CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 073585

Name: Sudafed (Pseudoephedrine Hydrochloride Extended-Release Tablet)
120 mg

Sponsor: Burroughs Wellcome Co.

Approval Date: October 31, 1991

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 073585

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Chemistry Review(s)	X
Bioequivalence Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 073585

APPROVAL LETTER

ANDA 73-585

Burroughs Wellcome Co.
Attention: Ms. Anne F. McKay
3030 Cornwallis Road
Research Triangle Park, NC 27709

OCT 31 1991

Dear Madam:

Reference is made to your abbreviated new drug application dated June 12, 1990, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for SUDAFED (Pseudoephedrine Hydrochloride Extended-release Tablet), 120 mg (Caplet). The application provides for the over-the-counter marketing of this drug product.

Reference is also made to your amendments dated May 3, June 25, September 25, October 23, and October 24, 1991.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your drug product can be expected to have the same therapeutic effect as that of the listed drug, Sudafed 12-hour capsule, 120 mg, manufactured by your firm.

The dissolution testing should be incorporated into the stability and quality control program.

The dissolution testing should be conducted in 900 mL of distilled water at 37°C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than 25% and not more than 45% of the labeled amount of drug in the dosage form is dissolved in 1 hour.
>
> Not less than 50% and not more than 75% of the labeled amount of drug in the dosage form is dissolved in 3 hours.
>
> Not less than 75% of the labeled amount of drug in the dosage form is dissolved in 6 hours.

Any significant change in the conditions outlined in this abbreviated application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.70 of the Regulations.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80 and 314.81 of the Regulations.

This administration should be advised of any change in the marketing status of this drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate 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.

For Subsequent Campaigns: We call your attention to Section 314.81(b)(3) of the Regulations which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

10/31/91

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-585
DUP/Division File
HFC-130/JAllen
HFD-19
HFD-82
HFD-600 Reading File
HFD-638/JPhillips
HFD-634/MSmela/MShaikh/10/23/91
HFD-634/VVashio/10/24/91
R/D initialed by MSmela
cls/10/24/91/d:73-585.LTR
F/T by cls/10/24/91
Approval

F Phillips 10/28/91

Mujahid Shaikh 10-25-91

Washio 10/28/91

MSmela 10/28/91

RF Reed 10/30/91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

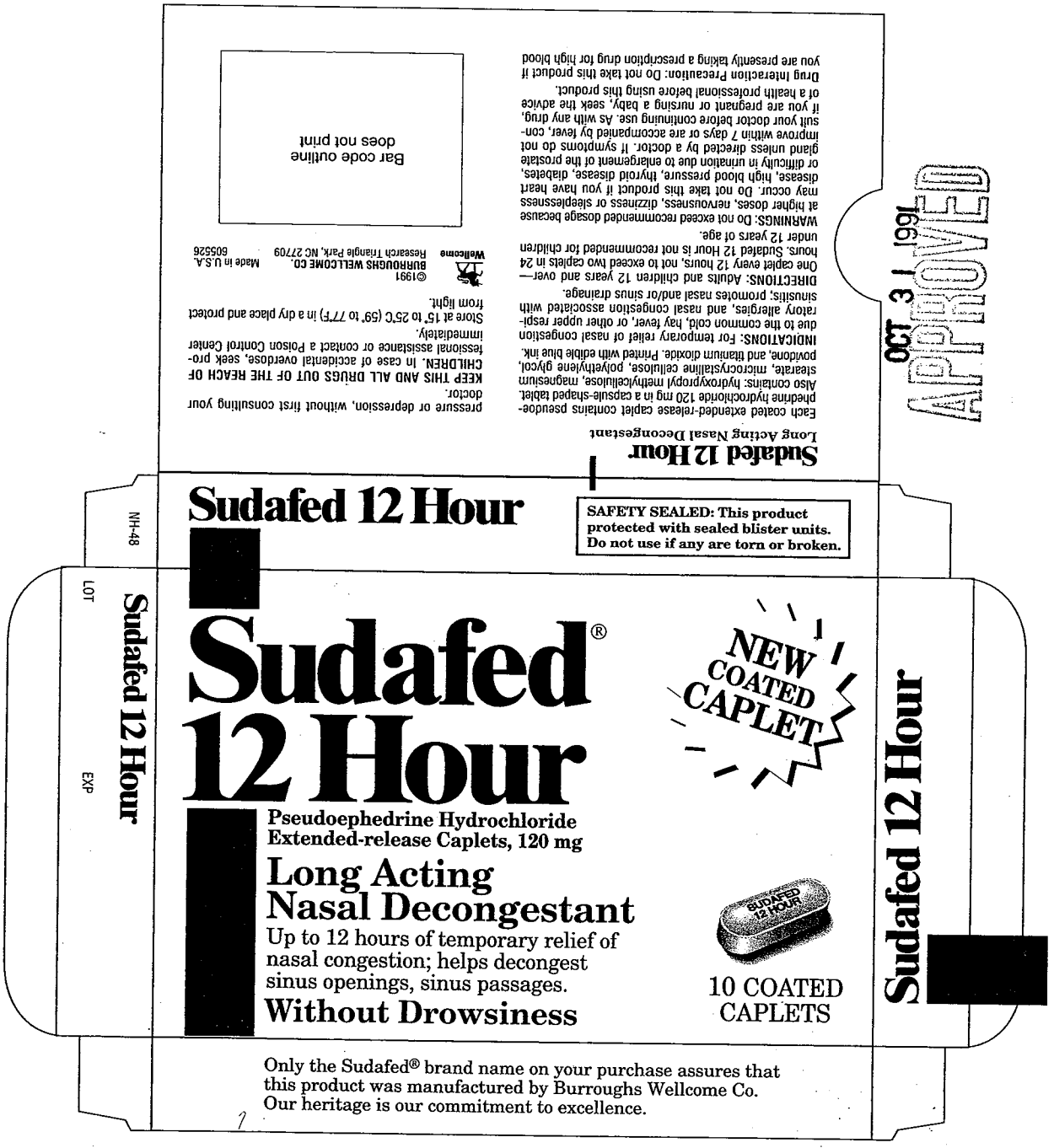
ANDA 073585

LABELING

FINAL PRINTED LABELING

SUDAFED® 12 Hour Caplets
(PSEUDOEPHEDRINE HYDROCHLORIDE 120 mg)

Carton x 10



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 073585

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING

ANDA

DRAFT

DATE OF REVIEW: October 10, 1990

ANDA #: 73-585

NAME OF FIRM: Burroughs Wellcome

NAME OF DRUG: Trade: SUDAFED 120 mg Caplet
Generic: (Pseudoephedrine Hydrochloride Extended-release)

DATE OF SUBMISSION: June 12, 1990

COMMENTS:

Carton: Not Satisfactory

FRONT:

A. We would recommend that the phrase "[redacted] (b) (4)" be replaced with "Extended-release". This term is currently used in the USP.

B. Define "Caplets" (capsule-shaped tablet).

C. Separate the statement of identity (Nasal Decongestant) from the established name. In addition, revise the established name and strength to read:

> Pseudoephedrine Hydrochloride Extended-release Caplets, 120 mg.

BACK:

A. Revise to read:

Each coated Extended-release caplet....

B. The labeling for this product should be updated to follow the tentative final monograph for OTC nasal decongestant drug products (January 15, 1985; 50 FR 2220). However, if you elect to retain your current labeling you will be expected to conform to the "final monograph", when issued.

In any case, the Drug-Interaction Precaution must be updated to read:

> Do not take this product if you are presently taking a prescription drug for high blood pressure

or depression, without first consulting your physician.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their carton labeling, then prepare and submit a draft copy of their revised carton labeling.

Jerry Phillips 10/25/90
Jerry Phillips

cc;
HFD-638
JPhillips/TPoux
hab 10/19/90
73585

Burroughs Wellcome LABELING WORKSHEET

ANDA #: 73-585 ANDA#: ANDA#:
PRODUCT NAME: Sudafed (Pseudoephedrine 120mg Extended-release) Caplet
NDA HOLDER(S): BW
NDA NUMBER(S): ~~18-996~~ 17-941

LABELING OF THE LISTED DRUG

DATE NOTED:	FIRM:	NDA#:	APPROVAL DATE:	REV. DATE:
10-88	BW	17-941	10-6-88	

CONTAINER LABELS:
APPROVED COPY ON FILE? ✓ Y ___ N ___ COMMENT
USP CONTAINER/CLOSURE REQUIREMENTS: —
OTHER KEY ISSUES: NONE

INSERT LABELING:
PATENT ISSUES: NONE
EXCLUSIVITY ISSUES: NONE
BIO ISSUES: Bio FOUND SATISFACTORY on April 9, 1991
OTHER KEY ISSUES: NONE

SUMMARY FOR APPLICATION APPROVAL:
CONTAINER LABELS:
CARTONING: Satisfactory (10a) on June 25, 1991
LABELING COMMENT/FURTHER REVISION:

E: July 8, 1991 REVIEWER: Terry P. Phillips
SUPERVISOR: T. Parr 7/9/91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 073585

CHEMISTRY REVIEWS

File Copy

1. CHEMIST'S REVIEW NO.1

2. ANDA # 73-585

3. NAME AND ADDRESS OF APPLICANT
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park
NC 27709

4. AF NUMBER
-

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
SUDAFED

7. NONPROPRIETARY NAME
Pseudoephedrine HCl

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

9. AMENDMENTS AND OTHER DATES:
Original Submission 5-30-90

10. PHARMACOLOGICAL CATEGORY
Nasal Decongestant

11. Rx or OTC
OTC

12. RELATED IND/NDA/DMF(s)
DMF [redacted] (b) (4)
DMF

13. DOSAGE FORM
Tablet (Caplet)

14. POTENCY
120 mg

15. CHEMICAL NAME AND STRUCTURE
Name: (+)-(S,S)-2-Methylamino-1-Phenyl-1-propanol Hydrochloride

Structure:

16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. **General Comments:**

i. Pre-approval EER - Acceptable
ii. in-vivo Bioequivalence and in-vitro dissolution testing - approved
iii. Container/closure system - satisfactory
iv. Environment Impact Consideration/Categorical Exclusion- Analysis submitted- satisfactory
v. DMF [redacted] (b) (4) - Unsatisfactory
vi. The drug product will be manufactured , processed,

packaged, labeled, and controlled at applicant's Greenville, North Carolina facility.

vii. Reprocessing procedures are not described.

viii. Stability data for the executed test batch (bio-batch) # 9S6005 is not submitted.

ix. Post-Approval stability commitment is not submitted.

B. **Comments to be included in the NA letter to the firm:**

(b) (4)

i.

ii.

iii.

iv.

v.

vi.

vii.

viii.

ix.

x.

xi.

xii.

xiii. Labeling issues should be included.

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approved.

19. REVIEWER: DATE COMPLETED:
Mujahid L. Shaikh 4-15-91
cls/04/17/91/b:73-585.REV

Mujahid Shaikh 4-17-91

Following this page, 6 pages withheld in full (b)(4)-CCI/TS

Not satisfactory per Jerry Phillips's review dated 10-25-90. the deficiencies are being included in the NA letter to the firm.

33. ESTABLISHMENT INSPECTION

EER were requested by V.Vashio on 6-7-90 for the following firms:

i. Burroughs Wellcome Co.
Greenville, NC 27834.

ii. [redacted] (b) (4)

iii. [redacted] (b) (4)

Comments: EER acceptable dated 6-18-90
Pre-Approval EER acceptable dated 4-12-91.

34. BIOEQUIVALENCY STATUS

Dr. James D. Henderson, Review Branch II, Division of Bioequivalence reviewed this ADNA 73-585 and his recommendations are as follows:

1. Pseudoephedrine HCl 12-Hour Caplet 120 mg is biequivalent to the reference product Sudafed 12- Hour Capsule 120-mg manufactured by BW.
2.The dissolution testing should be included into the firm's manufacturing controls and stability program.
3. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and in-vitro dissolution testings and **the application is approvable.**

Comment: BW does not have the Bio approval for the executed test batch # 9S6005. A request for Comparative dissolution data of all the batches manufactured by BW, especially for the lots 7U2752 and 9S6005, is being made to the firm.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Environmental Impact Analysis Report is submitted and is satisfactory

36. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes_____
No__X__

If no, explain reason(s) below:
Expedited review of this ANDA was requested by the Commissioner of FDA and the Director of OGD due to Sudafed capsule ~~scandal~~ product tampering nationwide.

4/18/91

#2

2.1

1. CHEMIST'S REVIEW NO.2

2. ANDA # 73-585

3. NAME AND ADDRESS OF APPLICANT
Burroughs-Wellcome Co.
3030 Cornwallis Road
Research Triangle Park
NC 27709

4. AF NUMBER
-

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Sudafed

7. NONPROPRIETARY NAME
Pseudoephedrine HCl

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

9. AMENDMENTS AND OTHER DATES:
Original Submission 5-30-90
Amendment 5-3-91
FDA Correspondence: 4-18-91

10. PHARMACOLOGICAL CATEGORY
Nasal Decongestant

11. Rx or OTC
OTC

12. RELATED IND/NDA/DMF(s)
DMF (b) (4)
DMF

13. DOSAGE FORM
Tablet (Caplet)

14. POTENCY
120 mg

15. CHEMICAL NAME AND STRUCTURE
Submitted in Review No. 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Pre-approval EER - Acceptable.
2. in-vivo Bioequivalence and in-vitro dissolution testing - approved.
3. Container/closure system - satisfactory
4. Stability data and commitment - satisfactory
5. Expiration date - 24 months acceptable
6. Release specifications for drug substance and drug product - satisfactory
7. Batch size post-approval - (b) (4) tablet and executes test batch size - (b) (4) tablet.
8. Manufacturing batch records - satisfactory
9. Laboratory controls in process and finished dosage form satisfactory.
10. Control numbers - satisfactory.
11. Environmental impact analysis report - satisfactory.

12. DMF [redacted] (b) (4) satisfactory

18. CONCLUSIONS AND RECOMMENDATIONS
Not approved. A information request letter is being sent to the firm including our analyst's and Atlanta Regional Director's comment regarding Method Validation of the subject drug product.

