Conditions: The subjects fasted for overnight until 30 minutes prior to their scheduled dosing times, when they were given a standard breakfast. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American processed cheese, 1 slice of Canadian bacon, 120 g of hash brown potatoes, 180 ml

of orange juice and 250 ml whole milk.

Treatments and Sampling:

Treatment A(Test Product, Fasted): Two of Par's Buspirone Hydrochloride 15 mg tablets, lot # 012155(Batch size of units, potency of 98.8%; manuf. April 27, 1998) given under fasted conditions

Treatment B(Test, Fed): Two of Par's Buspirone Hydrochloride 15 mg tablets, lot # 012155(Batch size of units, potency of 98.8%; manuf. April 27, 1998) given under fed conditions

Treatment C(Reference, Fed): Two of Bristol-Myers' BuSpar® 15 mg buspirone hydrochloride tablets, lot # C8J238A (Potency: 97.2%); exp.2/2001 given under fed conditions

Blood samples collected: predose, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 10, 12, 16 and 24 hours postdose. Plasma samples were stored at -12^{0}C pending assay.

Assay Methodology: Same as in Fasting Study Protocol except that:

Reproducibility:

Buspirone:

Interday CV = 6.8% at 151.6 pg/mL (n=39), 3.1% at 4044 pg/mL(n=39), and 2.4% at 8088pg/mL(n=38).

1-PP:

Interday CV = 8.1% at 600.2 pg/mL (n=42), 5.0% at 8003 pg/mL(n=41), and 4.1% at 20,007 pg/mL(n=41).

Sensitivity: **Buspirone**: 50.3 pg/mL (back-calculated standard CV=10.0%(n=20); prestudy QC CV=19.4%(n=6)); **1-PP**: 200 pg/mL (back-calculated standard CV=14.8%(n=20); prestudy QC CV=9.1%(n=8)).

Accuracy:

Buspirone:

Recovery=103.0% at 151.6pg/mL(n=39), 103.2% at 4044 pg/mL(n=39), and 99.7% at 8088 pg/mL(n=38).

1-PP:

Recovery=94.6% at 600.2 pg/mL(n=42), 104.0% at 8003 pg/mL(n=41), and 101.0% at 20,007 pg/mL(n=41).

Pharmacokinetic Results:

For pharmacokinetics and statistical analysis methods, see pp. 2015-6, Vol. 1.4. There was no deviation from the standard methods.

Results:

Seventeen of 21 enrolled volunteers completed the clinical portion of the study. Subjects #12, 16 and 17 were withdrawn due to medical events. Subject #15 withdrew for personal reasons. Since Subject #12 completed two periods of the study, his data were included in the final pharmacokinetic and statistical analyses (Total number of subjects included is 18). For Subject #19 (Period 3, Treatment C, buspirone), the first time point was CMAX. This subject data for this treatment were not included in the analyses.

Buspirone:

There were expected significant differences (alpha=0.05) between treatments for LAUC(0-T)(p=0.0001) and LAUC(0-Inf)(p=0.0001), but not for LCMAX(p=0.0540). The results are summarized in the tables below:

Table V

Buspirone Comparative Pharmacokinetic Parameters

Dose=30 mg; n=18

Non-Fasting Study

Parameters	Test's (Fasted)A Mean(CV%)	Test's (Fed)B Mean(CV%)	Reference's (Fed)C Mean(CV%)	Ratio T(fed)/R(fed) (B/C)
AUC (0-T) pg.hr/mL	5523*	10710*	10661*	1.01
AUC(0-Inf) pg.hr/mL	5806*	11105*	10956*	1.01
CMAX pg/mL	2604*	3459*	3321*	1.04
TMAX (hrs)	0.676(25)	1.504(90)	1.647(56)	
KEL (1/hrs)	0.333(41)	0.260(31)	0.264(29)	
T1/2 (hrs)	2.306(28)	2.949(34)	2.881(34)	

*Geometric LSMeans

Table VI
Comparative Mean Plasma Levels of Buspirone
Dose=30 mg; n=18
pg/ml(CV%)
Non-Fasting Study

TIME (HR)	TEST (FASTED)	TEST(FED)	REF(FED)
0	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
0.25	455.47 (157.9)	411.47 (216.2)	256.56 (243.2)
0.33	1397.16 (135.9)	1849.49 (199.2)	652.09 (187.1)
0.5	2725.49 (95.1)	2925.50 (157.3)	1504.86 (132.8)
0.75	2270.75 (67.9)	2588.91 (107.7)	3113.69 (161.4)
1	1916.72 (73.5)	2921.79 (91.2)	2657.75 (101.0)
1.5	1176.64 (75.2)	3092.70 (54.5)	2721.24 (60.8)
2	1285.55 (97.3)	3184.10 (66.9)	3230.28 (65.9)
2.5	1046.36 (109.9)	2503.44 (61.4)	2391.58 (52.7)
3	800.42 (90.0)	2081.84 (57.0)	2040.48 (52.5)
4	583.37 (88.8)	1543.34 (51.3)	1631.77 (58.7)
6	302.07 (67.3)	695.69 (61.3)	677.68 (63.6)
7	212.23 (66.6)	510.53 (56.5)	481.66 (61.4)
8	120.79 (85.7)	326.22 (50.9)	318.68 (59.8)
10	60.08 (94.5)	183.12 (48.7)	152.65 (58.1)
12	37.45 (107.6)	114.33 (79.0)	112.64 (56.8)
16	12.66 (221.4)	65.20 (118.1)	52.69 (109.3)
24	0.00 (0.0)	10.21 (231.3)	6.10 (282.4)
AUCT [pg.hr/mL]	6370.0 (82.0)	13898.2 (60.9)	13149.3 (61.5)
AUCI [pg.hr/mL]	6602.3 (79.5)	14270.2 (59.8)	13439.3 (60.5)
Cmax [pg/mL]	3097.00 (79.1)	5134.66 (80.2)	4724.71 (96.3)

1-PP:

There was expected significant difference (alpha=0.05) between treatments for LCMAX(p=0.0001) but not LAUC(0-T)(p=0.0543) and LAUC(0-Inf)(p=0.1010). The results are summarized in the tables below:

Table VII
1-PP Comparative Pharmacokinetic Parameters
Dose=30 mg; n=18
Non-Fasting Study

Parameters	Test's (Fasted)A Mean(CV%)	Test's (Fed)B Mean(CV%)	Reference's (Fed)C Mean(CV%)	Ratio T(fed)/R(fed) (B/C)
AUC (0-T) pg.hr/mL	96089*	89062*	89522*	0.99
AUC(0-Inf) pg.hr/mL	101190*	94067*	94529*	0.99
CMAX pg/mL	12849*	10713*	10607*	1.01
TMAX (hrs)	1.147(62)	2.778(54)	2.583(42)	
KEL (1/hrs)	0.152(22)	0.152(28)	0.151(27)	
T1/2 (hrs)	4.829(30)	4.974(34)	4.892(27)	

*Geometric LSMeans

Table VIII
Comparative Mean Plasma Levels of 1-PP
Dose=30 mg; n=18
pg/ml(CV%)
Non-Fasting Study

TIME (HR)	TEST (FASTED)	TEST (FED)	REF(FED)
0	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
0.25	1412.45 (98.6)	616.90 (175.7)	371.72 (195.2)
0.33	4102.91 (83.8)	1638.56 (157.3)	875.26 (165.3)
0.5	9689.16 (51.9)	3379.85 (125.7)	2016.13 (129.8)
0.75	11742.32(35.6)	4443.17 (92.0)	3643.48 (103.0)
1	11447.46(23.8)	5423.04 (68.1)	4496.35 (80.1)
1.5	10898.98(23.1)	8257.73 (32.6)	7848.22 (49.0)
2	10203.22(22.5)	8594.43 (25.5)	9398.41 (35.2)
2.5	10276.43(24.4)	9484.58 (24.9)	9505.21 (25.7)
3	9655.38 (25.2)	9496.51 (21.6)	9411.09 (25.0)
4	8561.31 (30.7)	8757.62 (23.9)	9038.43 (23.1)
6	7025.64 (40.0)	7120.70 (34.0)	7412.62 (35.8)
7	6440.30 (44.6)	6304.46 (39.9)	6453.50 (41.0)
8	5640.65 (49.9)	5710.42 (44.4)	5929.01 (44.8)
10	4179.39 (60.0)	4236.26 (53.6)	4224.69 (52.7)
12	3046.56 (70.3)	3158.79 (65.6)	3427.43 (68.3)
16	2235.04 (98.0)	2047.77 (86.0)	2182.78 (84.8)
24	812.88 (133.5)	745.00 (127.3)	768.62 (117.7)
AUCT [pg.hr/mL]	105249.4 (45.9)	96083.1 (42.7)	98412.3 (43.7)
AUCI [pg.hr/mL]	108300.7 (55.3)	103831.3(51.0)	105506.2(49.7)
Cmax [pg/mL]	13579.44 (26.6)	10663.97(18.4)	11047.59(22.4)

Adverse Effects:

There was no serious adverse event reported. Twelve, thirteen and fourteen mild to moderate adverse reactions were reported during the test(fasted), test(fed) and reference(fed) treatment, respectively. The probably and possibly drug-related reactions included dizziness, lightheadedness, hot flashes, light vertigo, fatigue, nausea, stomach cramps, vomiting, diarrhea, weakness, sleepiness and dry mouth.

III. Dissolution Testing: USP's method

Drug (Generic Name): Buspirone Hydrochloride Tablets Firm: Par Pharm..
Dose Strength: 15 mg, 10 mg & 5 mg ANDA# 75-467
Submission Date: September 29, 1998

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: 0.01N HCl Volume: 500 ml
Reference Drug: (Manuf.) BuSpar Tablets (Bristol-Myers)
Assay Methodology
Specifications:

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 18545 Strength (mg) 5 Mean % Dissolved(CV%)	Range	Reference Product Lot # B8J164A Strength (mg) 5 Mean % Dissolved(CV%)	Range
10	83.2(21.7)		95.2(2.7)	
20	96.5(5.4)		97.7(1.2)	
30	99.2(2.6)		98.8(1.2)	
45	100.6(1.6)		99.8(0.95)	

Sampling Times (Min.)	Test Product Lot # 18546 Strength (mg) 10 Mean % Dissolved(CV%)	Range	Reference Product Lot # C8J020A Strength (mg) 10 Mean % Dissolved(CV%)	Range
10	86.3(4.6)		92.3(1.9)	
20	91.6(2.3)		97.3(2.6)	
30	94.2(2.1)		98.7(1.9)	
45	97.3(1.8)		99.3(1.7)	

Sampling Times (Min.)	Test Product Lot # 18547(same as 012155) Strength (mg) 15		Reference Product Lot # C8J238A Strength (mg) 15	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
10	81.2(9.3)		89.3(5.4)	
20	90.7(5.8)		94.5(3.8)	
30	95.9(3.7)		96.4(3.4)	
45	99.1(2.4)		98.0(3.1)	

IV. Comments:

1. The single-dose, fasting bioequivalence study and the single-dose postprandial bioequivalence study for the 15 mg strength demonstrate that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) of buspirone and 1-PP under fasting and non-fasting conditions.

2. The in vitro dissolution data for the test and reference products of all strengths are acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.01 N HCl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. The formulations of the 5 and 10 mg strengths of the test product are proportionally similar to that of the 15 mg which underwent the bio studies (See comparative formulations attached).

V. Recommendations:

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Par Pharmaceutical on the test product,

Buspirone Hydrochloride Tablets, 15 mg, lot # 012155, comparing it with the reference product, Bristol-Myers' BuSpar® 15 mg Tablets, lot # C8J238A, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Par's Buspirone Hydrochloride Tablets, 15 mg, is bioequivalent to the reference product, Bristol-Myers' BuSpar® 15 mg Tablets, under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by Par on its Buspirone Hydrochloride Tablets, 5 mg, 10 mg and 15 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.01 N HCl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than f the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. The firm has demonstrated that the formulations of its Buspirone Hydrochloride Tablets, 5 mg and 10 mg, are proportionally similar to that of the 15 mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 5 mg and 10 mg tablets is granted. The firm's Buspirone Hydrochloride Tablets, 5 mg and 10 mg, are therefore deemed bioequivalent to Bristol-Myers' BuSpar®Tablets, 5 mg and 10 mg, respectively.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 12/14/98

Concur: Date: 12/15/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-467

ADMINISTRATIVE DOCUMENTS

APPROVAL PACKAGE SUMMARY FOR 75-467

ANDA: 75-467

FIRM: Par Pharmaceutical, Inc.

DRUG: Buspirone Hydrochloride

DOSAGE: Tablets

STRENGTH: 5 mg, 7.5 mg, 10 mg, 15 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 10/8/99

BIO STUDY/BIOEQUIVALENCE STATUS: Bio is satisfactory 12/15/98, 3/12/99

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has provided satisfactory three months accelerated stability data at 40°C/75%RH and 24 months room temperature at 25°C/60%RH for all packaging sizes. Also, submitted 3 months room temperature for the product packaged in bulk.

LABELING REVIEW STATUS: Labeling is satisfactory 11/13/00

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided blank batch records for intended production tablets for 5 mg, tablets for 7.5 mg, tablets for 10 mg, and Tablets for 15 mg. Also, submitted copies of the executed batch records for 5 mg tablets), 7.5 mg tablets), 10 mg tablets, 15 mg olets) The firm will be using the same drug substance manufacture, same equipment and same manufacturing procedure.

COMMENTS: The Application is Approvable.

REVIEWER: Nashed E. Nashed, Ph.D. Date: 11/14/00

SUPERVISOR: Paul Schwartz, Ph.D.

PS 11/14/00

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-467 Date of Submission: September 29, 1998 and February 11,1999

Applicant's Name: Par Pharmaceutical, Inc.

Established Name: Buspirone Hydrochloride Tablets USP, 5 mg, 7.5 mg, 10 mg, and 15 mg

Labeling Deficiencies:

1. CONTAINER - 5 mg, 7.5 mg, and 10 mg (100s and 500s)
   15 mg (60s)

   Satisfactory in draft

2. INSERT

   GENERAL COMMENTS

   a. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or the title of the package insert.

   b. Revisions are included on the enclosed "mock-up of your proposed labeling.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John J. Grace for/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Mock-up labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-467

CORRESPONDENCE

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

Copy 1 (archival)
Copy 2 (review)
Copy 3 (field)*

March 28, 2001

NEW CORRESP
NC

Mr. Gary Buehler (HFD-600)
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 75-467
BUSPIRONE HYDROCHLORIDE TABLETS, USP, 5 MG, 7.5 MG, 10 MG AND 15 MG

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application dated September 29, 1998 regarding Buspirone Hydrochloride Tablets, USP, 5 mg, 7.5 mg, 10 mg, and 15 mg. Reference is also made to our amendment dated December 1, 2000 in which Par Pharmaceutical, Inc. amended its original patent certification for the referenced application.

In accordance with the above, Par Pharmaceutical, Inc. hereby amends ANDA 75-467 for Buspirone Hydrochloride Tablets, USP, 5 mg, 7.5 mg, 10 mg, and 15 mg by withdrawing the Paragraph IV Certification for Patent Number 6,150,365 submitted on December 1, 2000.

Par certifies that a field copy of this amendment has been provided to the FDA New York District Office. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 29 2001
OGD

* Jerome G. Woyshner
Acting District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

NC

NEW CORRESP

March 14, 2001

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 286
Rockville, Maryland 20855

RE: ANDA 75-467
Buspirone Hydrochloride Tablets USP 5 mg, 7.5 mg, 10 mg and 15 mg

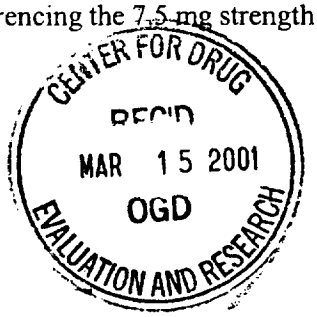
Dear Mr. Buehler:

On May 23, 2000 Par Pharmaceutical was notified that the above referenced Abbreviated New Drug Application was tentatively approved. In correspondence from you on March 23, 2000 you indicated that Par could not begin marketing the 7.5 mg strength until November 22, 2000 due to Buspar's pediatric exclusivity.