19. REVIEWER:
Mujahid L. Shaikh

Mujahid Shaikh
7-29-91

DATE COMPLETED:
6-3-91
Revised 7-26-91

Following this page, 3 pages withheld in full (b)(4)-CCI/TS

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes___X___
No _____

If no, explain reason(s) below:

NOTE: I was informed on 5-31-91 regarding BW's submission of response letter dated 5-3-91.

cls/07/29/91/d:73-585.REV2

File in ANDA

1. CHEMIST'S REVIEW NO.3

2. ANDA # 73-585

3. NAME AND ADDRESS OF APPLICANT
Burroughs-Wellcome Co.
3030 Cornwallis Road
Research Triangle Park
NC 27709

6. PROPRIETARY NAME
Sudafed® 12 hour Caplets

7. NONPROPRIETARY NAME
Pseudoephedrine HCl

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

9. AMENDMENTS AND OTHER DATES:
Original Submission 5-30-90
Amendment 5-3-91 (Response to our NA letter dated 4-18-91)
O-NC: 6-14-91
Amendment: 6-25-91(FPL)
*Amendment: 9-25-91
* : 10-22-91 (Response to our letter dated 10-15-91)
FDA Correspondence: 10-22-90 (Bio deficiency letter)
4-18-91
7-31-91
10-15-91

10. PHARMACOLOGICAL CATEGORY
Nasal Decongestant

11. Rx or OTC
OTC

12. RELATED IND/NDA/DMF(s)
DMF
DMF (b) (4)

13. DOSAGE FORM
Tablet (Caplet)

14. POTENCY
120 mg

15. CHEMICAL NAME AND STRUCTURE
Refer to Chem. Review No. 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Pre-approval EER - Acceptable. Update Submitted.
2. in-vivo Bioequivalence and in-vitro dissolution testing requirements - approved.
3. Container/closure system - satisfactory
4. Stability data and commitment - satisfactory
5. Expiration date - 24 months acceptable
6. Release specifications for drug substance and drug product - satisfactory

7. Production Batch (post-approval) - [(b) (4)] tablet and executes test batch size - [(b) (4)] tablet.
8. Manufacturing batch records - satisfactory
9. Laboratory controls in process and finished dosage form satisfactory.
10. Control numbers - satisfactory.
11. Environmental impact analysis report - satisfactory.
12. DMF [(b) (4)] and DMF [(b) (4)] for [(b) (4)] - satisfactory
13. MV is satisfactory. (Refer to section # 31 of this review).

18. CONCLUSIONS AND RECOMMENDATIONS
Approved

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
10-22-91

Mujahid Shaikh
10-25-91

cc: ANDA 73-585
73-585/Division File

M. Smela
10/28/91

Following this page, 4 pages withheld in full (b)(4)-CCI/TS

34. BIOEQUIVALENCY STATUS

Dr. James D. Henderson, Review Chemist of Division of Bioequivalence reviewed this ANDA and he found that Sudafed 12 Hours Caplet, 120 mg is bioequivalent to the reference product Sudafed 12-Hour capsule, 120 mg manufactured by BW and also meets in-vitro dissolution testing requirements. According to his acceptable review, the drug product should meet the following specifications:

NLT 25% and NMT 45% of the labeled amount of drug in the dosage form is dissolved in 1 hour.

NLT 50% and NMT 75% of thee labeled amount of drug in the dosage form is dissolved in 3 hours.

NLT 75% of the labeled amount of drug in the dosage form is dissolved in 6 hours.

Comments: Satisfactory per bio review dated 4-4-91 whose copy is enclosed.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory pe CR # 1

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes X
No _____

If no, explain reason(s) below:

Note: This ANDA has a Expedited Review status granted by the office of Commissioner, FDA per Memorandum dated 3-18-91 by the Director OGD.

cls/10/24/91/d:73-585.REV

APPROVAL PACKAGE SUMMARY

ANDA NUMBER: 73-585

FIRM: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

DOSAGE FORM: Tablets (Caplets)

STRENGTH: 120 mg (Pseudoepedrine HCl)

DRUG: Sudafed^{R} 12 hour Extended-release Caplets

CGMP STATEMENT & EI UPDATE: Establishment Inspection - satisfactory for the foollowing facilities dated (b) (4), (b) (4)(updated), and (b) (4) (updated):

1. Burroughs Wellcome Co.
   P.O. Box. 1887, Greenville, NC 27834
   (manufacturing site for drug product)
2. (b) (4)
3. (b) (4)

Request for Updating the EER is submitted on 10-11-91 OK 10/21/91

NOTE: Product specific inspection was completed.

METHOD VALIDATION:
Satisfactory. For detailed review in this regard, refer to section # 31 Of CR # 3.

STABILITY: 24 months expiration dating period is acceptable based on the submitted stability data. BW submitted stability data for 36 months for batch 7U2752, 24 months for batch 8Z6023 and 12 months for batch 9S6005. Containers used in the study are identical to those in container section. Shaikh 10-30-91

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH : Batch 7U2752 & 9S6005 - (b) (4) Tablets each.

SOURCE OF NDS: DMF (b) (4)- Satisfactory
DMF (b) (4) - Satisfactory per M. Shaikh's review dated 6-3-91.
Burroughs Wellcome - Information submitted with original submission was found satisfactory per CR # 1.

SIZE OF STABILITY BATCHES (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?):
same as stability batches.

PROPOSED PRODUCTION BATCH MANUFACTURED PROCESS THE SAME AS BIO/STABILITY? The manufacturing process for the stability batches is identical to the proposed production batches. Proposed production size is (b)(4).

Mujahid L. Shaikh Mujahid Shaikh 10-25-91
Review Chemist
Division of Chemistry I
OGD/CDER
10-23-91 M. Smela 10/28/91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 073585

BIOEQUIVALENCE REVIEWS

Pseudoephedrine Hydrochloride
120 mg 12-hr caplet
ANDA 73585
Reviewer: James D. Henderson

Burroughs Wellcome
Research Triangle Park, NC
Submitted:
May 30, 1990

Review of Bioequivalence Studies and Dissolution Data

I. Introduction

The sponsor's product Sudafed (120 mg Pseudoephedrine Hydrochloride) 12-Hour Capsules (NDA 17-941) is currently available OTC. On 8/28/87, the sponsor filed a petition requesting permission to submit an ANDA for a change in dosage form to a Pseudoephedrine Hydrochloride 120 mg CR tablet. This petition was granted by FDA (11/3/87) and the present submission (ANDA 73-585) contains the bioequivalence study information required for approval of the new dosage form. In this submission, the sponsor has reported the results of two pilot studies and two bioequivalence studies along with dissolution data.

II. Background

Pseudoephedrine is an indirect-acting sympathomimetic amine which stimulates adrenergic nerve endings to release norepinephrine (NE). The released NE acts at vascular α-receptors in the upper respiratory tract (where its action is more specific) to cause vasoconstriction of nasal vessels and decongestion of swollen nasal mucosal tissues. It is indicated for the temporary relief of nasal congestion due to the common cold, hay fever or other allergies, or sinusitis. After oral dosing of immediate-release dosage forms, absorption is rapid and almost complete. Half-life ranges from 4.5-10 hr (average 7 hr) and depends on both urine flow and pH. After a 60-mg dose, the following results were obtained: 1) 87-96% of the dose is eliminated in 24 hr, with 55-75% excreted unchanged in the urine, and the rest metabolized by several pathways including formation of an active metabolite (6% of dose); 2) half-life was 5.5 hr; 3) Tmax was 2.6 hr; 4) Cmax was 189 ng/ml. Currently marketed OTC products include: 1) 30- and 60-mg immediate-release tablets (Sudafed, Burroughs Wellcome); 2) Children's Sudafed Liquid 30 mg/5 ml; 3) Sudafed Cough Syrup 15 mg/5 ml (combination product); and, 4) Sudafed 12-Hour Capsules 120 mg (SR capsule). For the immediate-release dosage forms, onset and duration of action are 30 min and $\geq$ 3 hr, respectively; adult dosage is 60-120 mg qid prn. For the slow-release capsule, onset and duration of action are 1 hr and 8-12 hr, respectively; adult dosage is 120 mg q8-12 hr. Pseudoephedrine used in pharmaceutical preparations is a single stereoisomer d-pseudoephedrine.

III. Pilot Study # 1 (R08-01)

Single Dose Bioequivalency Study of Two Formulations of Pseudoephedrine 12-Hour Controlled-Release Caplets and Sudafed

12-Hour Capsules in Healthy Male Volunteers

A. Site: Medical and Technical Research Associates, Jamaica Plain, MA; Miguel A. Zinny, MD, Principal Investigator

B. Objective: The objective of this pilot study was to compare the bioavailability/bioequivalence parameters of two different formulations ("intermediate" and "slow") of controlled-release ([redacted](b)(4)) Pseudoephedrine Hydrochloride caplets to Sudafed 12-Hour Capsules. Formulations of the test products and other information are shown in Attachments 1-3.

C. Study Design: This was a randomized, three-treatment, three-way crossover, single dose study using six healthy male volunteers. Subjects were 19-35 years old, 60-90 kg (within normal weight limits), nonsmokers, and had acceptable results for medical history, physical examination, and laboratory values.

Exclusion criteria included the following:

- acute or chronic illness
- any medication taken within one week prior to the study
- any drug allergy or idiosyncrasy
- urine pH < 5 or > 7
- organ disease that might interfere with drug elimination
- abnormal bleeding
- evidence or past history of psychiatric disorder, seizures, or head injury
- regular smoking within 3 months prior to the study
- illicit drug use
- alcohol abuse (> 2 oz. per day of 190 proof alcohol)

Xanthine-containing beverages or foods were prohibited during each study period. On Day 1 of each study period, subjects received one of the following treatments according to a randomized sequence:

1) Treatment A: one 120-mg Sudafed 12-Hour Capsule (Lot 5F2815, reference product)

2) Treatment B: one 120-mg Pseudoephedrine Hydrochloride "intermediate" controlled-release caplet (test product, Batch 6H2725, batch size [redacted](b)(4) units)

3) Treatment C: one 120-mg Pseudoephedrine Hydrochloride "slow" controlled-release caplet (test product, Batch 6I2745, batch size [redacted](b)(4))

During the remaining periods, subjects were crossed over to the two alternative treatments. Subjects were fasted for seven hours prior to and for 4 hours after dosing. Each dose was administered with 200 ml of water. Blood samples (7 ml, EDTA Vacutainers) were taken at 0, 15, 30, 45, 60, and 90 minutes, and at 2, 3, 4, 6, 8,

12, 16, 24, and 36 hours after dosing. Plasma was separated and stored frozen at -20° until assayed at Burroughs Wellcome. Plasma samples were analyzed for pseudoephedrine by radioimmunoassay. Pharmacokinetic parameters (AUC 0-36, Cmax, and Tmax) were determined; statistical analysis of the results was not done since this was a pilot study.

D. Study Results

	Treatment			Ratios	
(N = 6)	A	B	C	B/A	C/A
AUC 0-36h (ng-hr/ml)	3513	3547	3541	1.01	1.01
Cmax (ng/ml)	267	310	248	1.16	0.93
Tmax (hr)	5.7	6.0	6.3	1.05	1.11

A = Sudafed 120 mg 12-Hour Capsule
B = "Intermediate" CR Pseudoephedrine HCl 120 mg caplet
C = "Slow" CR Pseudoephedrine HCl 120 mg caplet

E. Conclusions

1. Both the "intermediate" and "slow" CR Pseudoephedrine HCl caplets gave similar bioavailability parameters to the reference product Sudafed 12-Hour Capsules.
2. The higher Cmax value for treatment B ("intermediate" release formulation) was considered clinically insignificant.
3. The "slow" release formulation was not suitable for large scale production due to its physical characteristics.
4. A second pilot study would be done using a different "slow" release formulation.

III. Pilot Study # 2 (R08-02)

Single Dose Bioequivalence Study of Two Formulations of Pseudoephedrine 12-Hour Controlled-Release Caplets and Sudafed 12-Hour Capsules in Healthy Male Volunteers

A. Site: Harris Laboratories, Lincoln, NE; James C. Kisicki, MD, Principal Investigator

B. Objective: The objective of this study was to compare two new formulations ("intermediate" and "slow") of controlled-release Pseudoephedrine Hydrochloride 120 mg caplets to Sudafed for bioavailability/bioequivalence parameters. Formulations are shown in Attachment 1. The formulation of both test products was significantly changed for the second pilot study.

C. Study Design: The study design was essentially the same as for Pilot Study #1 with the following exceptions:

1) Treatment B: "intermediate" CR Pseudoephedrine Hydrochloride 120 mg caplet (test product, Batch 7N2733, batch size (b) (4))

2) Treatment C: "slow" CR Pseudoephedrine Hydrochloride 120 mg caplet (test product, Batch 702748, batch size (b) (4))

3) blood samples were taken at 0, 20, 40, 60, and 90 minutes, and at 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours

D. Study Results

	Treatment			Ratios	
(N = 6)	A	B	C	B/A	C/A
AUC 0-36h (ng-hr/ml)	3589	3649	3818	1.02	1.06
Cmax (ng/ml)	279	275	283	0.99	1.01
Tmax (hr)	5.2	5.0	5.5	0.96	1.06

A = 120 mg Sudafed 12-Hour Capsule
B = 120 mg "intermediate" CR Pseudoephedrine HCl caplet
C = 120 mg "slow" CR Pseudoephedrine HCl caplet

E. Conclusions

1. Both formulations gave similar bioavailability parameters to Sudafed.
2. The "intermediate"-release formulation was chosen for full-scale production (b) (4).