Bristol listed a new patent, patent no. 6,150,365, on November 21, 2000 thereby delaying Par's final approval.

On March 13, 2001 Civil Action No.: 00-2876 (RMU), (Mylan Pharmaceuticals v. Tommy C. Thompson and Bristol-Myers Squibb Co.), the plaintiff's request for preliminary injunction was granted. The judge ordered Bristol to immediately delist patent 6,150,365. Par thereby requests immediate approval of Par's ANDA upon the delisting of Bristol's patent.

Based on this ruling, Par Pharmaceutical requests that Par's ANDA 75-467 for 7.5 mg buspirone tablets are immediately approved, and a final approval letter issued. We reiterate what was stated in our September 26, 2000 minor amendment to reactivate the application prior to final approval, there are no changes in the conditions under which the product was tentatively approved. Furthermore, on October 31, 2000 we submitted revised package insert labeling referencing the 7.5 mg strength only. All references to the 5 mg,



10 mg and 15 mg strengths were deleted.

Sincerely yours.

Kenneth I. Sawyer
President and CEO
Par Pharmaceutical, Inc.

cc: Robert West
Acting Deputy Director
Office of Generic Drugs
Center for Drug Evaluation and Research (HFD 601)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 286
Rockville, Maryland 20855

ANDA 75-467

JAN 17 2001

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application dated September 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Buspirone Hydrochloride Tablets USP, 5 mg, 7.5 mg, 10 mg, and 15 mg.

Reference is also made to the tentative approval letters issued by this office on December 28, 1999, and May 23, 2000, and to your amendments dated September 26, ~~November 21,~~ MPK 1/24/01 November 29, and December 1, 2000.

Our tentative approval letter dated May 23, 2000, outlines the conditions which must be met before final approval may be granted to this abbreviated application. Your December 1, 2000, submission provides a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act, a "Paragraph IV Certification", stating that (U.S.) "Patent No. 6,150,365 which claims the listed drug product will not be infringed by the manufacture, use, or sale of Buspirone Hydrochloride Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg for which this application is submitted." The '365 patent is listed in the current supplement to the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book" and is scheduled to expire on August 5, 2019.

ANDA applicants submitting applications containing Paragraph IV Certifications must comply with the notification requirements stated in 21 CFR 314.95. We have not received documentation that Par Pharmaceutical, Inc. provided a notice of certification of invalidity or non-infringement to either the owner of the '365 patent or to the owner's representative who is designated to receive the notice, or to the holder of the new drug application (NDA) for the reference listed drug product (RLD). Absent this information, the application is

deficient and not approvable under 21 CFR 314.127(a)(12). To correct this deficiency, please submit an amendment providing the following information to this application:

1. As noted under 21 CFR 314.95(b), provide a statement certifying that the proper notice has been provided to the patent owner and application holder as described under 314.95(a)(1) and (2), and that the notice met the content requirements described under 21 CFR 314.95(c).

2. Provide documentation under 21 CFR 315.95(e) that each recipient received the notice. A copy of a certified or registered U.S. Postal Service return receipt or a letter acknowledging receipt will satisfy this requirement.

Your application cannot resume its tentative approval status until the above requirements are satisfactorily addressed. The amendment submitted to your application in response to this not approvable letter will be considered as a MINOR AMENDMENT. We suggest that you submit your amendment between 60 to 90 days prior to the date you believe that your application will be eligible for final approval. Please note that this letter does not address issues related to the 180-day generic drug exclusivity provisions under Section 505(j)(5)(B)(iv) of the Act which may impact the date this application becomes eligible for final approval.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Gary Buehler 1/17/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

Copy 1 (archival) ✓
Copy 2 (review)
Copy 3 (field)

NEW CORRESP
NC

December 1, 2000

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 75-467
BUSPIRONE HCl TABLETS USP, 5 MG, 7.5 MG, 10 MG AND 15 MG

Dear Sir/Madam:

In accordance with 21 CFR §314.94(a)(12)(viii)(C), Par Pharmaceutical, Inc. wishes to amend the submitted certification of November 29, 2000 with the attached Paragraph IV Certification for Patent Number 6,150,365 for its Abbreviated New Drug Application for Buspirone HCl Tablets USP 5 mg, 7.5 mg, 10 mg and 15 mg. Although we were not formally notified, it is our understanding that the Agency is not accepting the type of certification filed on November 29, 2000 at this time in this matter.

Par Pharmaceutical, Inc. certifies that the field copy is a true copy of the technical information contained in the archival and review copies of this amendment and was submitted to the New York District Office. Please contact us if you require any additional information or have any questions regarding this certification.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

*Brenda Holman, District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 0 4 2000
OGD

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

✓ Copy 1 (archival)
Copy 2 (review)
Copy 3 (field)

NEW CORRESP
NC

November 29, 2000

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 75-467
BUSPIRONE HCl TABLETS USP, 5 MG, 7.5 MG, 10 MG AND 15 MG

Dear Sir/Madam:

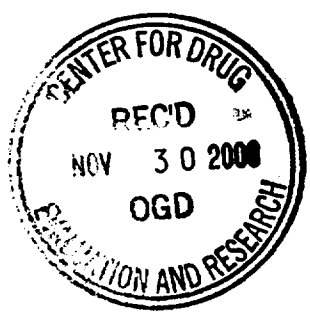
In accordance with Section 505 (j) (2) (A) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355), Par Pharmaceutical, Inc. provides the enclosed Patent Certification for its Abbreviated New Drug Application for Buspirone HCl Tablets USP 5 mg, 7.5 mg, 10 mg and 15 mg:

Please contact us if you require any additional information or have any questions regarding this certification.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

*Brenda Holman, District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433



Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

ORIG AMENDMENT
N/AF

Copy 1 ✓
Copy 2

October 31, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

LABELING AMENDMENT

RE: ANDA 75-467
Buspirone HCl Tablets USP, 5 mg, 7.5 mg, 10 mg and 15 mg

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated September 29, 1998 and all subsequent amendments relative to Buspirone HCl Tablets 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to our telephone conversation with Lilly Golson of the Labeling Review Branch on October 30, 2000. Ms. Golson called to request that Par remove from its package insert references to the 5 mg, 10 mg and 15 mg strengths and submit to the applicaiton revised labeling for the 7.5 mg strength only.

In light of the above, enclosed in Attachment I, please find twelve (12) final printed copies of our revised package insert. The insert was revised to remove all references to the 5 mg, 10 mg and 15 mg strengths from the **DESCRIPTION** and **HOW SUPPLIED** sections of the insert and delete the Patient Instruction Sheet for the 15 mg tablet. The balance of the text remains the same. In order to facilitate the review of this submission, a side by side comparison of the proposed package insert with that of our submission of October 8, 1999 is provided in Attachment II.

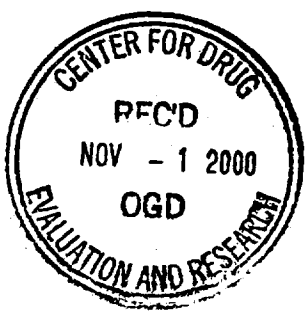
This concludes our response to the Agency's comments of October 30, 2000. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

Enclosures



Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

ORIG AMENDMENT

N/A M

Requested removal of reference to 5 mg, 10 mg, 15 mg strengths from labeling
10/30/00

Copy 1 (archival)
Copy 2 (review)
Copy 3 (field)*

September 26, 2000

Ms. Elaine Hu
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

MINOR AMENDMENT

RE: ANDA 75-467
Buspirone HCl Tablets USP, 5 mg, 7.5 mg, 10 mg and 15 mg

Dear Ms. Hu:

Reference is made to our abbreviated new drug application dated September 29, 1998 and all subsequent amendments relative to Buspirone HCL Tablets 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to the Agency's tentative approval letter dated May 23, 2000, pertaining thereto. A photostatic copy of the Agency's correspondence is enclosed for reference as Attachment I.

In accordance with the above, we submit this minor amendment to reactivate the application prior to final approval. Please be advised that there are no changes in the conditions under which the product was tentatively approved.