IV. Bioequivalence Study #1 (R08-03)

An Evaluation of the Relative Bioavailability of Pseudoephedrine 12-Hour Controlled-Release Caplets

A. Site: Pharmaco-Dynamics Research, Inc., Austin , TX
Thomas L. Hunt, MD, PhD, Principal Investigator
Study dates: 1/15/88 to 2/7/88

B. Objectives: The study assessed the bioequivalence of:

1. Pseudoephedrine Hydrochloride 12-hour (12hr) controlled-release (CR) caplets (120 mg) compared to Sudafed 12-Hour Capsules (120 mg)

2. Pseudoephedrine Hydrochloride 12hr CR caplets (120 mg) after a meal compared to the fasted state

3. Pseudoephedrine Hydrochloride 12-hr CR caplets (120 mg) compared to two 60-mg doses (6 hr apart) of Children's Sudafed Liquid

C. Study Design: This study was a randomized, four-period, four-sequence, four-treatment, Latin square crossover design using 24 healthy male volunteers. Inclusion and exclusion criteria were essentially the same as for the pilot studies above with the following differences:

1) age range from 19-40 years
2) Subjects who had participated in any investigational drug study in the previous three months, or who had donated blood in the previous three weeks were excluded from the study.

Restrictions and actions which constituted protocol violations were the same as in the pilot studies. Xanthine-containing beverages and foods were prohibited during the study periods. Water was not allowed for two hours prior to dosing. Subjects were fasted from 7.5 hr prior to dosing until 4 hr post-dosing (except for the food study in which a meal was given 30 minutes before dosing). The standardized meal for the food study consisted of two eggs, two bacon strips, toast with butter, 4 oz. hash browns, and 8 oz. whole milk.

Subjects were randomly assigned to one of four treatment sequences and received one of the following four treatments during each of the four study periods:

1) Treatment A: one dose (120 mg) of Pseudoephedrine Hydrochloride 12hr CR caplet (Batch 7U2752, batch size (b) (4))

2) Treatment B: one dose (120 mg) of Pseudoephedrine Hydrochloride 12hr CR caplet (Batch 7U2752) 30 minutes after a standardized breakfast

3) Treatment C: one Sudafed 12-Hour Capsule (120 mg), Batch 7U2753

4) Treatment D: two 60-mg doses 6 hr apart of Children's Sudafed Liquid (Batch 7U2754). The first dose was in the fasted state, and the second dose was given 2 hr after the scheduled meal (4 hr post-dosing).

Formulations of the Pseudoephedrine Hydrochloride 12hr CR caplets are shown in Attachment 1. Each dose was administered with 200 ml of water. There was a washout period of one week between each of the four treatments. Blood samples (7 ml, EDTA Vacutainers) were taken at the following times:

1) for Treatments A, B, and C: 0, 20, 40, 60, and 90 minutes, and at 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hr

2) Treatment D: 0, 20, 40, 60, and 90 minutes, and at 2, 2.5, 3, 4, 6, 6.33, 6.67, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 24, and 36 hr

Plasma was separated immediately and stored frozen at -20° until assayed. Plasma samples were assayed for pseudoephedrine at Burroughs Wellcome using a published radioimmunoassay (RIA) procedure (Findlay et al., J. Pharm. Sci., 70 (6): 624 (1981)).

D. Study Results

1) Analytical Methodology

-Sensitivity: 1.0 ng/ml d-pseudoephedrine

-Specificity: The RIA procedure is highly specific for pseudoephedrine. The highest cross-reacting (1.75%) substance is norpseudoephedrine which is not a major metabolite in humans. Other substances that represent slight structural modifications from pseudoephedrine cross-react at ≤ 0.4%. The assay is also stereospecific for d-pseudoephedrine.

-Day-to-day Accuracy and Precision: (Multiple-Dose Study is described below in Section IV.)

	Single Dose (N = 19)		Multiple Dose (N = 38)	
Spiked Conc. (ng/ml)	Measured Conc. (Mean, ng/ml)	CV (%)	Measured Conc. (Mean , ng/ml)	CV (%)
1	-	-	0.94	20.2
3	3.29	11.6	2.96	13.2
30	30.2	9.9	29.1	11.7
300	296	6.9	303	13.0

-Within-day Precision (controls prepared by pooling human plasma samples from a previous study):

Single-Dose Study	Control A	Control B	Control C
Mean Conc. (ng/ml)	26.3	109	162
CV (%)	7.0	8.2	10.6
N	10	20	10

Multiple-Dose Study	Control A	Control B	Control C
Mean Conc. (ng.ml)	28.6	147	226
CV (%)	8.7	11.0	15
N	38	38	38

2) Mean Pseudoephedrine Plasma Concentrations (ng/ml, CV%)

Table I. Summary of Pseudoephedrine Plasma Concentrations (N= 24)

Time	Trt A		Trt B		Trt C		Trt D	
(hr)	Mean	CV	Mean	CV	Mean	CV	Mean	CV
0.00	0.8	490	0.3	339	0.0	-	0.1	490
0.33	8.0	92.3	4.9	149	11.0	160	87.8	51.8
0.67	40.3	38.0	30.8	86.7	75.1	54.1	169.1	21.2
1.0	68.2	29.6	56.6	70.5	124.1	30.6	193.3	20.2
1.5	112.4	23.3	97.5	50.8	161.1	25.9	199.7	19.1
2.0	147.3	19.0	134.3	44.4	191.5	25.3	197.0	20.8
2.5	-	-	-	-	-	-	193.1	18.8
3.0	214.2	23.0	208.3	30.4	230.6	23.2	182.5	20.9
4.0	247.7	21.0	257.9	26.8	252.1	21.3	161.1	21.8
5.0	283.8	20.6	280.5	20.2	271.7	23.4	-	-
6.0	280.4	23.2	269.3	21.2	263.7	21.5	132.0	24.4
6.33	-	-	-	-	-	-	150.0	24.6
6.67	-	-	-	-	-	-	202.0	23.8
7.0	-	-	-	-	-	-	239.9	23.0
7.5	-	-	-	-	-	-	280.6	22.4
8.0	262.0	26.6	250.7	21.1	246.5	20.4	294.6	22.2
8.5	-	-	-	-	-	-	295.5	23.1
9.0	-	-	-	-	-	-	288.9	24.1
10.0	223.6	27.1	230.5	25.3	206.5	26.6	266.3	28.8
12.0	171.5	29.5	178.5	27.9	160.3	30.6	204.7	28.1
16.0	120.9	31.5	109.8	37.2	105.0	34.5	128.8	34.6
24.0	50.1	32.7	43.3	43.3	47.8	50.6	51.3	43.9
36.0	16.2	53.6	13.1	65.6	19.1	58.7	17.0	60.8

Trt A = one Pseudoephedrine Hydrochloride 12hr CR caplet (120 mg)
Trt B = one Pseudoephedrine Hydrochloride 12hr CR caplet administered 30 minutes after a standardized breakfast
Trt C = one Sudafed 12-Hour Capsule (120 mg)
Trt D = two 60-mg doses of Children's Sudafed Liquid given 6 hr apart

3) Pharmacokinetic Parameters for Pseudoephedrine (Mean,CV%)

Table II. Summary of Pseudoephedrine Pharmacokinetic Parameters (N = 24); treatments are as listed above in Table I.

Parameter	Trt A		Trt B		Trt C		Trt D	
	Mean	CV	Mean	CV	Mean	CV	Mean	CV
AUC36 *	4187	23.8	4004	23.5	4063	24.3	4264	25.1
AUCINF *	4346	23.9	4127	24.6	4251	26.3	4424	26.3
CMAX **	292.8	20.8	293.1	18.6	283.3	20.8	214***	16.8
TMAX (hr)	5.5	17.6	5.9	38.3	5.4	27.3	1.6***	43.8
ke (1/hr)	0.12	22.3	0.13	25.8	0.13	29.4	0.12	22.0
$t_{1/2}$ (hr)	6.3	21.2	5.78	24.7	5.83	36.5	5.98	19.2
TLAG (hr)	0.17	81.7	0.28	85.6	0.31	35.8	0.15***	62.4

* ng*hr/ml ** ng/ml *** first dose

3) Pharmacokinetic Parameter Ratios for Pseudoephedrine

Table III. Pharmacokinetic Parameter Ratios (Mean, CV %); treatments are as listed above in Table I (N = 24).

Ratio	Trt A/Trt C		Trt B/Trt A		Trt A/Trt D	
	Mean	CV	Mean	CV	Mean	CV
AUCINF	1.06	23.6	0.98	22.4	1.02	25.5
CMAX	1.05	20.0	1.02	19.6	-	-
TMAX	1.10	30.9	1.08	41.7	3.44*	-

* first dose of Treatment D

4) Statistical Analysis

Table IV. Summary of ANOVA Results (N = 24); treatments are as listed above in Table I.

Parameter	Test Product	Reference Product	90% C.I.	Difference (% ref.)
Trt B (test, fed) vs. Trt A (test, fasted)				
AUC36 *	4004	4187	88-104	-4.6
AUCINF *	4127	4346	87-103	-5.0
CMAX (ng/ml)	293.1	292.8	92-108	0.1
Trt A (test) vs. Trt C (ref., capsule)				
AUC36 *	4187	4063	95-111	3.1
AUCINF *	4346	4251	94-111	2.2
CMAX (ng/ml)	292.8	283.3	95-112	3.4
Trt A (test) vs. Trt D (ref., liquid)				
AUC36 *	4187	4264	90-106	-1.8
AUCINF *	4346	4424	90-106	1.8

* ng*hr/ml

IV. Bioequivalence Study #2 (R08-04)

Steady-State Pharmacokinetics of Sudafed 12-Hour Capsules and Pseudoephedrine 12-Hour Controlled-Release Caplets in Healthy Male Volunteers

A. Site: Pharmaco-Dynamics Research, Inc., Austin, TX
Thomas L. Hunt, MD, PhD, Principal Investigator
Study dates: 6/15/88 to 6/13/88

B. Objective: The study assessed the bioequivalence of Pseudoephedrine Hydrochloride 12-hour (12hr) controlled-release (CR) caplets (120 mg) compared to Sudafed 12-Hour Capsules after multiple dosing to steady-state conditions.

C. Study Design: This study was a randomized, two-period, two-sequence, two-treatment crossover design using 26 healthy male volunteers. Inclusion and exclusion criteria were the same as for the previous studies with age limits at 19-35 years. Restrictions and protocol violations were the same as in the pilot and single dose studies.

Subjects were randomly assigned to one of two treatment sequences and received one of the following treatments during each period:

1) Treatment A: one Sudafed 12-Hour Capsule (120 mg) q12h for 8 doses, Batch 7U2753

2) Treatment B: one Pseudoephedrine Hydrochloride 12hr CR caplet (120 mg) q12h for 8 doses, Batch 7U2752 (batch size (b) (4))

Each dose was administered with 200 ml water. The following dosing schedule was used:

Period 1	Day 1	1900 hours	Dose #1	of first treatment
	2	0700	#2	
	2	1900	#3	
	3	0700	#4	
	3	1900	#5	
	4	0700	#6	
	4	1900	#7	
	5	0700	#8	
Period 2	Day 5	1900	Dose #1	of second treatment
	6	0700	#2	
	6	1900	#3	
	7	0700	#4	
	7	1900	#5	
	8	0700	#6	
	8	1900	#7	
	9	0700	#8	

Standardized meals were given 1, 4, and 10 hr after the 0700 dose on days 2, 3, 4, 6, 7, and 8, and 4 and 10 hr after the AM dose on days 5 and 9. Subjects were confined to the study facility for the entire study.

Blood samples (7 ml) were drawn into EDTA Vacutainers as follows:

1) immediately prior to the 0700 dose on days 3, 4, 5, 7, 8, and 9. These sampling times correspond to 36, 60, and 84 hr after the initial dose during each treatment period, and represent the minimum steady-state concentration.

2) at 0 (84 hr after each initial dose as above), 20, 40, 60, and 90 min, and at 2, 3, 4, 5, 6, 7, 8, 10, and 12 hr after the 0700 dose on days 5 and 9

Plasma was separated, frozen, and shipped to BW for analysis by the RIA procedure noted above.

D. Study Results

1) Attainment of Steady-State Conditions (N = 26)

Table V. Minimum Concentrations during Multiple Dosing

Sample	Time after Initial Drug Administration (hr)	Trt A CMIN (ng/ml)	Trt A CV (%)	Trt B CMIN (ng/ml)	Trt B CV (%)
pre-dose 3rd day	36	220	34	246	35
pre-dose 4th day	60	226	37	219	37
pre-dose 5th day	84	243	32	243	30

These results indicate that steady-state was achieved with both treatments after 36 hr.

Trt A = one Sudafed 12-Hour Capsule q12h x 8 doses
Trt B = one Pseudoephedrine Hydrochloride 12-hr CR caplet (120 mg) q12h x 8 doses

2) Plasma Concentrations of Pseudoephedrine after Multiple Dosing (N = 26)

Table VI. Pseudoephedrine Concentrations during a Dosing Interval

Time (hr)	Trt A * Mean (ng/ml)	Trt A * CV (%)	Trt B Mean (ng/ml)	Trt B CV (%)
0 **	243	32	243	30
0.33	229	35	242	34
0.67	266	36	281	35
1	300	30	303	35
1.5	334	29	321	32
2	353	30	350	29
3	394	28	375	31
4	406	30	400	31
5	421	28	403	26
6	396	31	391	30
7	396	27	392	25
8	377	25	379	27
10	317	30	328	32
12	278	37	280	34

* Treatments A and B are defined in Table V
** 84 hr post-dose for each treatment

There were no significant differences (significance defined as $p < 0.05$) between the two treatments at any sampling time. In all cases, the 90% C.I. were within the 80-120 equivalence intervals.

3) Pharmacokinetic Parameters of Pseudoephedrine after Multiple Dosing (N = 26)

Table VII. Pharmacokinetic Parameters of Pseudoephedrine after Multiple Dosing

Parameter	Trt A * Mean	Trt A * CV%	Trt B Mean	Trt B CV%	90% C.I.	Difference (% ref.)
AUC (0-12)**	4254	26	4229	27	95-103	0.6
CMAX (ng/ml)	459	24	451	22	94-103	1.8
CMIN (ng/ml)	243	32	243	30	93-107	0
TMAX (hr)	4.8	41	5.4	32	-	11.1

* Treatments A and B are defined in Table V
** ng*hr/ml

V. Comments

A. Dissolution

1. The sponsor has proposed the following dissolution methods and specifications for the test product Pseudoephedrine Hydrochloride 12-Hour CR Caplets (120 mg) which, according to the sponsor, satisfy the USP Requirements for Drug Release (Acceptance Table 1):

- USP Apparatus II (paddle) at 50 rpm
- 900 ml Distilled Water
- colorimetric detection (400 nm)
- sampling times: 1 hour NLT 25%, NMT (b)(4)
  3 NLT 50%, NMT
  6 NLT 75%

2. The dissolution data reported for the reference product (see Table VIII attached) is not acceptable since:

- only 10 individual units were tested
- no ranges of values for % dissolved were given
- details of the (b)(4) method used were not given

However, it is doubtful that direct comparison of two different controlled-release dosage forms (caplet vs. capsule) will be of any real value, as long as an acceptable controlled-release pattern is exhibited by the test product.