Per your instructions, we are submitting 24 months long term stability data conducted at 25°/60%RH for the 5 mg, 7.5 mg, 10 mg and 15 mg strengths. The updated stability data are provided in Attachment II. Final printed labeling was submitted on October 8, 1999 and appropriate updated chemistry, manufacturing and controls information were submitted on October 26, 1999 and November 19, 1999, respectively.

We acknowledge that final approval will not be made effective until the additional exclusivity period granted to the reference listed drug holder for US patent 4,182,763 has expired, currently November 22, 2000. Introduction or delivery into interstate commerce of the drug products will not occur before the effective date of approval of the application.

CENTER FOR DRUG
REC'D
SEP 27 2000
OGD
EVALUATION AND RESEARCH

RECEIVED

Par Pharmaceutical, Inc. certifies that a field copy of this minor amendment has been provided to the FDA New York District Office. Please contact us if additional information is required.

Sincerely
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

* Brenda Holman
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

ANDA 75-467

MAY 23 2000

Par Pharmaceutical, Inc.
Attention: Janis A. Picurro
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application dated September 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Buspirone Hydrochloride Tablets USP, 5 mg, 7.5 mg, 10 mg, and 15 mg.

Reference is also made to the tentative approval letter issued by this office on December 28, 1999, and to your amendment dated March 30, 2000 requesting that final approval be made effective May 22, 2000.

We have completed the review of this abbreviated application as amended and have concluded that based upon the information you have presented to date, the drug product remains safe and effective for use as recommended in the submitted labeling. However, the application remains **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, BuSpar Tablets of Bristol Myers Squibb Co. Pharmaceutical Research Institute (BMS), is currently subject to periods of patent protection which were due to expire on May 22, 2000, (U.S. Patent No. 4,182,763, the '763 patent) and May 14, 2008, (U.S. Patent No. 5,015,646, the '646 patent). Your application contains a Paragraph IV Certification to the '646 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your commercial manufacture, use, or sale of this drug product will not infringe on this patent. You have notified the Agency that Par Pharmaceutical, Inc. (Par) has complied with the

requirements of Section 505(j)(2)(B) of the Act and that no legal action regarding the '646 patent was brought against Par within the statutory forty-five day period. In addition, your application contains a Paragraph III Certification to the '763 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent.

As noted in the current edition of the Agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the "Orange Book", the '763 patent was scheduled to expire on May 22, 2000. However, Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) created Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505A permits the sponsor of the new drug application for the RLD to obtain an additional six months of exclusivity if, in accord with the statute, the sponsor submits data previously requested by the Agency relating to the safe and effective use of the drug in a pediatric population. In this case, the RLD holder, BMS, has submitted data to support the use of buspirone hydrochloride in a pediatric population. The agency's Pediatric Exclusivity Board has determined that the data support the granting of 6 months of exclusivity to the RLD. Consequently, the awarding of this exclusivity will effectively lengthen the life of the two patents referenced above by an additional 6 months. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the additional exclusivity period granted to the RLD holder for the '763 patent has expired; i.e., November 22, 2000.

To reactivate your application, please submit an amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. Please note that this amendment should be submitted even if none of these changes were made. The amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit such an amendment requested by the Agency will prompt a review of the application which may result in rescission of the tentative approval status of your

application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to November 22, 2000, you should amend your application accordingly.

At the time you submit any amendments, you should contact Ms. Elaine Hu, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler 5/23/00

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telex 131336 • Telecopier (914) 425-7907

NDA ORIG AMENDMENT
N/AM

March 30, 2000

Copy 1✓
Copy 2
Copy 3 (field)*

Ms. Elaine Hu
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

MINOR AMENDMENT

RE: **ANDA 75-467**
BUSPIRONE HYDROCHLORIDE TABLETS, USP, 5 MG, 7.5 MG, 10 MG AND 15 MG

Dear Ms. Hu:

Reference is made to our abbreviated new drug application dated September 29, 1998 and all subsequent amendments relative to Buspirone Hydrochloride Tablets, USP, 5 mg, 7.5 mg, 10 mg, and 15 mg. Reference is also made to FDA's tentative approval dated December 28, 1999, pertaining thereto. A photostatic copy of FDA's correspondence is herewith enclosed for reference as Attachment II.

In accordance with the above, we herewith submit this minor amendment to reactivate the application prior to final approval. Please be advised that there are no changes in the conditions under which the product was tentatively approved.

As per your instructions, we are submitting 18 months room temperature stability data for the 5 mg, 7.5 mg, 10 mg and 15 mg strengths. The stability data are appended in Attachment III. Final printed labeling was submitted October 8, 1999 and appropriate updated chemistry, manufacturing, and controls information were submitted on October 26, 1999 and November 19, 1999, respectively.

We acknowledge that final approval will not be made effective until US patent 4,182,763 has expired, currently May 22, 2000. Introduction or delivery into interstate commerce of the drug products will not occur before the effective date of approval of the application.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 3 1 2000
OGD

NW 4-3-00

Par certifies that a field copy of this minor amendment has been provided to the FDA New York District Office. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D

* Brenda Holman
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

ANDA 75-467

DEC 28 1999

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application dated September 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Buspirone Hydrochloride Tablets USP, 5 mg, 7.5 mg, 10 mg, and 15 mg.

Reference is also made to your amendments dated November 9 (2 amendments), December 9, and December 18, 1998; and February 11, April 9, October 8, October 26, November 19, and December 20, 1999.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacturing and testing of the drug product), and is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, BuSpar Tablets of Bristol Myers Squibb Co. Pharmaceutical Research Institute, is subject to periods of patent protection which expire on May 22, 2000, (patent 4,182,763, the '763 patent) and May 14, 2008, (patent 5,015,646, the '646 patent). Your application contains a Paragraph IV Certification to the '646 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your commercial manufacture, use, or sale of this drug product will not infringe on this patent. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made

effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified the agency that Par Pharmaceutical, Inc. (Par) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for infringement against the '646 patent was brought against Par within the statutory forty-five day period. In addition, your application contains a Paragraph III Certification to the '763 patent under Section 505(j)(2)(A)(vii)(III) of the Act. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '763 patent has expired, i.e., currently May 22, 2000.

Because the agency is granting a tentative approval for this application, please submit an amendment to this application at least 60 days (but not more than 90 days) prior to the expiration of the '763 patent. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved and should include updated information such as final-printed labeling (to include appropriate changes made to the labeling of the RLD), as well as updated chemistry, manufacturing, and controls data as appropriate. The amendment serves to reactivate this application prior to final approval, and should be submitted even if none of these changes were made. This submission should be clearly designated as a MINOR AMENDMENT in your cover letter. In addition to, or instead of, the amendment requested above, the Agency may request that you submit a similar amendment at any time prior to the final date of approval.

Failure to submit such an amendment requested by the Agency will prompt a review of the application which may result in rescission of this tentative approval letter.

Any significant change in the conditions outlined in this abbreviated application requires Agency approval before the change may be made effective.

Prior to the issuance of a final approval letter by the Agency, your product will not be deemed approved for marketing under 21 U.S.C. 355 and not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to the expiration of the '763 patent on May 22, 2000, you should amend your application accordingly.

Prior to submitting an amendment, please contact Ms. Elaine Hu, R.Ph., Project Manager, at (301)827-5848, for further instructions.

The introduction or delivery for introduction into interstate commerce of the drug before the effective approval date is prohibited under 21 U.S.C. 311(d).

Sincerely yours,

D. L. Sporn 12/28/99

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

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

NEW CORRESP
NC

Copy 1 ✓
Copy 2
Copy 3 (Field*)

December 20, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

GENERAL CORRESPONDENCE

RE: ANDA 75-467
BUSPIRONE HCl TABLETS 5 MG, 7.5 MG, 10 MG AND 15 MG

Dear Sir/Madam:

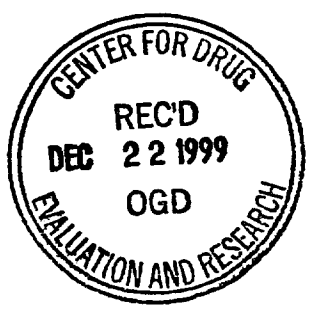
Reference is made to our abbreviated new drug application submitted September 29, 1999, our amendment dated February 11, 1999 and our telephone conversation with Greg Davis of the Agency today. Lt. Davis called to request a copy of the Return Receipt of the Patent Notification to Bristol-Myers Squibb for the 7.5 mg strength and a statement stating Par was not sued by Bristol-Myers Squibb within the 45 day period.