3. The sponsor suggests (Table X attached) that dissolution of the test product is not affected by pH over the pH range 1.5-7.5; therefore, distilled water would be an acceptable medium. Current Division requirements for dissolution testing of CR products employ SGF without enzyme (pH 1.2) for the first hour and SIF without enzyme (pH 7.5) thereafter.

4. The test product used in the biostudies (batch 7U2752) is the (b)(4) formulation the sponsor intends to market and is film-coated. However, the final product the sponsor intends to market will be imprinted and (b)(4). The sponsor conducted dissolution testing on a batch 906019 with and without the imprinting and (b)(4) (see Table IX attached). The number of individual units tested and the range of values for % dissolved were not given. The exact relationship of this batch 906019 to the batch 7U2752 actually used in the biostudies was never explicitly stated.

B. Analytical Methodology

1. The firm refers to an assay procedure (Findlay et al., J. Pharm. Sci., 70: 624, 1981) which serves as the basis for the radioimmunoassay (RIA) used in the biostudies. However, the firm

has deviated significantly from the method reported in the literature. The literature method uses an assay buffer of 0.05 M phosphate (pH 7.4), 0.25 M NaCl, 0.01 M EDTA, and 1% bovine serum albumin (BSA), while the firm has used (b) (4) (b) (4). The literature method uses a BSA-coated charcoal suspension, while the firm used a (b) (4) (b) (4).

2. In the one standard curve presented for the single-dose study, back-calculation of the 0.195 ng/ml standard gave a value of 0.260 ng/ml which is a -33.3% difference.

C. Single Dose Bioequivalence Study

1. Significant ($p < 0.05$) differences in pseudoephedrine plasma concentrations between Treatment A (test product) and Treatment C (reference product, Sudafed 12-Hour Capsule) occurred over 0.67-2 hr after dosing. It is unlikely that these differences are due to lag time since the plasma concentrations are higher for Treatment C, but the lag time is longer for Treatment C. Since the test product exhibited lower concentrations over the absorption phase compared to the reference product (with CR properties established), the absence of dose dumping in the fasted state is demonstrated.

2. There were no significant differences between Treatment A and Treatment C with regard to AUC36, AUCINF, or CMAX. The 90% C.I. for these parameters all fell within the 80-120% equivalence interval. The TMAX ratio Trt A/Trt C was 1.1. The similarity of these parameters suggests that the test product exhibits a CR pattern resembling the reference product.

3. Since the proposed labeling for the test product allows twice daily administration (q12h) without regard to meals, Treatment B (test product, 30 minutes after a high fat content meal) was compared to Treatment A (test product, fasted). There were no significant differences between plasma concentrations at any time, or between pharmacokinetic parameters (AUC36, AUCINF, and CMAX). The 90% C.I. for the parameters fell within the 80-120% equivalence interval. The TMAX ratio was 1.08. The results demonstrated a lack of food effect on bioavailability and the absence of dose dumping.

4. Comparison of Treatment A (test product) with Treatment D (reference product, conventional release liquid) showed no significant differences between AUC36 and AUCINF with the 90% C.I. for both parameters falling within the 80-120% equivalence interval. Therefore, the extent of absorption from the 120 mg CR 12-hour caplet is similar to that from two 60-mg doses of the liquid formulation given 6 hr apart. The TMAX ratio Trt A/Trt D (using the first dose of Trt D) was 3.44, indicating the much longer TMAX for the CR caplet (5.5 hr) compared to the immediate

release liquid (1.6 hr).

5. From Table I, it is noted that pre-dose (0.0 hr) levels of pseudoephedrine are nonzero for Treatments A, B, and D. The individual plasma concentration data for Treatment A shows values of 0.0 ng/ml for 23 subjects and 18.0 ng/ml for Subject 23. For Treatment B, 22 subjects had values of 0.0 ng/ml with Subjects 12 and 23 having values of 3.8 and 3.5 ng/ml, respectively. For Treatment D, 23 subjects had values of 0.0 ng/ml with Subject 13 having a value of 2.6 ng/ml. The following table summarizes this data and related data:

Subject	Period	Pre-Dose Conc. (ng/ml)	Period 1 Trt $t_{1/2}$ (hr)	Period 2 Trt $t_{1/2}$ (hr)	Period 3 Trt $t_{1/2}$ (hr)	Period 4 Trt $t_{1/2}$ (hr)
23	4	18.0	D 7.93	C 4.73	B 7.65	A 8.02
23	3	3.5	D 7.93	C 4.73	B 7.65	A 8.02
12	4	3.8	C 3.90	A 5.11	D 3.68	B 4.81
13	4	2.6	A 7.06	B 5.54	C 5.76	D 6.84

Three of the four nonzero pre-dose concentrations occurred in the last period, and Subject 23 had nonzero levels in the next to last and last periods. However, none of the half-life values for these subjects is exceptionally long and nonzero pre-dose concentrations occurred in only 4 out of 96 cases. Therefore, these values most likely represent contaminations and not any residual effect.

D. Multiple Dose Bioequivalence Study

1. Table V summarizes the results of three consecutive trough concentrations of plasma pseudoephedrine comparing Treatment B (test product) with Treatment A (reference product). Steady-state conditions were attained with both treatments by 36 hours after starting the dosage regimen (q12h x 8 doses).

2. Table VI shows pseudoephedrine plasma concentrations for both treatments following the eighth dosing interval. There were no significant differences ($p > 0.05$ in all cases) between the two treatments at any sampling time. For all plasma concentrations, the 90% C.I. were within the 80-120% equivalence intervals.

3. Table VII compares the pharmacokinetic parameters AUC (0-12h), CMAX, and CMIN for both treatments. There were no significant differences ($p > 0.05$ in all cases) for any of these parameters and the 90% C.I. were all within the 80-120% equivalence intervals.

4. The mean AUC (0-12h) values during the eighth dosing

interval for the test product and reference product under steady-state conditions were 4229 and 4254 ng*hr/ml, respectively. The mean AUCINF value for Treatment D in the single-dose study was 4424 ng*hr/ml. In theory, these values should be equal if the extent of absorption is the same; the absolute difference was -0.6% between the test product and reference product at steady-state, and 4.4% between the test product at steady-state vs. Treatment D in the single-dose study.

5. For the test product, the degree of fluctuation at steady-state is calculated as follows:

Cave,ss = AUC,ss / τ = 4229 ng*hr/ml / 12 hr = 352.4 ng/ml

(Cmax,ss - Cmin,ss) / Cave,ss = (451 - 243) / 352.4 = 0.590

For the reference product, the corresponding value is 0.609. The degree of fluctuation for the test product Pseudoephedrine Hydrochloride 12-hour CR caplet 120 mg at steady-state appears to be similar to that of the reference product.

6. Significant ($p < 0.05$) period effects were noted for CMIN, and plasma concentrations at 0, 0.67, 1, 1.5, 2, and 3 hr.

VI. Deficiencies

1. The firm should be advised to conduct dissolution testing on 12 individual dosage units of the test product (batch 7U2752 before and after imprinting and (b) (4)) and to report individual and mean data. The firm should conduct dissolution testing using 900 ml of the following media: 1) simulated gastric fluid (SGF) without enzymes for the first hour; 2) simulated intestinal fluid (SIF) without enzymes thereafter. Testing should be done at 1, 2, 3, 4, 6, and 8 hours using USP apparatus II (paddle) at 50 rpm and a validated assay method. Data supporting the assay validation should be included. The Division of Bioequivalence will then evaluate the proposed dissolution specifications for the test product.

2. There is no frozen stability data for either study. The firm should have determined the maximum period of time from sample drawing to sample analysis over both biostudies and verify frozen stability for this length of time.

3. The firm has not supplied any raw data in this submission, except for one example of a standard curve from each biostudy. All of the standard curves used for analysis of subject samples from the two bioequivalence studies should be submitted along with the results of curve statistics and subject samples.

4. The firm has not supplied any results or raw data for quality control samples (target concentrations in the low, middle, and

high range of the standard curve) that should have been analyzed with every standard curve.

VII. Recommendation

The bioequivalence study conducted by Burroughs-Wellcome on its Sudafed (Pseudoephedrine Hydrochloride) 12-Hour Caplet (120 mg, batch 7U2752), comparing it to Burroughs-Wellcome Sudafed 12-Hour Capsule (120 mg, batch 7U2753) has been found incomplete by the Division of Bioequivalence. The firm should submit additional data in response to the deficiencies cited above. The firm should be informed of these deficiencies and the recommendation.

James S Henderson

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED FPELSOR
for FT INITIALED FPELSOR B. Chen

Concur: Charles M Ise Date 10/1/90
Charles M. Ise, Ph.D.
Deputy Director
Division of Bioequivalence

JDH/err/9-28-90/A73585

cc: ANDA #73-585, original, HFD-630, HFD-604 (Hare)
HFD-22 (Hootne), HFD-655 (Pelsor, Henderson), Drug file

Attachment 1

Composition of SUDAFED 12-Hour Caplets Used in Clinical Studies

Batch No.	6H2725	6I2745	7N2733 7U2752	7O2748
Formulation No.	BLK-01A1	BLK-01B1	BLK-02A1	BLK-03A1
Composition (mg per caplet):				
(b) (4)				
Pseudoephedrine Hydrochloride, USP	120.0	120.0	120.0	120.0
Hydroxypropyl Methylcellulose (b) (4) USP (b) (4)	(b) (4)			
(b) (4)				
(b) (4)				
Magnesium Stearate, NF				
Microcrystalline Cellulose, NF				
Povidone, USP				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				

Attachment 2

SUDAFED 12-Hour Caplets Used in Clinical Studies

Study No.	R08:01	R08:01	R08:02	R08:02	R08:03 R08:04
Batch No.	6H2725	6I2745	7N2733	7O2748	7U2752
Formulation No.	BLK-01A1	BLK-01B1	BLK-02A1	BLK-03A1	BLK-02A1
Batch Size (Caplets)					(b) (4)
Date of Manufacture	9-2-86	9-8-86	3-10-87	4-3-87	10-22-87
Drug Substance Lot No.	6C0486	6C0486	6K0060	6K0060	7T0368
Assay[1]	98.2	98.4	103.1	105.6	100.1
Release Profile[2]					
1 Hour	40.8 (1.55)	35.8 (1.37)	34.4 (1.45)	32.0 (0.41)	33.1 (1.12)
3 Hours	73.0 (1.88)	64.7 (0.89)	64.9 (1.90)	60.1 (1.08)	61.6 (2.67)
6 Hours	98.7 (2.51)	90.4 (2.30)	92.1 (1.59)	83.2 (1.47)	88.7 (2.83)

[1] Percent label strength pseudoephedrine hydrochloride by HPLC

[2] Mean (Std. dev.) percent label strength pseudoephedrine hydrochloride dissolved

Method: USP Rotating Paddle, 50 rpm

Medium: 900 ml 0.01% sodium lauryl sulfate, 37°C (batches 6H2725 and 6I2745)

900 ml distilled water, 37°C (batches 7N2733, 7O2748, and 7U2752)

TABLE 1
SUMMARY OF BIOPHARMACEUTICS STUDIES

A. PILOT OR BACKGROUND STUDIES

Study Number	Route	Study Design	Dose*	Batch Numbers (Date Manufactured)	Number of Subjects	IND #	Protocol Submission Date	Applicant Conclusion	Previous Agency Responses
01	Oral	Open, randomized, single-dose, 3-way, crossover	One SUDAFED® 12 Hour Capsule	5F2815‡ (11-22-85)	6	29,026	9-25-86	The "slow" controlled-release pseudoephedrine 12-hour caplets are more similar than the "intermediate" controlled-release pseudoephedrine 12-hour caplets to SUDAFED 12 Hour Capsules, although both formulations appear to be acceptable for further development.	None
			One "intermediate" controlled-release caplet	6H2725 (9-2-86)					
			One "slow" controlled-release caplet	6I2745 (9-8-86)					
02	Oral	Open, randomized, single-dose, 3-way, crossover	One SUDAFED 12 Hour Capsule	6H2727‡ (11-22-85)	6	29,026	5-28-87	Bioavailability of pseudoephedrine from either the "slow" or "intermediate" controlled-release caplet formulations is similar to SUDAFED 12 Hour Capsules. The "intermediate" controlled-release formulation was chosen for full-scale testing.	None
			One "intermediate" controlled-release caplet	7N2733 (3-10-87)					
			One "slow" controlled-release caplet	7O2748 (4-3-87)					
B. BIOAVAILABILITY/BIOEQUIVALENCE AND PHARMACOKINETICS STUDIES									
03	Oral	Randomized, balanced, open, 4-way, crossover	One controlled-release caplet	7U2752 (10-22-87)	24	29,026	1-12-88	Pseudoephedrine 12-hour controlled-release caplets are bioequivalent to either SUDAFED 12 Hour Capsules or two doses of Children's SUDAFED Liquid. There is no food effect on the bioavailability of pseudoephedrine from the caplet formulation.	None
			One controlled-release caplet with food	7U2752 (10-22-87)					
			One SUDAFED 12 Hour Capsule	7U2753 (10-24-85)					
			SUDAFED Liquid: 60 mg pseudoephedrine HCl at 0.0 hour and 60 mg at 6.0 hours	7U2754 (2-4-87)					
04	Oral	Open, randomized, 2-way, crossover	One SUDAFED 12 Hour Capsule, q 12 hours x 8 doses	7U2753 (10-24-85)	26	29,026	6-1-88	Pseudoephedrine 12-hour controlled-release caplets are bioequivalent to SUDAFED 12 Hour Capsules following multiple dosing	None
			One controlled-release caplet, q 12 hours x 8 doses	7U2752 (10-22-87)					

*Each capsule/caplet contained 120 mg pseudoephedrine HCl.

‡5F2815 is the production number and 6H2727 is the Clinical Trial Material batch number assigned to the same batch of SUDAFED 12 Hour Capsules

Attachment 3

Drug (Generic Name): Pseudoephedrine HCl Firm: Burroughs Wellcome
Dose Strength: 120mg 12hr caplet
ANDA # 73585 Submission Date: May 30, 1990

Table VIII – In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing: [redacted] (Test) ; [redacted] (Reference) 10-Ref

USP XXII Basket ____ Paddle ✓ RPM 50 No. Units Tested: 12-Test

Medium: Distilled Water Volume: 900 ml

Reference Drug; (Manuf.): Sudafed 12-Hour Capsule (BW)

Assay Methodology: Colorimetry (Vis 400 nm)

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product Pseudoephedrine HCl CR caplet Lot # 7U2752 Strength (mg) 120 Mean % Dissolved	Range	(CV)	Reference Product Sudafed 12 Hour Capsule Lot # 7U2753 Strength (mg) 120 Mean % Dissolved	Range	(CV)
1	33.1	[redacted]	(3.4)	42.0	—	(—)
3	61.6		(4.3)	68.8	—	(—)
4	72.3		(4.9)	81.8	—	(—)
6	88.7		(3.2)	90.8	—	(—)
8	96.5		(2.9)	94.1	—	(—)

	Lot # ____ Strength (mg) ____			Lot # ____ Strength (mg) ____		
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )

Drug (Generic Name): Pseudoephedrine HCl Firm: Burroughs-Wellcome
Dose Strength: 120 mg 12hr caplet
ANDA # 73-585 Submission Date: May 30, 1990

Table IV In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ____ Paddle √ RPM 50 No. Units Tested: —

Medium: Distilled Water 37° Volume: 900 ml

Reference Drug; (Manuf.): Pseudoephedrine 120mg 12hr caplet (BW)

Assay Methodology: Colorimetry (VIS 400nm)

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product imprinted (b) (4) Lot # 906019 Strength (mg) 120 Mean % Dissolved	Range	(CV)	Reference Product not imprinted (b) (4) Lot # 906019 Strength (mg) 120 Mean % Dissolved	Range	(CV)
1	44.4	—	(8.7	41.6	—	(10.4
3	78.1	—	(4.9	75.1	—	(5.2
4	85.8	—	(2.9	83.0	—	(4.4
6	95.6	—	(2.1	93.0	—	(2.8
8	100.2	—	(1.8	97.4	—	(2.4

	Lot # ____ Strength (mg) ____			Lot # ____ Strength (mg) ____		
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )

Drug (Generic Name): Pseudoephedrine HCl Firm: Burroughs-Wellcome
Dose Strength: 120 mg CR caplet
ANDA # 73-585 Submission Date: 5-30-90

Table X - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ____ Paddle ✓ RPM 50 No. Units Tested: —

Medium: see below (37°) Volume: 900 ml

Reference Drug; (Manuf.): test product - effect of pH

Assay Methodology: Colorimetric (Vis 400 nm)

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	~~Test Product~~ 0.1N HCl pH 1.5 Lot # 7U2752 Strength (mg) 120 Mean % Dissolved	Range	(CV) %	Distilled Water ~~Reference Product~~ Lot # 7U2752 Strength (mg) 120 Mean % Dissolved	Range	(CV) %
1	33.6	—	(3.6)	33.9	—	(2.3)
3	63.6	—	(2.7)	62.8	—	(1.8)
4	73.8	—	(2.4)	71.4	—	(2.0)
6	88.8	—	(2.1)	85.8	—	(1.8)
8	96.3		(2.7)	93.1	—	(1.5)
	0.2M Phthalate buffer pH 4.5 Lot # 7U2752 Strength (mg) 120			SIF w/o enzymes pH 7.5 Lot # 7U2752 Strength (mg) 120		
1	36.5	—	5.4	34.0	—	(6.8)
3	61.8	—	(2.6)	60.9	—	(4.1)
4	69.7	—	(2.1)	70.2	—	(3.6)
6	81.4	—	(1.8)	84.0	—	(2.5)
8	88.9	—	(1.6)	92.8	—	(2.1)

APR -9 1991 2-1

Pseudoephedrine Hydrochloride
120 mg 12-hr caplet
ANDA # 73-585
Reviewer: James D. Henderson

Burroughs-Wellcome
Research Triangle Park, NC
Submitted:
March 13, 1991

Response to the Review of Bioequivalence Studies and Dissolution Data

On May 30, 1990, the sponsor submitted ANDA #73-585 which contained the results of a single dose, four-way crossover bioequivalence study, a multiple dose, two-way crossover study, and dissolution data. This application was reviewed by the Division of Bioequivalence (file date 10/4/90) and a deficiency letter sent to the sponsor. The present submission is an amendment to the ANDA in which the sponsor has responded to the deficiencies.

Comments:

1. The sponsor was requested to conduct dissolution testing on the batch of test product (batch 7U2752) used in the biostudies under the conditions specified by the Division of Bioequivalence. This testing was done before and after imprinting and (b) (4) since the sponsor intends to market the test product imprinted and (b) (4) but conducted the biostudies without imprinting and (b) (4).

The results of dissolution testing are shown in Tables 1 and 2 (attached). The sponsor performed testing in two media: 1) SGF w/o E for 0-1 hr, then SIF w/o E for 1-8 hr as requested by the Division; and, 2) distilled water as proposed by the sponsor. In both media, ink imprinting and (b) (4) had virtually no effect on the dissolution profiles (see Figure 1 attached). The dissolution testing is acceptable.

The sponsor has proposed the following criteria for dissolution of its Pseudoephedrine HCl 12-hr caplet:

Hour	Specification
1	NLT 25%, NMT (b) (4)
3	NLT 50%, NMT
6	NLT 75%

Based on the submitted data, the Division of Bioequivalence recommends the following conditions and specifications for dissolution testing for the test product Pseudoephedrine HCl 120 mg 12-hr caplet:

Apparatus: USP XXII Apparatus II (Paddle)
Rotation Speed: 50 rpm
Medium: Distilled Water
Volume: 900 ml (37°)
Number of Dosage Units: 12
Specifications:

Hour	Specification
1	NLT 25%, NMT 45%
3	NLT 50%, NMT 75%
6	NLT 75%

2. The sponsor was requested to determine the longest period of time between sample drawing and sample analysis for each biostudy, and then to provide frozen stability data for that same length of time. The sponsor had three responses:

1) The sponsor's first response is that the Quality Control (QC) samples that were stored frozen along with the subject samples demonstrate stability of pseudoephedrine. However, there were only three QC samples (one Low Control, one Medium Control, and one High Control) ran with each standard curve (SC) over a two-month period. Furthermore, the only stability data that matters is that data which the reviewer specifically requested, namely, the longest time interval between sample drawing and sample analysis for any sample in the study. The sponsor supplied dates for sample receipt and for the beginning and end of sample analysis, but still did not supply the requested information. Finally, in the opinion of the reviewer, the QC samples are intended to demonstrate proper operation of the assay for each analytical run and are too few in number (N=3) to establish long-term frozen stability.

2) The sponsor's second response is that pooled plasma samples of pseudoephedrine from previous studies also demonstrate frozen stability. The following results are given for pooled controls 84/0664/2:

	Mean Conc. (ng/ml)	N	CV (%)
Low Control			
10-11/84	26.3	10	7.0
3/86	23.3	24	21.5
% Difference	-11.4		
Medium Control			
10-11/84	109	20	8.2
3/86	96	24	10.6
% Difference	-11.9		
High Control			
10-11/84	162	10	10.6
3/86	158	24	16.4
% Difference	-2.5		

Although the CV for the Low Control in 3/86 is somewhat high, the % difference between mean values is acceptable.

3) The sponsor's third response is that literature studies demonstrate stability of frozen pseudoephedrine plasma samples. A reference cited by the sponsor (Brendel et al., J. Chromatogr., 426: 406, 1988) shows stability of pseudoephedrine in frozen (-20°) human plasma samples (20-500 ng/ml) for "at least six months".

The reviewer concurs that the data presented by the sponsor in the second response effectively serves as a pre-study validation of frozen stability over a sufficient length of time, and that the literature reference cited in the third response supports the claim for frozen stability of pseudoephedrine in plasma samples.

3. The sponsor was requested to provide all standard curve sample data for all analytical runs for both studies.

(Note: The reviewer had several telephone conversations with the sponsor in order to clarify the data and to supply missing data. Records of all these conversations are attached to this review.)

In a telephone conversation, the sponsor confirmed that there are actually 54 standard curves (SC) in the single-dose study (which agrees with the reviewer's count) instead of 53 curves as indicated on p. 98, and that there are 31 SC in the multiple-dose study (reviewer agrees) instead of 35 as indicated on p. 185. The typed run # in the upper left hand corners of the data sheets are the correct numbers.

Table 3 (attached) shows the determined concentration values for the back-calculated SC samples from each run in the single-dose study. The following results are noted:

1) In runs 1, 3, 6, 7, 8, 9, 11, 12, 15, 17, 18, 20, 25, 28, 30, 35, 44, 45, and 49 (a total of 19 of the 54 analytical runs), the sponsor has reported % deviations of 0 for all standards; in other words, perfect results.

2) Recalculations of the SC were done for analytical runs 32, 33, and 34. In run 32, the 6.250 ng/ml standard gave a determined value of (b)(4) ng/ml. In run 34, the 3.130 and 12.5 ng/ml standards gave determined values of (b)(4) and (b)(4) ng/ml, respectively. There is no apparent reason why run 33 was repeated; on the data sheet (p.159 of the submission) several of the cpm values are crossed out. In a phone conversation, the sponsor stated that reasons for recalculation usually involved some gross error in the procedure, eg. a broken tube. In all cases, the sponsor used the results from the repeat run.

3) The mean determined value for the 0.195 ng/ml standard was 0.218 ng/ml, with a CV of 29.3% and accuracy of 111.8%. If the value of (b)(4) ng/ml from run 43 is deleted as an outlier, the results are: mean, 0.210 ng/ml; CV, 14.6%;

and, accuracy, 107.7%.

The mean determined value for the 0.390 ng/ml standard was 0.395 ng/ml, with CV of 18.1% and accuracy of 101.3%. If the value of (b)(4) ng/ml from run 43 is deleted as an outlier, the results are: mean, 0.387 ng/ml; CV, 8.9%; and, accuracy, 99.2%.

It is not stated why the sponsor did not repeat run 43.

4) The remaining mean values for determined concentrations and their CV's and accuracy are acceptable.

Table 4 (attached) shows the % deviations of the determined SC sample concentrations from their prepared concentrations. The sponsor stated (phone) that, in general, SC samples that deviated by more than ±20% from their prepared values were not used in computation of subject sample concentrations, and that the plots of the SC for each run show discontinuities when both duplicates of SC samples were rejected (for example, p. 171, run 43). The results from Table 4 show at least 13 instances where deviation exceeded ±20%. Inspection of the corresponding SC plots for the runs in question shows only 4 places where discontinuities were evident:

1) run 39, where the lowest standard deviated by 71.6%
2) run 43, where the two lowest standards deviated by 211.3% and 117.7%, respectively
3) run 53, where the lowest standard deviated by 75.9%.

In all other cases, the SC plot shows a smooth, uninterrupted fit. As explained by the sponsor, all SC samples are run in duplicate and when large CV's occur between these duplicates, the counter will reject the outlier value. For example, in run 34 (p. 161), the 12.500 ng/ml standard (duplicate tubes #23-24) had a % deviation of 214.2%. The notation "broken" is written by tube #24, and this value was rejected. The SC was fitted using tube #23, and the SC plot is smooth and continuous.

Table 5 (attached) shows the back-calculated values of the SC samples used in the multiple-dose study. The following results were obtained:

1) In several cases, apparent outliers were not included by the reviewer for calculation of means, CV, and accuracy:

   - run 1, 6.25 ng/ml standard, determined (b)(4) ng/ml
   - run 4, 0.780 ng/ml standard, determined ng/ml
   - run 15, 1.56 ng/ml standard, determined ng/ml
   - run 17, 12.5 ng/ml standard, determined ng/ml

2) The calculated mean values, CV, and accuracy are acceptable. The high CV for the 0.390 ng/ml standard is

most likely due to two possible outliers ((b) (4) ng/ml).

3) In runs 5, 6, and 8, a different liquid scintillation counter was used which did not generate curve statistics. Rather, the sponsor used the "F value" from the run as a measure of adequate fit. An F-value ≤ 1 is acceptable; the F-values for runs 5, 6, and 8 were all (b) (4) .

Table 6 (attached) shows the % deviations of the determined standard curve samples from their prepared concentrations. There are 15 instances where the % deviation exceeds ±20%, but there were discontinuities in only two plots (runs 9 and 24, where the lowest standard was rejected). In all but 5 instances, the sponsor stated that broken tubes or other gross errors resulted in one of the duplicate samples being rejected, and the remaining sample used to fit the SC. In the other 5 instances, the sponsor stated that there was no obvious explanation for the observed deviations (22.6-49.4%).

4. The sponsor was requested to provide data from QC samples that should have been run daily with every standard curve.

The sponsor has provided the requested data in two forms:

1) QC samples assayed with each standard curve that consisted of a series of spiked controls at concentrations of 1, 3, 30, and 300 ng/ml in pooled plasma from healthy volunteers

The data for the single-dose and multiple-dose studies is shown in Tables 7 and 8, respectively (attached). The reviewer has added the % deviations of each QC sample from its prepared value, and the CV (%) for each mean value. The reviewer applied the following criteria: 1) a ±30% deviation was allowed for the lowest QC concentration; 2) a ±20% deviation was allowed for the remaining QC concentrations; 3) greater than 50% of the QC samples from each analytical run should meet their individual criteria (either 3/4 samples or 2/3 samples). (Note: only one QC sample was analyzed at each concentration.)