Enclosed, please find the Patent Certification Notice forwarded to Bristol-Myers Squibb on February 23, 1999 with regard to the 7.5 mg strength and a copy of the associated Return Receipt dated MAR 01, 1999.

Par Pharmaceutical, Inc., was not sued by Bristol-Myers Squibb within the 45 day period on patent challenge noted in Section III, Patent Certification & Exclusivity Statements, of the original application as well as the amended Patent Certification Statement provided on February 11, 1999.

Par Pharmaceutical, Inc., certifies that a field copy of this general correspondence has been provided to the FDA Brooklyn District Office. In addition, a faxed copy of this Telephone Amendment was also forwarded to Greg Davis at 301-594-01174.

Please contact us if additional information is required.



Sincerely.
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

* Brenda Holmes, District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

OCT 19 1999

3.1

38. Chemistry Comments to be Provided to the Applicant.

ANDA: 75-467 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Buspirone Hydrochloride Tablets USP, 5 mg, 7.5 mg, 10 mg, 15 mg

The deficiencies presented below represent FACSIMILE deficiencies.

1. Please revise your specifications for the finished drug product to include IR test for identification and provide IR spectra according to USP.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

1. Please submit all available room temperature stability data for each strength.

Sincerely yours,

RC Patel 10/15/99

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

NDA ORIG AMENDMENT
N/AF

Copy 1
Copy 2

October 8, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

LABELING AMENDMENT

RE: ANDA 75-467
BUSPIRONE HCl TABLETS 5 MG, 7.5 MG, 10 MG AND 15 MG

Dear Sir/Madam:

Reference is made to our abbreviated new drug application submitted September 29, 1999 as well as the Agency's correspondence of March 30,1999 and our amendments dated February 11, 1999 and April 9, 1999 for Buspirone HCl Tablets USP.

Reference is also made to the Agency's facsimile dated September 27, 1999. The facsimile outlined the labeling deficiencies due to many changes in the insert labeling of the reference listed drug, Bristol-Myers Squibb's BuSpar, approved March 2, 1998. The facsimile also outlined additional comments from the Agency for the insert and patient instruction sheet.

Both the package insert and patient instruction sheet were revised in accordance with the deficiencies noted in the Agency's September 27, 1999 facsimile, with the exception of the inclusion of the "Rx only" statement below the title of the insert and patient instruction sheet. Our insert is folded to 1¼ x 1¼. The amount of printed text is limited and the space does not allow for the additional text under the title. Because the "Rx only" statement is not a requirement for package insert labeling per the Industry Guidance for Implementation of Section 126 of the FDA Modernization Act of 1997, the statement has not been added.

Enclosed, please find twelve (12) final printed copies of our revised package insert and patient instruction sheet for tentative approval. In order to facilitate the review of this submission, a side-by-side comparison of our proposed labeling with that of our submission of April 9, 1999 is provided.

In addition, the container labels were found satisfactory in draft on March 30, 1999. Therefore, we enclose twelve (12) final printed computer generated container labels, true in size and color, for the 5 mg (100's and 500's), 7.5 mg (100's and 500's), 10 mg (100's and 500's) and 15 mg (60's) strengths for tentative approval.

Par acknowledges that prior to approval, it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug. The web-site will be monitored for any approved changes.

This concludes our response to the Agency's facsimile of September 27, 1999. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Director, Regulatory Affairs R&D

Enclosure

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

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Copy 2
Copy 3 (*Field)

N/A.C

NDA ORIG AMENDMENT

April 9, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

MAJOR AMENDMENT

RE: ANDA # 75-467
BUSPIRONE HCL TABLETS, USP 5 MG, 7.5 MG, 10 MG AND 15 MG

Dear Sir/Madam:

This is in reference to our abbreviated new drug application, submitted September 29, 1998 for buspirone HCl tablets, USP 5 mg, 10 mg and 15 mg and our amendment submitted in February 11, 1999 for buspirone HCl tablets, USP 7.5 mg.

Reference is also made to your facsimile dated March 30, 1999 outlining chemistry and labeling deficiencies (enclosed as Attachment I) pertaining to AND 75-467.

In the light of the foregoing we offer the following response and supporting documents.

Chemistry Deficiencies

A. Deficiencies:

Comment 1:

Response 1:

Comment 2:

Response 2:

Comment 3:

Response 3:

Comment 4:

Response 4:

B. In addition to responding to the deficiencies presented above, Par Pharmaceutical, Inc., notes and acknowledges the following comments:

1. The firms referenced in our application are in compliance with cGMP at the time of approval.

2. USP are the regulatory methods and will prevail in the event of dispute.

3. The gratuitous submission dated February 11, 1999 was received by the Agency after the review of the original application. Therefore, the 2/11/99 submission was not reviewed in the previous cycle. It will be reviewed along with our response to this major amendment.

Labeling Deficiencies:

Comment 1: CONTAINER - 5 mg, 7.5 mg, and 10 mg (100s and 500s)
15 mg (60s)
Satisfactory in draft

Comment 2: INSERT

a. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or the title of the package insert.

b. Revisions are included on the enclosed "mock-up" of your proposed labeling.

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

To facilitate review of your next submission and in accordance with 21 CFR 314.94 (a) (8) (iv), please provide a side-by-side comparison of your proposed labeling with your last submission with the differences annotated and explained.

Response:

The package insert labeling was revised according to the Agency's recommendations with the exception of the inclusion of "Rx Only" beneath the title. Our insert is folded to 1¼ x 1¼, the amount of printed text is limited and the space does not allow for additional text under the title. Since the "Rx only" statement is not required for package insert labeling per the Industry Guidance for Implementation of Section 126 of the FDA Modernization Act of 1997, Par would like to request the removal of the "Rx only" statement from our packaging insert. Enclosed please find four (4) draft copies of our revised insert for your review (Attachment IV). In addition, a side-by-side comparison of our proposed labeling with that of our 02/11/99 submission, with differences annotated and explained, is provided to facilitate the review of the labeling (Attachment V).

This concludes our response to the agency's facsimile received on March 30, 1999. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Teresa Tung
Senior Associate, Regulatory Affairs/R&D

Enclosed

* Brenda Holman, District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, NY 11232-1593

BIOEQUIVALENCY COMMENTS

ANDA: 75-467 APPLICANT: Par Pharmaceutical

DRUG PRODUCT: Buspirone Hydrochloride Tablets, 7.5 mg, 5 mg, 10 mg & 15 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

✓Copy 1
Copy 2
Copy 3 (field)*

February 11, 1999.

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

NDA ORIG AMENDMENT
N/AB

RE: ANDA #: 75-467
BUSPIRONE HYDROCHLORIDE TABLETS, USP 5 MG, 10 MG AND 15 MG

Dear Sir or Madam:

We submit, herewith, in duplicate, an amendment to our original application submitted on September 29, 1998 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act on the basis of a petition, Docket No. 98P-0967/CP1, filed on October 29, 1998 by Lachman Consultant Services, Inc. in accordance with 21 CFR 10.30, requesting permission to file an Abbreviated New Drug Application for Buspirone HCl Tablets 7.5 mg and approved on February 1, 1999. A copy of the Approval Letter is enclosed in ADDENDUM II.

The proprietary name of said drug is BuSpar®. The certification concerning the patent is set forth under ADDENDUM III.
Par Pharmaceutical, Inc., believes that we are the first to file an amendment for the 7.5 mg strength of Buspirone HCl Tablets with a Paragraph IV Certification. Therefore, Par also believes that we are entitled to 180 day exclusivity for this strength, please adjust your files accordingly.

Par Pharmaceutical, Inc. hereby requests a waiver of the *in-vivo* bioequivalence study requirements for Buspirone HCl Tablets, USP 7.5 mg on the basis of proportionally similar quantitative formulation, *in-vitro* dissolution data and the *in-vivo* bioavailability studies performed under fasting and fasting/fed conditions comparing Par's Buspirone HCl Tablets, USP 15 mg with the listed reference product, BuSpar® (Buspirone HCl), USP 15 mg.

Please contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Michelle Bonomi-Huvala
Associate Director, Regulatory Affairs/R&D
Enclosures

RECEIVED
FEB 12 1999
GENERIC DRUGS

* Brenda Holman
District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

Peter Rickman (Cover Letter Only)
CDER, Metro Park North 2
7500 Standish Place
Rockville, Maryland 20855

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

February 11, 1999.

Brenda Holman
District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

RE: ANDA #: 75-467
BUSPIRONE HYDROCHLORIDE TABLETS, USP 5 MG, 10 MG AND 15 MG

Dear Sir or Madam:

We submit, herewith, in duplicate, an amendment to our original application submitted on September 29, 1998 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act on the basis of a petition, Docket No. 98P-0967/CP1, filed on October 29, 1998 by Lachman Consultant Services, Inc. in accordance with 21 CFR 10.30, requesting permission to file an Abbreviated New Drug Application for Buspirone HCl Tablets 7.5 mg and approved on February 1, 1999. A copy of the Approval Letter is enclosed in ADDENDUM II.

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Par Pharmaceutical, Inc. hereby requests a waiver of the *in-vivo* bioequivalence study requirements for Buspirone HCl Tablets, USP 7.5 mg on the basis of proportionally similar quantitative formulation, *in-vitro* dissolution data and the *in-vivo* bioavailability studies performed under fasting and fasting/fed conditions comparing Par's Buspirone HCl Tablets, USP 15 mg with the listed reference product, BuSpar® (Buspirone HCl), USP 15 mg.

Please contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Associate Director, Regulatory Affairs/R&D

Enclosures

Par
Pharmaceutical,
Inc.

NDA ORIG AMENDMENT
A3

One Ram Ridge Road, Spring Valley, NY 10977
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✓ Copy 1
Copy 2

December 18, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

BIOEQUIVALENCE AMENDMENT

RE: ANDA #75-467
Buspirone HCl Tablets, USP 5 mg, 10 mg and 15 mg

a. A comparative, randomized, single-dose, 2-way crossover bioavailability study was conducted of Par's and Bristol-Myers Squibb's (BuSpar®) 15 mg buspirone hydrochloride tablets in healthy adult males under fasting conditions (Phoenix Project No.

b. A comparative, randomized, single-dose, 3-way crossover bioavailability study was conducted of Par's and Bristol-Myers Squibb's (BuSpar®) 15 mg buspirone hydrochloride tablets in healthy adult males under fasting and fed conditions. (Phoenix Project No.

Dear Sir/Madam:

Reference is made to our abbreviated new drug application, submitted September 29, 1998 for Buspirone HCl Tablets, USP 5 mg, 10 mg and 15 mg. At this time we submit, in duplicate, copies of final report amendments for the above referenced studies (Attachment 1 and Attachment 2).

a. The Report Amendment, Phoenix Project No Attachment 1) is to amend the total number of events reported for "Dizziness" in Appendix 6 Table C3 (Par's ANDA reference pages 460 and 461).

Page No. 7 (Par's ANDA reference page 460): The total post-dose medical events with a probable association to the study drug was changed from "49" to "48" and the number of events reported for "Dizziness" (Product Code A) was changed from "9" to "8". The pagination was updated to read "Page No. 7A".

Page No. 8 (Par's ANDA reference page 461): The total post-dose events was changed from "59" to "58". The pagination was updated to read "Page No. 8A".

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GENERIC DRUGS

b. The Report Amendment, Phoenix Project No. 980564 (Attachment 2) is to amend a number of medical events dosing dates, in Appendix 7 Table C4 (Par's ANDA reference pages 2198 - 2210).

Page No. 10 (Par's ANDA reference page 2199): "Dizziness" and "Feels "strange" (lightheaded)" were changed from "AUG" to read "JUL".

Page No. 11 (Par's ANDA reference page 2200): "Dizziness" and "Light vertigo" were changed from "AUG" to "JUL".

Page No. 12 (Par's ANDA reference page 2201): "Upper body feels hot", "Hot flashes (intermittent)" and "Feels sleepy" were changed from "AUG" to read "JULY"; "Dizziness" was changed from "SEP" to read "AUG".

Page No. 13 (Par's ANDA reference page 2202): "Frequent urination" was changed from "AUG" to read "JUL".

Page No. 17 (Par's ANDA reference page 2206): "Vomited" was changed from "AUG" to read "JUL".

Page No. 21 (Par's ANDA reference page 2210): "Light dizziness" was changed from "AUG" to read "JUL".

The report amendments received from Phoenix International Life Science, Inc. are provided for your reference. If you need any further assistance, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Teresa Tung
Senior Regulatory Affairs Associate

BIOEQUIVALENCY COMMENTS

ANDA: 75-467 APPLICANT: Par Pharmaceutical

DRUG PRODUCT: Buspirone Hydrochloride Tablets, 5 mg, 10 mg & 15 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

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

ATTACHMENTS (5 pages)

FIGURE 1A

BUSPIRONE PLASMA CONCENTRATIONS (PG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #980563
(LINEAR PLOT)

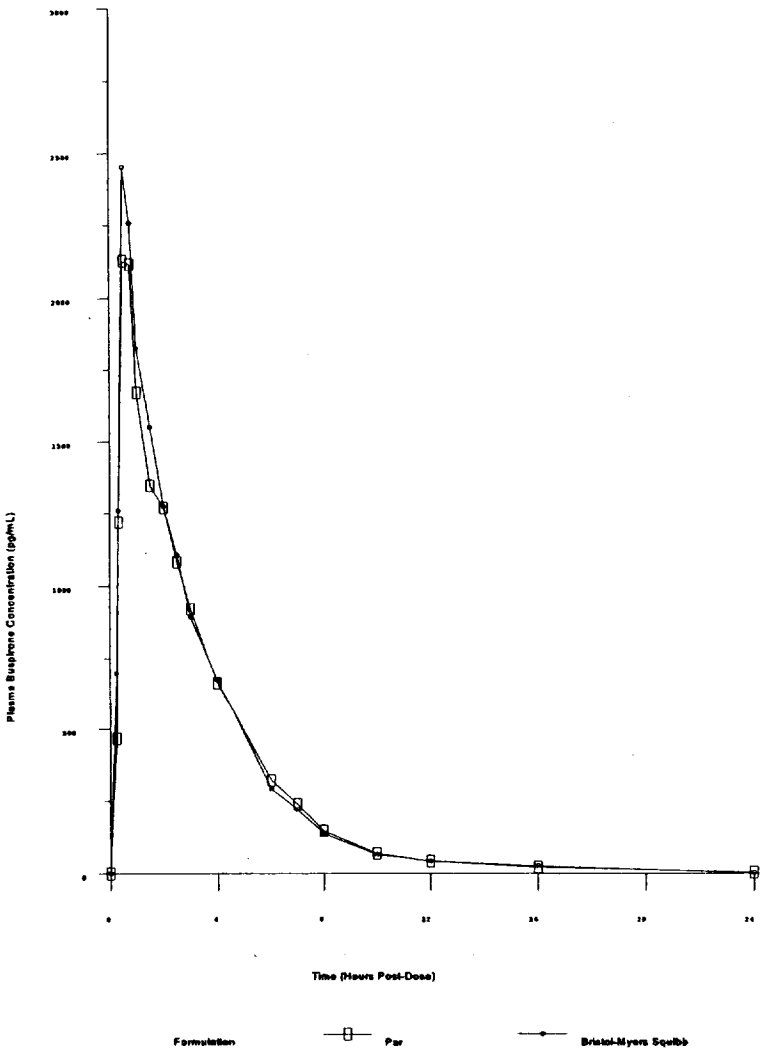


FIGURE 1B

1-PP PLASMA CONCENTRATIONS (PG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #980563
(LINEAR PLOT)