From Table 7 (single-dose study), runs 47 and 49 do not meet the third criterion. From Table 8 (multiple-dose study), runs 1, 9, and 21 do not meet the third criterion.

2) The sponsor has presented results from pooled QC samples which were prepared by combining plasma samples from healthy volunteers who had participated in earlier pseudoephedrine studies (Control A, Control B, and Control C).

The sponsor stated (phone) that the criteria used for assay acceptance in this study was that 3/7 samples were allowed to

deviate from target values by more than 15%. The 7 samples the sponsor referred to were the 4 QC samples from above and the 3 "pooled Controls A, B, and C". However, in a phone conversation, the sponsor admitted that these "pooled" samples have no predetermined starting value and, therefore, may not be used for QC assessment. This data was not reviewed since it cannot be used to support QC for this study.

5. The sponsor has noted that the original submission (5/30/90) inadvertently contains data from an earlier study.

From the original Division of Bioequivalence review, p. 6, day-to-day accuracy and precision, single-dose results should be replaced with the following data:

Spiked Conc. (ng/ml)	Measured Conc. (ng/ml)	CV (%)	N
1	0.94	17.0	54
3	3.05	11.5	53
30	30.0	10.0	54
300	278	10.6	49

and p. 6, within-day precision, single-dose results should be replaced with the following data:

	Control A	Control B	Control C
Mean Conc. (ng/ml)	28.6	148	219
CV (%)	10.5	10.8	10.5
N	54	54	53

6. The reviewer has analyzed the single-dose study results comparing the standard statistical model used by the sponsor with a model that incorporates a residual effect.

The four-way crossover design used in the single-dose study permits separation of possible sequence and residual effects. The sponsor did not present any analysis of the results for the possibility of unequal residual effects. Table 9 (attached) shows the 90% confidence intervals using a residual model and a standard model (as calculated by the reviewer). In both cases, all of the 90% confidence intervals for the parameters AUC36, AUCINF, and CMAX, tested for the three treatment comparisons used by the sponsor, were within the allowed 80-120% equivalence interval. There was no significant ($p < 0.1$) residual effect for any of the parameters in any comparison.

7. Expiration dates for reference products used in biostudies:
   - Sudafed 12-Hour Capsules, Batch 7U2753 - 10/89
   - Sudafed Liquid, Batch 7U2754 - 2/89

8. Adverse reactions reported during both studies are summarized in Tables 10 (single-dose) and 11 (multiple-dose), respectively.

9. **In the original ANDA, the sponsor states that the sensitivity limit for the assay is 1 ng/ml. However, the sponsor is using standard curve concentrations of 0.195, 0.390, and 0.780 ng/ml.**

In a telephone conversation with Dr. John Findlay, the following explanations were given:

1) Dr. Findlay states that the original value of 1 ng/ml as the sensitivity limit was probably too conservative and that the very few data points that were excluded would have no impact on the study outcome.

2) The subject plasma samples had pseudoephedrine concentrations much in excess of 0.195 ng/ml. The lowest reported plasma concentrations in the single-dose study (all at 20 minutes) were: Treatment A, (b) (4) ng/ml; Treatment B, (b) (4) ng/ml; Treatment C, (b) (4) ng/ml.

3) Dr. Findlay states that it was not an accepted practice for the lowest standard curve concentration to be the limit of quantitation for RIA procedures when this study was being conducted. However, the sponsor was able to demonstrate acceptable precision and accuracy for back-calculated values of the 0.195, 0.390, and 0.780 ng/ml standards in both the single-dose and multiple-dose studies (Tables 3 and 5 and Comment 3).

II. Conclusions

1. The additional data and explanations provided by the sponsor are adequate to answer Deficiencies 1, 2, and 3 from the original review.

2. As noted above, the QC data presented by the sponsor does not support the validity of the data from runs 47 and 49 in the single-dose study, and from runs 1, 9, and 21 in the multiple-dose study. In a phone conversation, the sponsor identified the following subjects and treatments associated with these analytical runs:

Study	Run	Subject	Treatment
Single-Dose	47	17	A
		18	D
		22	D
		23	B
	49	2	D
		3	B

Multiple-Dose	1	None	-
	9	7	A,B
	21	22	?

Using the GLM procedure of SAS, the reviewer has recalculated the ANOVA with the standard statistical model for the single-dose study under two sets of conditions: 1) excluding values of AUC36, AUCINF, and CMAX corresponding to the specific subjects and treatments listed above; 2) excluding all data from the six subjects in question. The multiple-dose study was reanalyzed similarly, but excluding all data from subjects 7 and 22. The following results were obtained:

Study	Comparison	Parameter	90% C.I.
Single-Dose (1)	Trt2 vs Trt1	AUC36	87.2-104.0
		AUCINF	86.1-103.3
		CMAX	93.0-111.4
	Trt1 vs Trt3	AUC36	95.8-112.7
		AUCINF	94.6-111.9
		CMAX	96.2-111.4
	Trt1 vs Trt4	AUC36	89.1-105.7
		AUCINF	89.2-106.3
Single-Dose (2)	Trt2 vs Trt1	AUC36	90.7-109.4
		AUCINF	90.2-108.8
		CMAX	96.6-113.5
	Trt1 vs Trt3	AUC36	92.7-111.8
		AUCINF	91.6-110.6
		CMAX	91.9-108.9
	Trt1 vs Trt4	AUC36	88.6-106.8
		AUCINF	88.8-107.0
Multiple-Dose	Trt2 vs Trt1	AUC	95.9-104.1
		CMAX	94.5-104.1

In all cases where data from questionable analytical runs is excluded, the 90% C.I. are all still within the allowed equivalence interval. The reviewer concurs that Deficiency 4 from the original review has been successfully answered.

III. Recommendations

1. The bioequivalence studies conducted by Burroughs Wellcome Co. on its Pseudoephedrine Hydrochloride 12-Hour 120-mg Caplet, lot #7U2752, comparing it to Sudafed^{R} 12-Hour Capsule 120 mg have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Burroughs Wellcome Pseudoephedrine Hydrochloride 12-Hour Caplet 120-mg is bioequivalent to the reference product Sudafed^{R} 12-Hour Capsule 120-mg manufactured by Burroughs Wellcome.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of distilled water at 37° using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than 25% and not more than 45% of the labeled amount of drug in the dosage form is dissolved in 1 hour.
>
> Not less than 50% and not more than 75% of the labeled amount of drug in the dosage form is dissolved in 3 hours.
>
> Not less than 75% of the labeled amount of drug in the dosage form is dissolved in 6 hours.

3. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence James D Henderson

RD INITIALED FPELSOR
for FT INITIALED FPELSOR

Concur: _____ Date 4-4-91
Agnes T. Wu, Ph.D.
Acting Deputy Director
Division of Bioequivalence

Concur: Shrikant V. Dighe Date 4/5/91.
Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

JDH/stm/3-29-91/73585

cc: ANDA #73-585, original, HFD-630, HFD-604 (OGD, Hare)
HFD-22 (Hooton), HFD-655 (Pelsor, Henderson), Drug file

Drug (Generic Name): Pseudoephedrine HCl Firm: BW
Dose Strength: 120 mg 12-hr caplet
ANDA # 73-585 Submission Date: 3-13-91

Table 1 - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ____ Paddle ✓ RPM 50 No. Units Tested: 12
Medium: SGF w/o E for 0-1 hr / SIF w/o E for 1-8 hr Volume: 900 ml
Reference Drug; (Manuf.): test product before imprinting and (b) (4)
Assay Methodology: AutoAnalyzer Colorimetry (400 nM)

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product after imprinting and (b) (4) (b) (4) Lot # 7U2752 Strength (mg) 120 Mean % Dissolved	Range	(CV)	Reference Product before imprinting and (b) (4) Lot # 7U2752 Strength (mg) 120 Mean % Dissolved	Range	(CV)
1	30.2	(b) (4)	(2.8	29.9	(b) (4)	(5.0
2	44.8		(1.5	44.5		(3.8
3	55.6		(2.4	55.1		(3.3
4	65.0		(2.9	64.4		(3.0
6	79.3		(3.9	78.3		(2.7
8	89.3		3.1	88.4		2.8
	Lot # ____ Strength (mg) ____			Lot # ____ Strength (mg) ____		
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )

Drug (Generic Name): Pseudoephedrine HCl Firm: BW
Dose Strength: 120 mg 12-hr caplet
ANDA # 73-585 Submission Date: 3-13-91

Table 2 - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ____ Paddle √ RPM 50 No. Units Tested: 12

Medium: Distilled Water Volume: 900 ml

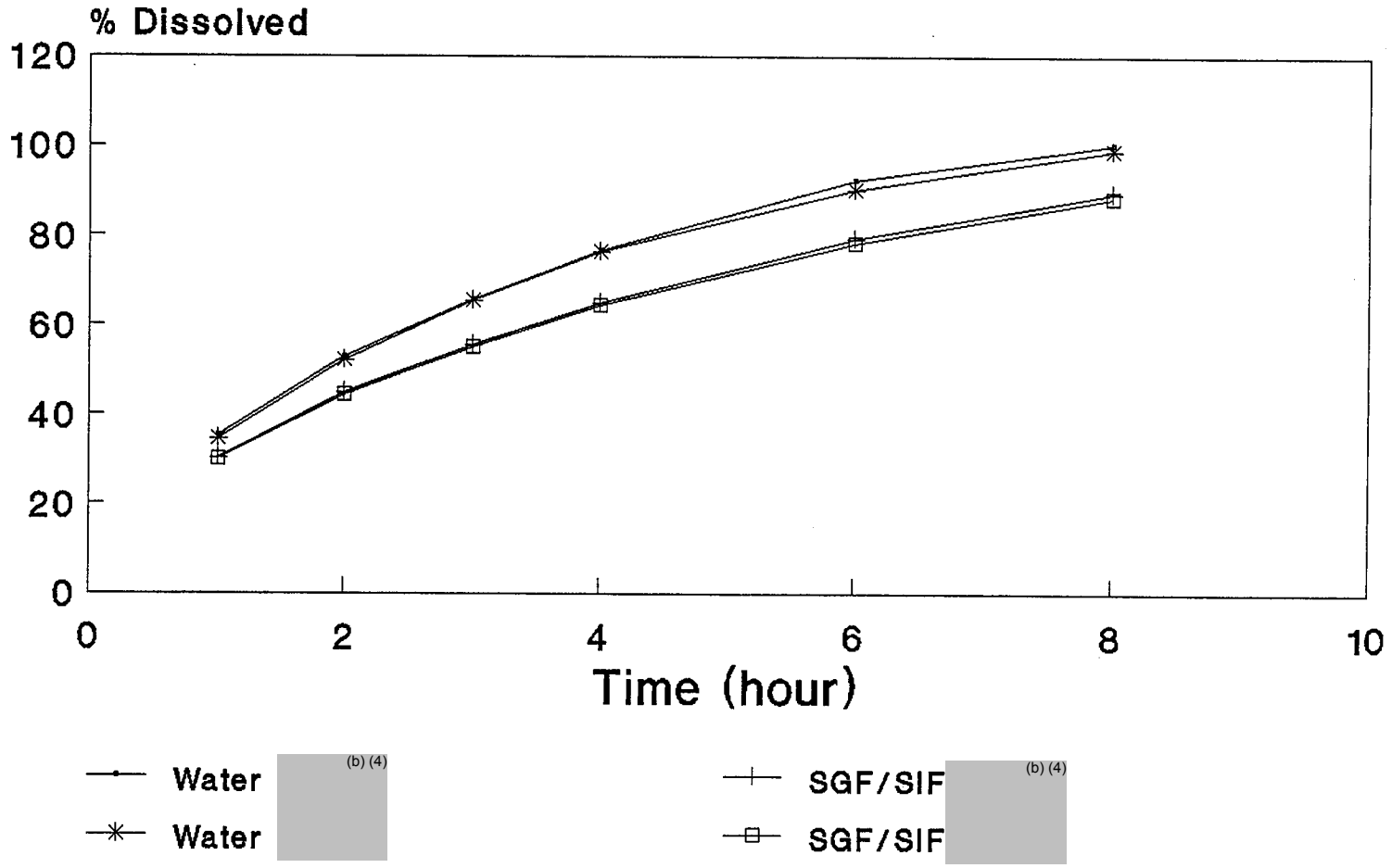
Reference Drug; (Manuf.): test product before imprinting and [redacted] (b) (4)

Assay Methodology: Auto Analyzer Colorimetry (400 nm)

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product after imprinting and [redacted] (b) (4) (b) (4) Lot # 7U2752 Strength (mg) 120 Mean % Dissolved	Range	(CV)	Reference Product before imprinting and [redacted] (b) (4) (b) (4) Lot # 7U2752 Strength (mg) 120 Mean % Dissolved	Range	(CV)
1	35.3	[redacted] (b) (4)	3.0	34.5	[redacted] (b) (4)	5.6
2	52.8		1.8	52.0		5.0
3	65.7		1.8	65.3		4.9
4	76.7		2.2	76.4		4.7
6	92.4		2.3	90.1		3.8
8	100.2		2.1	98.9		3.4
	Lot # ____ Strength (mg) ____			Lot # ____ Strength (mg) ____		
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )

In Vitro Dissolution Testing
Pseudoephedrine HCl Caplet CR.120 mg



Paddle 50 rpm, 900 ml medium

Figure 1

Table 3 - Back-Calculated Values of Standard Curve Samples - Single-Dose Study

Run	Date (1988)	Standard Curve Samples - Prepared Conc. (ng/ml)							
		0.195	0.390	0.780	1.560	3.130	6.250	12.500	25.000
		Standard Curve Samples - Determined Conc. (ng/ml)							
1	2-17	[redacted] (b) (4)							
2	2-17								
3	2-19								
4	2-20								
5	2-23								
6	2-24								
7	2-25								
8	2-26								
9	2-26								
10	2-27								
11	3-1								
12	3-2								
13	3-3								
14	3-4								
15	3-4								
16	3-4								
17	3-7								
18	3-8								
19	3-9								
20	3-9								
21	3-11								
22	3-11								
23	3-12								
24	3-14								
25	3-16								
26	3-16								
27	3-19								
28	3-17								
29	3-18								
30	3-19								
31	3-20								
32	3-21 *								
33	3-23 *								
34	3-24 *								
35	3-24								
36	3-25								
37	3-25								
38	3-26								
39	3-27								
40	3-30								

Table 3 - Continued

41	3-28	[redacted] (b) (4)						
42	3-30							
43	3-31							
44	3-29							
45	4-6							
46	4-6							
47	4-1							
48	4-6							
49	4-2							
50	4-7							
51	4-5							
52	4-6							
53	4-7							
54	4-12							
Mean (ng/ml)		0.218	0.395	0.776	1.542	3.135	6.353	12.569	24.782
CV (%)		29.3	18.1	6.9	7.2	2.5	3.8	3.2	2.8
N		50	54	54	54	54	54	54	54
Accuracy (%)		111.8	101.3	99.5	98.8	100.2	101.6	100.6	99.1

* Recalculation runs

In some cases, the photocopied material was not readable with regard to determined concentrations; % differences calculated by the sponsor were then used to obtain the determined value.