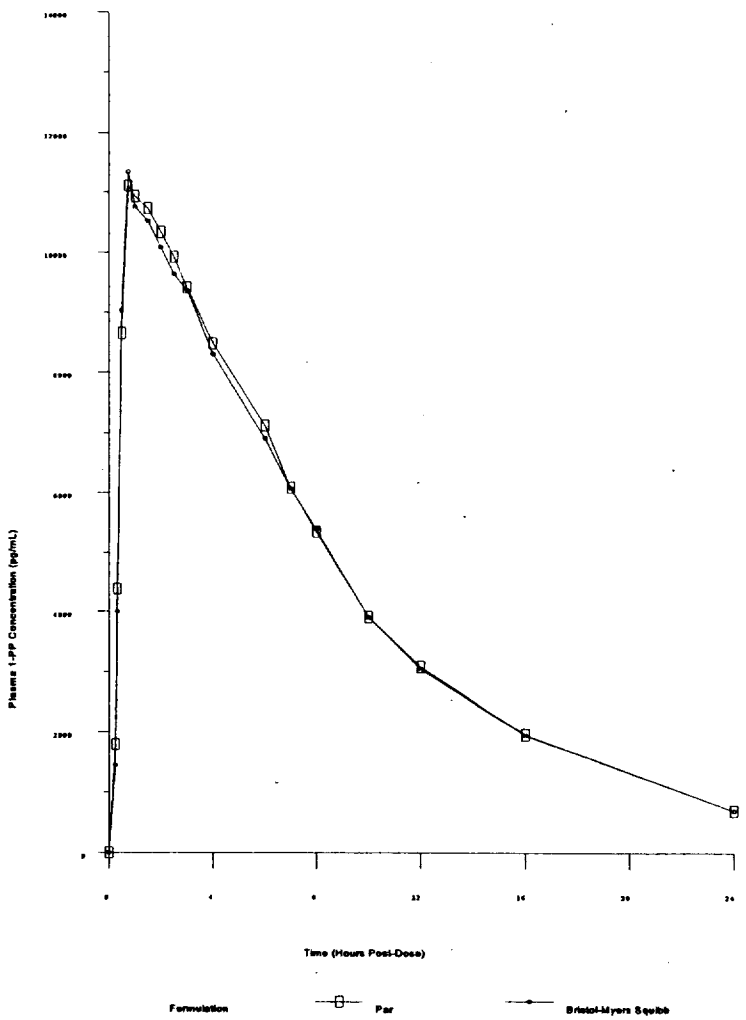


FIGURE 1C

BUSPIRONE PLASMA CONCENTRATIONS (PG/ML) VERSUS TIME

SINGLE-DOSE FED/FASTING STUDY #980564

(LINEAR PLOT)

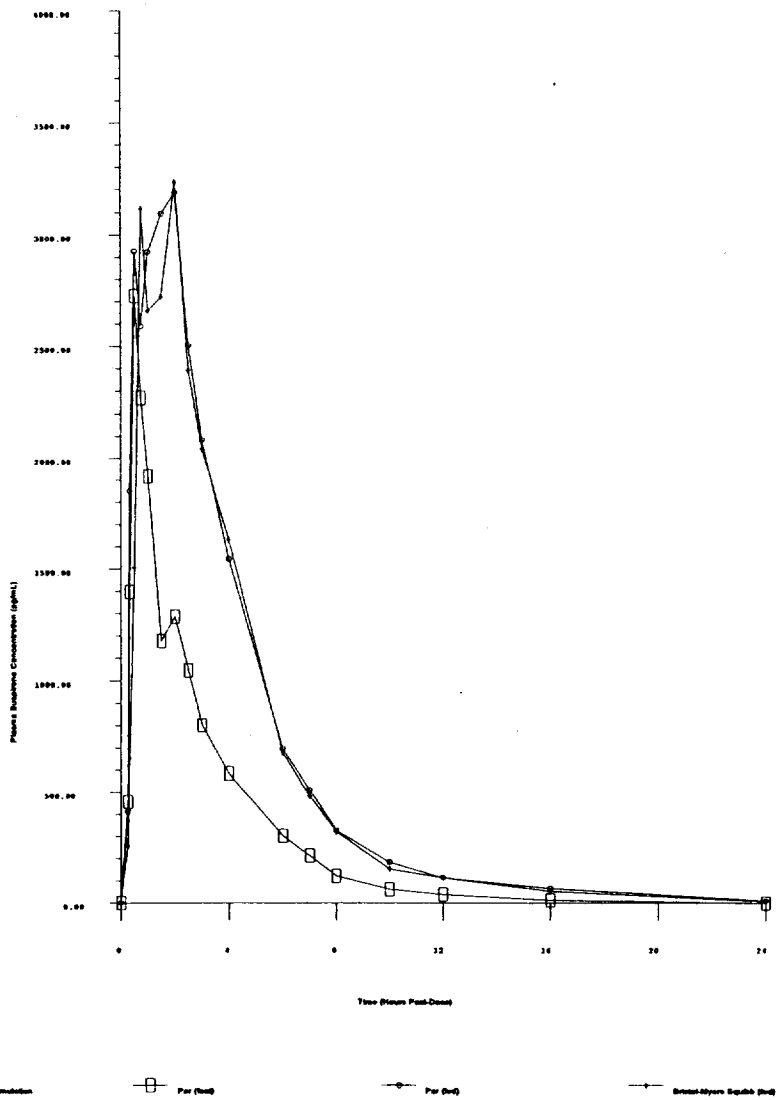
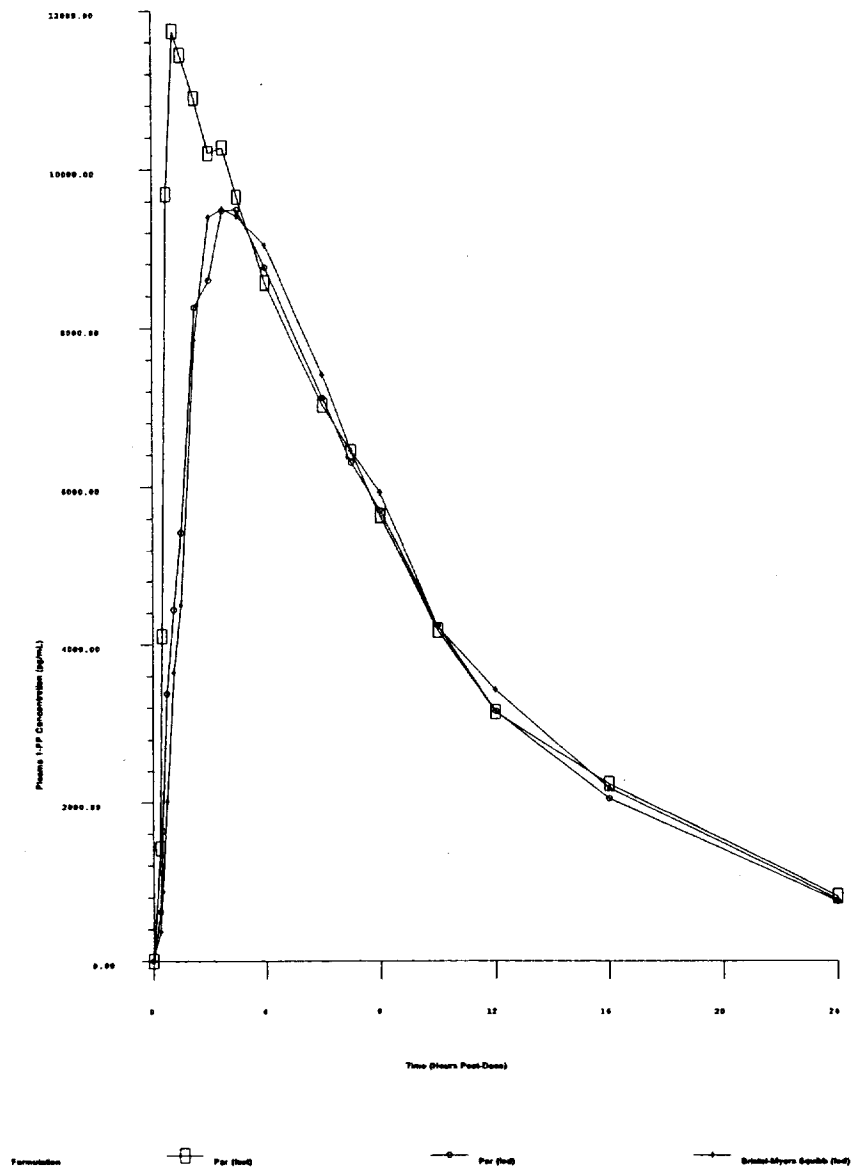


FIGURE 1D

1-PP PLASMA CONCENTRATIONS (PG/ML) VERSUS TIME

SINGLE-DOSE FED/FASTING STUDY #980564

(LINEAR PLOT)



Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

NDA ORIG AMENDMENT
tb

✓Copy 1
Copy 2

December 9, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

BIOEQUIVALENCE TELEPHONE AMENDMENT

RE: ANDA #75-467
Buspirone HCl Tablets, USP 5 mg, 10 mg and 15 mg

Dear Sir/Madam:

Reference is made to our abbreviated new drug application, submitted September 29, 1998 for Buspirone HCl Tablets, USP 5 mg, 10 mg and 15 mg. In response to the telephone call on December 7, 1998 regarding the manufacture date of the test product of the bio lot (15 mg), the manufacture date is April 27, 1998. This information is also provided on page 4747 in the above stated ANDA. If you need any further assistance, please do not hesitate to contact us.

As requested, a copy of this letter has been sent to the agency via facsimile with hard copy to follow in the mail.

Sincerely,
PAR PHARMACEUTICAL, INC.

Teresa Tung
Senior Regulatory Affairs Associate

DEC 10 1998
GENERIC DRUGS

Par
Pharmaceutical,
Inc.

UPS Tracking Number: N405 351 669 1

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

NEW CORRES.

✓Copy 1
Copy 2

November 9, 1998

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 75-467: BUSPIRONE HYDROCHLORIDE TABLETS, USP 5 MG, 10 MG AND 15 MG AMENDMENT : DOCUMENTATION OF RECEIPT OF NOTICE

Dear Sir or Madam:

We are amending our application for Buspirone Hydrochloride Tablets, USP 5 mg, 10 mg and 15 mg, in accordance with 21 CFR 314.95(e), to provide documentation that the holder of patents identified in Section III of ANDA 75-467 have been notified.

A photocopy of the United States Postal Service Return Receipt, which accompanied notification to Bristol-Myers Squibb Company is enclosed in this amendment.

Please contact us should you require additional information. Our facsimile number in Regulatory Affairs is 914-425-6105.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Teresa Tung
Sr. Regulatory Affairs Associate, Regulatory Affairs/R&D

Enclosures

NOV 10 1998

Par
Pharmaceutical,
Inc.

UPS Tracking Number: N405 351 820 6

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

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NDA ORIG AMENDMENT
AB

November 9, 1998

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: AMENDMENT: ELECTRONIC SUBMISSION DOCUMENTS FOR BIOEQUIVALENCE STUDY - EVA SUBMISSION
ANDA # 75-467: BUSPIRONE HYDROCHLORIDE TABLETS, USP 5 MG, 10 MG AND 15 MG

Dear Sir or Madam:

Enclosed please find two diskettes (the original copy and the archival copy) for the Electronic Submission Documents of Buspirone Hydrochloride Tablets Bioequivalence Studies which were submitted on September 29, 1998.

Attached are also the certification letters from Phoenix International Life Sciences Inc. where the Electronic Submission Documents are prepared.

Please contact us should you require additional information. Our facsimile number in Regulatory Affairs is 914-425-6105.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Teresa Tung
Sr. Regulatory Affairs Associate, Regulatory Affairs/R&D

NOV 10 1998

Enclosures

MAR 30 1999

38. Chemistry Comments to be provided to the Applicant.

ANDA: 75-467 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Buspirone Hydrochloride Tablets USP, 5 mg, 7.5 mg, 10 mg, 15 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please revise your drug substance specifications to include a test for melting point as a polymorph control. Indicate which polymorph was used in the bio batch and set controls for future batches.

2. Please revise the specifications for finished drug product to include limits and specifications for hydroxy analog impurity.

3. Please revise the stability specifications to include limits and specifications for hydroxy analog impurity.

4. Please provide RSD limits for the blend assay test.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application should be in compliance with CGMP at the time of approval.

2. USP are the regulatory methods and will prevail in the event of dispute.

3. The gratuitous submission dated February 11, 1999 was received after the review of the original application. Therefore, the 2/11/99 submission was not reviewed this cycle. It will be reviewed along with your response to this major amendment action.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: 75-467 APPLICANT: Par Pharmaceutical

DRUG PRODUCT: Buspirone Hydrochloride Tablets, 7.5 mg, 5 mg, 10 mg & 15 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

ANDA 75-467

Par pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

OCT 21 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Buspirone Hydrochloride Tablets USP, 5 mg, 10 mg and 15 mg

DATE OF APPLICATION: September 29, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 30, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Joseph Buccine
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NEW DRUG APPLICATION

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Ent
C. Holquist
10/9/98

Par
Pharmaceutical,
Inc.

Copy 1
Copy 2
Copy 3 (field)*

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

September 29, 1998

RE: BUSPIRONE HYDROCHLORIDE TABLETS, USP 5 MG, 10 MG AND 15 MG
ELECTRONIC SUBMISSION OF BIOAVAILABILITY/BIOEQUIVALENCE STUDY (EVA)
WILL BE SUBMITTED WITHIN 45 DAYS AFTER FILING THIS HARD COPY

Dear Sir or Madam:

We submit, herewith, in duplicate, an abbreviated new drug application for Buspirone Hydrochloride Tablets, USP 5 mg, 10 mg and 15 mg. The application is submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

The official name of the drug relied upon as the basis upon which this application may be filed is Buspirone Hydrochloride, USP. The proprietary name of said drug is BuSpar®. The certification concerning the patent is set forth under SECTION III. The approved insert labeling for the listed drug is enclosed in SECTION V. The third (field) copy certification is provided in SECTION XXI.

A copy of the appropriate pages of the Approved Drug Products with Therapeutic Equivalence Evaluations List is enclosed in SECTION II to show that the proposed drug is the same as the listed drug.

A comparative, randomized, single-dose, 2-way crossover bioavailability study was conducted of Par's and Bristol-Myers Squibb's (BuSpar®) 15 mg buspirone hydrochloride tablets in healthy adult males under fasting conditions and a comparative, randomized, single-dose, 3-way crossover bioavailability study was conducted of Par's and Bristol-Myers Squibb's (BuSpar®) 15 mg buspirone hydrochloride tablets in healthy adult males under fasting and fed conditions. The bioavailability studies are submitted along with the ***in-vitro*** dissolution data. These studies are also applicable to the 5 mg and 10 mg strengths as the formulations are doses proportional. A request for the waiver of the bioequivalency requirements for this application is submitted along with the *in-vitro* dissolution data.

Please contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Associate Director, Regulatory Affairs/R&D
Enclosures

RECEIVED
SEP 30 1998
GENERIC DRUGS

* Brenda Holmes
District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

September 29, 1998

Brenda Holmes
District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

RE: BUSPIRONE HYDROCHLORIDE TABLETS, USP 5 MG, 10 MG AND 15 MG
ELECTRONIC SUBMISSION OF BIOAVAILABILITY/BIOEQUIVALENCE STUDY(EVA)
WILL BE SUBMITTED WITHIN 45 DAYS AFTER FILING THIS HARD COPY.

Dear Sir or Madam:

We submit, herewith, in duplicate, an abbreviated new drug application for Buspirone Hydrochloride Tablets, USP 5 mg, 10 mg and 15 mg. The application is submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

The official name of the drug relied upon as the basis upon which this application may be filed is Buspirone Hydrochloride, USP. The proprietary name of said drug is BuSpar®. The certification concerning the patent is set forth under SECTION III. The approved insert labeling for the listed drug is enclosed in SECTION V. The third (field) copy certification is provided in SECTION XXI.

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Please contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Michelle Bonomi-Huvala
Associate Director, Regulatory Affairs/R&D
Enclosures