In every case, the reviewer used the typed analytical run # in the upper left hand corner of the data sheets.

Table 4 - % Deviations of Back-Calculated Standard Curve Samples from Prepared Concentrations (Single-Dose Study)

Run	Prepared Concentration (ng/ml)							
	0.195	0.390	0.780	1.560	3.130	6.250	12.500	25.000
	% Deviation							
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								
24								
25								
26								
27								
28								
29								
30								
31								
32*								
33*								
34*								
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

(b) (4)

Table 4 - continued

48	(b) (4)
49	
50	
51	
52	
53	
54	

* Recalculation run (original run not used).

Table 5 - Back-Calculated Values of Standard Curve Samples - Multiple-Dose Study

Run	Date (1988)	Standard Curve Samples - Prepared Conc. (ng/ml)							
		0.195	0.390	0.780	1.560	3.130	6.250	12.500	25.000
		Standard Curve Samples - Determined Conc. (ng/ml)							
1	7-11	[redacted] (b) (4)							
2	7-11								
3	7-11								
	*								
4	7-11								
5	7-12								
6	7-12								
7	7-12								
8	7-12								
9	7-12								
10	7-12								
11	7-12								
12	7-12								
13	7-12								
14	7-12								
15	7-13								
16	7-13								
17	7-14								
18	7-14								
19	7-14								
20	7-14								
	*								
21	7-14								
22	7-14								
23	7-21								
24	7-21								
25	7-14								
26	7-21								
27	7-21								
	*								
28	7-28								
29	7-28								
30	7-28								
31	8-3								
Mean (ng/ml)		0.210	0.415	0.775	1.520	3.104	6.583	12.437	24.638
CV (%)		7.7	33.2	14.7	11.0	3.4	11.6	3.8	3.5
Accuracy(%)		107.7	106.4	99.5	97.4	99.2	105.3	99.5	98.6
N		26	28	27	27	28	27	27	28

* Recalculation runs.
** A different liquid scintillation counter was used and curve statistics were not generated.
Run # is typed in upper left hand corner of data sheets.
Underlined values were deleted as outliers by the reviewer.

Table 6 - % Deviations of Back-Calculated Standard Curve Samples
from Prepared Concentrations (Multiple-Dose Study)

Run	Prepared Concentration (ng/ml)							
	0.195	0.390	0.780	1.560	3.130	6.250	12.500	25.000
	% Deviations							
1								
2								
3*								
4								
7								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20*								
21								
22								
23								
24								
25								
26								
27*								
28								
29								
30								
31								

(b) (4)

* Recalculation run (original run not used).

Runs 5, 6, and 8 are not included since curve statistics were not calculated.

Table 7

Spiked Quality Control Samples
Single-Dose Study (TBZZ/88/0031)

Assay	Date	1.0	% dev	3.0	% dev	30	% dev	300	% dev
1	2/17/88	[redacted] (b) (4)							
2	2/17/88								
3	2/19/88								
4	2/20/88								
5	2/23/88								
6	2/24/88								
7	2/25/88								
8	2/26/88								
9	2/26/88								
10	2/27/88								
11	3/1/88								
12	3/2/88								
13	3/3/88								
14	3/4/88								
15	3/4/88								
16	3/4/88								
17	3/7/88								
18	3/8/88								
19	3/9/88								
20	3/9/88								
21	3/11/88								
22	3/11/88								
23	3/12/88								
24	3/14/88								
25	3/16/88								
26	3/16/88								
27	3/19/88								
28	3/17/88								
29	3/18/88								
30	3/19/88								
31	3/20/88								
32	3/21/88								
33	3/23/88								
34	3/24/88								
35	3/24/88								
36	3/25/88								
37	3/25/88								
38	3/26/88								
39	3/27/88								
40	3/30/88								
41	3/28/88								
42	3/30/88								
43	3/31/88								
44	3/29/88								
45	4/6/88								
46	4/6/88								
47	4/1/88								
48	4/6/88								
49	4/2/88								
50	4/7/88								
51	4/5/88								
52	4/6/88								
53	4/7/88								
54	4/12/88								
Mean		0.9		3.1		29		278	
S.D.		0.2		0.4		3		30	
n		54.0		53.0		54		49	
CV%		22.2		12.9		10.3		10.8	

Table 8

Spiked Quality Control Samples
Steady-State Study (TBZZ/89/0001)

Assay	Date	1.0 % dev	3.0 % dev	30.0 % dev	300.0 % dev
1	6/20/88				
2	6/21/88				
3	6/21/88				
4	6/27/88				
5	6/21/88				
6	6/21/88				
7	6/22/88				
8	6/22/88				
9	6/22/88				
10	6/22/88				
11	6/23/88				
12	6/23/88				
13	6/27/88				
14	6/27/88				
15	6/27/88				
16	6/27/88				
17	6/28/88				
18	6/28/88				
19	6/29/88				
20	6/29/88				
21	6/29/88				
22	6/30/88				
23	6/30/88				
24	7/6/88				
25	7/6/88				
26	7/6/88				
27	7/6/88				
28	7/7/88				
29	7/7/88				
30	7/11/88				
31	7/12/88				
32	7/12/88				
33	7/13/88				
34	7/13/88				
35	7/25/88				
36	7/25/88				
37	7/25/88				
38	7/27/88				
Mean		0.9	3.0	29	303
S.D.		0.2	0.4	3	40
n		38	38	38	38
CV(%)		22.2	13.3	10.3	13.2

(b) (4)

Table 9 - 90% Confidence Intervals from Residual and Standard Models (all subjects)

Model	Comparison	90% C.I.	
		Normal Scale	Log Scale
	Trt B vs Trt A		
Residual	AUC36	-	88.0-104.5
	AUCINF	-	86.7-103.0
	CMAX	-	93.7-108.9
Standard	AUC36	87.6-103.7	-
	AUCINF	86.7-103.2	-
	CMAX	93.0-107.2	-
	Trt A vs Trt C		
Residual	AUC36	-	93.3-110.8
	AUCINF	-	92.6-110.0
	CMAX	-	95.2-110.7
Standard	AUC36	95.1-111.7	-
	AUCINF	93.8-110.7	-
	CMAX	96.1-110.7	-
	Trt A vs Trt D		
Residual	AUC36	-	91.0-108.1
	AUCINF	-	90.1-106.4
Standard	AUC36	90.3-106.1	-
	AUCINF	90.1-106.4	-

TABLE 10

SUMMARY OF ADVERSE EXPERIENCES – Single-Dose

VOL	DOSING PERIOD	TRT	ADVERSE EXPERIENCE	DATE		TIME		SEVERITY	ACTION TAKEN	RELATIONSHIP
				ONSET	CEASED	ONSET	CEASED			
1	2	D	Cough*	1/27/88	1/29/88	NA	NA	Moderate, not serious	Therapy required: 650 mg acetaminophen	Not associated with use of the drug
12	3	D	Headache*	1/31/88	1/31/88	NA	NA	Mild, not serious	Therapy required: 325 mg aspirin	Not associated with use of the drug
17	4	C	Fainted	2/7/88	2/7/88	0745	0750	Mild, not serious	None	Not associated with use of the drug
19	2	B	Upper Respiratory Infection*	1/24/88	1/26/88	NA	NA	Mild, not serious	Therapy required: 650 mg aspirin 1300 mg acetaminophen	Not associated with use of the drug

NA - not available

* Intercurrent illness. These events occurred following the noted Dosing Periods.

TABLE 11

SUMMARY OF ADVERSE EXPERIENCES – Multiple-Dose

VOL	DOSING PERIOD	TRT	ADVERSE EXPERIENCE	DATE		TIME		SEVERITY	ACTION TAKEN	RELATIONSHIP
				ONSET	CEASED	ONSET	CEASED			
1	1	A	Headache	6/6/88	6/7/88	2300	0700	Moderate, not serious	None	Not associated with use of the drug
4	1	B	Headache	6/6/88	6/6/88	1700	2000	Moderate, not serious	None	Not associated with use of the drug
5	1	A	Headache	6/7/88	6/7/88	0000	0200	Mild, not serious	None	Not associated with use of the drug
5	2	B	Coughing up Blood	6/11/88	6/11/88	0650	0652	Mild, not serious	None	Not associated with use of the drug
11	1	B	Headache	6/8/88	6/8/88	1730	1930	Mild, not serious	None	Not associated with use of the drug
12	1	A	Headache	6/7/88	6/7/88	1930	2330	Mild, not serious	None	Not associated with use of the drug

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 073585

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

dup (orange) to Bio.

505(j)(2)(A) OK
6-13-90
V.V.

Wellcome Acceptable
505(j)(2)(A)

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX 5109270915
tel. 919 248-3000

6/29/90

May 30, 1990

Richard A. Terselic, M.D., Acting Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research
HFD-230, Room 16-70
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: ABBREVIATED NEW DRUG APPLICATION
SUDAFED® (pseudoephedrine hydrochloride) 12 Hour Caplets

Dear Dr. Terselic:

In accord with Section 314.55 of the New Drug Regulations, we submit herewith an Abbreviated New Drug Application for SUDAFED 12 Hour Caplets, 120 mg pseudoephedrine hydrochloride per caplet.

Under Section 505(j)(2)(C)(i) of the Act, on November 3, 1987, the Agency approved a petition filed by the Health Policy Network Associates dated August 28, 1987, Docket No. 87P-0297/CP. The approved petition provides for a change in dosage form, from a capsule to a tablet, from the listed referenced drug product, Burroughs Wellcome Co.'s SUDAFED (pseudoephedrine hydrochloride) 12 Hour Capsules, (NDA 17-941).

Data supporting the Abbreviated New Drug Application for SUDAFED 12 Hour Caplets are enclosed.

If you have any questions regarding this ANDA, please contact J. Greg Perkins, Ph.D., at (919) 248-4453.

Sincerely,

Donald A. Knight
Director, Division of
Drug Regulatory Affairs

TRZO/90/0063/5-31-90/*tg
SUDAFED 12 Hour Caplets

Burroughs Wellcome Company

73585

H

Patel

ANDA CHECKLIST FOR COMPLETENESS AND ACCEPTABILITY OF THE APPLICATION

Pseudoephedrine HCl tablet 120mg

	YES	NO
Methods Validation package (3copies) 5/30/90 Cover Letter 5/31/90	✓ ✓	
356H Signed	✓	
Table of Contents	✓	
Information to show proposed product is the same as listed product: (i) (a) indications (ii) active ingredients (iii) (a) route (b) dosage form (c) strength (iv) labeling	✓	
Patent Certification	1	
Exclusivity Addresses (If Applicable)	N/A	
Labeling	✓	
Statement re Rx/OTC Status	no specific	
Components & Composition (Unit Composition)	✓	
Manufacturing Controls	✓	
Batch Formulation	✓	
Certification of GMP ✓	✓ rcvd 6-9-90	
Description of Facilities ✓	✓ recvd 6-9-90	
Manufacturing Procedures (Batch Records)	✓	
Specifications and Tests for Active Ingredient and Dosage Form	✓	
Stability Profile Including Stability Data (Use of Stability Indicating Method)	✓	
Samples Statement Plus Data	✓	
Bioavailability/Bioequivalence Protocol		
Study	✓	
In Vivo Study/Waiver Request		
Dissolution Data		
Environmental Impact Analysis	✓	

DD/4/25/90:Wang 223a

ORIGINAL

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Wellcome

cables & telegrams
Tabloid Raleigh, N.C.
TWX 5109270915
tel. 919 248-3000

June 12, 1990

Richard A. Terselic, M.D., Acting Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research
HFD-630, Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 73-585
AC

Re: SUDAFED® (pseudoephedrine hydrochloride) 12 Hour Caplets
ABBREVIATED NEW DRUG APPLICATION

Dear Dr. Terselic:

Reference is made to a telephone call received on June 8, 1990, from Ms. Valerie Vashio, of FDA, concerning our Abbreviated New Drug Application for SUDAFED 12 Hour Caplets, submitted on May 30, 1990.

As requested by Ms. Vashio, attached is a description and diagram of the facilities of the Burroughs Wellcome Co., Greenville, North Carolina manufacturing plant.

Also included is a certification that Burroughs Wellcome Co. conforms with current Good Manufacturing Practices in accord with 21 CFR 211.

Should you require additional information, please do not hesitate to call me at (919) 248-4453.

Sincerely,

Anne McKay for
J. Greg Perkins, Ph.D.
Head, Department of Consumer Products
Drug Regulatory Affairs

cc: Ms. Valerie Vashio

RECEIVED
JUL 09 1990
GENERIC DRUGS

TRZO/90/0066/6-12-90/*wgm
SUDAFED 12 Hour Caplets

ANDA Assignment Record

Appl Type/Number: N 073585 Status/Date: PN PENDING REVIEW 31-MAY-90
Firm: BURROUGHS WELLC
Trade Name:
PS OEPHEDRINE HYDROCHLORIDE USP:

Rx: ____ OTC: ✓ Dosage Form: TAB Strength: 120 MG (CAPLET

Therapeutic Class: _____

Doc Set Type: N 000 Amend/Type: _____ Letter Date: 30-MAY-90
Rec-d Date: 31-MAY-90 Acknl. Date: 7-25-90
Bio Rev Type: STUDY/DISSOLUTION To Bio: 7-16-90
unspec 7-16-90

			Assigned	Completed
Lbl:	___	J. Phillips	7-25-90	10-5-90
Chm:	✓	Mrs. S Brown	7-24-90	___-___-___
Bio:	___	_____	___-___-___	___-___-___
Ins:	___	_____	___-___-___	___-___-___
Co1:	___	_____	___-___-___	___-___-___
Co2:	___	_____	___-___-___	___-___-___

DESI Drug: _____ Similar or Related: _____

Applicant Manufacturer: Yes ✓ No _____

If No: Name of Mfg: _____

ANDA #_____ Approved: _____ Pending: _____ Same Formulation: _____

ication Complete: Yes ✓ No _____

Application Acceptable: Yes ✓ No _____

If No: Non-Acceptable Letter to Firm: ___-___-___

CSO/CST: Valerie Vashus Date: 7-16-90
505(j)(2)(A) OK

JUL 25 1990

ANDA 73-585

Burroughs Wellcome Company
Attention: J. Greg Perkins, Ph.D.
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Dear Sir:

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

NAME OF DRUG: Pseudoephedrine Hydrochloride Extended Release Tablet, 120 mg (Caplet)

DATE OF APPLICATION: June 12, 1990

DATE OF RECEIPT: July 9, 1990

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

Please provide a statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practioner licensed by law to administer it.

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

Sincerely yours,

Kent C. Johnson 1/Be 7.27.90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-585
DUP/Division File
HFD-634/RPatel/7-17-90
HFD-632/VVashio/7-17-90
R/D initialed by VVashio
jmk/7-17-90/73585ack.ltr
F/T by jmk/7-18-90
Acknowledgement letter

Related 7/24/90
Johnston 7-23-90

ORIG 1.1

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

August 7, 1990

Richard A. Terselic, M.D., Acting Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research
HFD-230, Room 16-70
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

ORIG NEW CORRES

Re: ANDA 73-585
SUDAFED® (pseudoephedrine hydrochloride 120 mg) 12 Hour Caplets

Dear Dr. Terselic:

Reference is made to a letter dated July 25, 1990, received from Dr. Kent Johnson of your division, concerning our abbreviated new drug application dated June 12, 1990, for Pseudoephedrine Hydrochloride Extended Release Tablets, 120 mg (SUDAFED 12 Hour Caplets).

Please be advised this product will not be limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

Similar to the listed drug, SUDAFED 12 Hour Capsules, the caplets are intended for over-the-counter use.

Should you require any additional information, please do not hesitate to call me at (919) 248-4453.

Sincerely,

J. Greg Perkins, Ph.D.
Head, Department of Consumer Products
Drug Regulatory Affairs

RECEIVED

TRZO/90/0473/8-6-90/*tg
GP/SUDAFED 12 Hour Caplets

Pseudoephedrine Hydrochloride
120 mg 12-hr caplet
ANDA # 73-585

OCT 22 1990

Donald A. Knight, Director
Division of Drug Regulatory Affairs
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Mr. Knight:

Reference is made to the in-vivo bioequivalence study and dissolution data dated May 30, 1990 which you submitted in support of Pseudoephedrine Hydrochloride 120 mg 12-hr caplets.

The material has been reviewed by the Division of Bioequivalence and we have the following comments:

Deficiencies:

1. The firm should be advised to conduct dissolution testing on 12 individual dosage units of the test product (batch 7U2752 before and after imprinting and (b)(4)) and to report individual and mean data. The firm should conduct dissolution testing using 900 mL of the following media: 1) simulated gastric fluid (SGF) without enzymes for the first hour; 2) simulated intestinal fluid (SIF) without enzymes thereafter. Testing should be done at 1, 2, 3, 4, 6, and 8 hours using USP apparatus II (paddle) at 50 rpm and a validated assay method. Data supporting the assay validation should be included. The Division of Bioequivalence will then evaluate the proposed dissolution specifications for the test product.

2. There is no frozen stability data for either study. The firm should have determined the maximum period of time from sample drawing to sample analysis over both biostudies and verify frozen stability for this length of time.

3. The firm has not supplied any raw data in this submission, except for one example of a standard curve from each biostudy. All of the standard curves used for analysis of subject samples from the two bioequivalence studies should be submitted along with the results of curve statistics and subject samples.

4. The firm has not supplied any results or raw data for quality

control samples (target concentrations in the low, middle, and high range of the standard curve) that should have been analyzed with every standard curve.

Recommendation:

The bioequivalence study conducted by Burroughs-Wellcome on its Sudafed (Pseudoephedrine Hydrochloride) 12-Hour Caplet (120 mg, batch 7U2752), comparing it to Burroughs-Wellcome Sudafed 12-Hour Capsule (120 mg, batch 7U2753) has been found incomplete by the Division of Bioequivalence. The firm should submit additional data in response to the deficiencies cited above.

All responses and correspondence with regard to this letter should be sent to the Division of Generic Drugs, HFD-630.

Sincerely yours,

10/24/90

for Shrikant V. Dighe
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
HFD-632
Pollock/SSBrown
HFD-650 (Dighe, CST)
lsg 10-4-90 (N73585.STD)
bio letter

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service 140

s/Shirley Brown

Memorandum

Date 6-7-90

From Division of Generic Drugs HFD- 632

Requestor's Name Valerie Vashio Phone 4430193

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product ✓

Application and Supplement No. 73-585

Brand Name *(if any)* *

Establishment Name, Dosage Form and Strength Pseudoephedrine Hydrochloride 12 HOUR (CAPLET) Profile Class Code: TTR

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: ~~Burroughs Wellcome Co~~

Address: 3030 CORNWALLIS ROAD RESEARCH TRIANGLE PARK, NC 27709

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*) **For HFD 320 Use** Status & Date of Inspection:

(b) (4)

1. mnfctr of finished product, analytical testing and packaging Applicant, P.O. Box 1887, GREENVILLE, NC. 27834 OK 7/23/90

(b) (4)

2.

3.

4. _____

5. _____

Other Information or Special Requests: _____

****

For HFD-320 Use Only: Date Received: 6-18-90

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: Cathi Broadway Date Completed: 1/9/91

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

DIRS-7001.

O>IN+320

DBN

FORM FDA 3274 (3/90)

I N T E R O F F I C E M E M O R A N D U M

Date: 03-Mar-1991 08:14pm EST
From: VMSMail User PECK
PECK@PLUTO@MRGATE
Dept:
Tel No:

TO: MICHELS@PLUTO@MRGATE
TO: WILLIAMSR@PLUTO@MRGATE
TO: TYSON@PLUTO@MRGATE
TO: MEYER@PLUTO@MRGATE
TO: BURLINGTON@PLUTO@MRGATE

Subject: TAMPERING

CHECKING IN FROM SOUTH CAROLINA (CONTACT NUMBER: [redacted](b) (6)). I HAVE COORDINATED PRIMARILY WITH ROGER W AND B BURLINGTON ON THIS SO FAR WITHIN CDER; ROGER WILL COORDINATE FURTHER WITH DAN AND BRUCE IN AM WHEN ANDA FACTS BECOME APPARENT. AT BENSONS REQUEST, I SPOKE WITH DAVID BEARY, MED DIR OF BW ABOUT 3:15 TODAY. BASED UPON DISCUSSIONS WITH BENSON AND KESSLER HE IS EXPECTING FDA TO CONSIDER APPROVING THEIR ANDA NO 73585 FOR PSEUDOEPHEDRINE HCL CAPLETTS; HE SAY IT WAS SUBMITTED ON 11/3/90! BEARRY THINKS ALL IS FINE WITH ANDA NOW, THE INSPECTION MATTER HAS BEEN CLEARED UP AND THAT PHARMACOLO IS OK. HIS ARGUMENT IS THAT THE MARKET NEEDS A 'TAMPER RESISTANT' PRODUCE AND THE CAPLET IS THE ONE TO APPROVE NOW. HE CLAIMED TO BE UNAWARE OF COMPETING PRODUCTS AND PUBLIC HEALTH MATTERS. CITED COOPERATION WITH THE AGENCY. I INFORMED HIM OF THE RX PRODUCT AVAIABLE (NOVAFED, DOW) AND OF THE FISONS PRODUCT (PSEUDOEPHEDRINE POLISTRIREX SUSPENSION) AND THE SCHERING PRODUCT (AFRINOL) WITHOUT FURTHER COMMENT. I MADE NO COMMITMENTS OR PROMISES OTHER T' THAT WE ARE LOOKING INTO IT.

KESSLER IS EXPECTING US TO BRIEF HIM TOMMOROW ON THE ANDA. AFTER ROGER ANb DAN HAVE GONE OVER THE ANDA FACTS, BRUCE CAN CONFER. AN OPPORTUNE TIME TO PRESENT TO COMMISSIONER MAY BE AT THE HEARING BRIEFING IN EARLY AFTERNOON BUT THIS INFO MAY BE NEEDED EARLIER. KESSLER AND BENSON ARE FEELING GOOD ABOUT BW'S COOPERATION SO ARE PRONE TO SEE IF THE ANDA CAN BE APPROVED. MY CONCERNS ABOUT MEDICAL NEED, ANGER OF DINGEL, BARR, MYLAN AND OTHER COMPETITORS SEEMED LESS IMPORTANT THAN BW'S COOPERATION. SO GO GENTLY BUT STATE ALL OF THE PIT-FALLS. CALL ME IF YOU NEED ME.
CARL

I N T E R O F F I C E M E M O R A N D U M

Date: 04-Mar-1991 06:28am EST
From: Roger Williams
WILLIAMSR
Dept: HFD-600
Tel No: 301-443-8340

TO: Robert Pollock (POLLOCK)
TO: Doug Sporn (SPORN)

Subject: Attached EMAIL

Doug and Bob:

A brief summary: tampering with Burroughs-Wellcome's Sudafed 12 Hour capsule product in the Seattle area will result in nationwide recall. BW has been extremely cooperative so FDA at the Commissioner's level is considering expediting approval of BW's ANDA 73-585--a 12 hour caplet of Sudafed. I need an update of the full status of the ANDA--when it was received and what has happened to it since coming it. Next possible step--what would be involved in expediting the review. This is the current hot topic--I need data fast.

I ne know if you have any questions.

Roger

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE
3-12-91

ANDA NUMBER
73585

IND NUMBER

TELECON/MEETING

INITIATED BY
☐ APPLICANT/SPONSOR
☒ FDA

MADE
☒ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
Pseudoephedrine 12-hr caplet

FIRM NAME
Burroughs-Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. Greg Perkins

TELEPHONE NO.
919-248-4453

10:30 AM
Regarding ANDA 73585
The randomization schedule indicates which treatment each subject received during each study period. However, the submission does not state which Sequence #'s were assigned to these subjects.

Dr. Perkins: will call back

11:00 AM
Drs. Perkins & Lai
– will have to consult another section in company, will call back

11:30 AM
Dr. Perkins

Sequence I – Trt ABCD
" II – " BDAC
" III – " CADB
" IV – " DCBA

SIGNATURE
James P Hardeman

DIVISION
Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

ARCHIVAL COPY ORIGINAL

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

March 13, 1991

NONVIABILITY MATERIAL

NDA ORIG AMENDMENT

Roger Williams, M.D., Director
Office of Generic Drugs, MPN II, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 73,585
SUDAFED® 12 Hour Caplets, 120 mg
pseudoephedrine hydrochloride per caplet

Dear Dr. Williams:

Reference is made to letter dated October 22, 1990, received by us from the Division of Biopharmaceutics regarding our ANDA for SUDAFED 12 Hour Caplets, 120 mg pseudoephedrine hydrochloride per caplet. Reference is also made to our telephone conversations of March 8, 1991 with Dr. S. Dighe of your Office regarding clarification of the data requested in the October 22nd letter.

The items of deficiency (Items 1 through 4), as outlined in the October 22nd letter, are addressed herein in Attachments 1 through 4, respectively. As discussed with Dr. Dighe, the raw data required for Item 3 is comprised of all standard curves used in deriving patient data for the pilot and full bioequivalence studies. For Item 4, the listings of the quality control data for the two bioequivalence studies have been provided, in lieu of the notebook data.

In addition, we are amending our ANDA (Attachment 5) to provide for corrections to the Technical Report (Document TBZZ/88/0031) for Study 03 appearing in Volume 1.3 of our original ANDA. As indicated herein, these revisions do not effect the findings of the study.

Should you have any questions concerning this submission, please call me at (919) 248-4453.

Sincerely,

J Greg Perkins

J. Greg Perkins, Ph.D., Head.
Consumer Products Department
Drug Regulatory Affairs

TRZO/91/0258
JGP/mg*

Enclosure

RECEIVED
MAR 13 1991
GENERIC DRUGS

cc 7 Mar 91 P. Miller

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 14 1991

93-585

FROM: Director, Center for Drug Evaluation and Research

SUBJECT: Over The Counter Capsules

TO: Office of Drug Evaluation I
Office of Drug Evaluation II
Office of Generic Drugs
Office of Compliance
Office of Drug Standards

In view of the recent tampering episode with pseudosphedrine 12 hour capsules marketed by Burroughs-Wellcome, Inc., Dr. Kessler has committed the agency to do what we can to expedite handling and review of certain applications seeking to use non-capsule dosage forms. Capsules have been targets of opportunity in several tampering incidents, yet no dosage form is entirely tamper proof. Nevertheless, experience and common sense suggest that unsealed capsules are easy to adulterate and have, in fact, been the subject of serious tampering episodes. Some sponsors of approved applications for over-the-counter capsule dosage forms products, whether the capsule is sealed or unsealed, wish to pursue alternative dosage forms, tablets, caplets, one piece soft gelatin capsules, for products that would directly substitute for such two piece capsule products. The Center directs the Drug Evaluation Offices to handle and review such applications or supplemental applications with high priority where the company has committed that upon approval of the alternative dosage form it will cease marketing the approved capsule dosage form.

In the specific tampering incident cited above, it is our current assessment that the actual product was not tampered with, but rather the tamperer substituted a similar capsule. Additionally, there was a failure on the part of some unfortunate consumers to recognize that the tamper-resistant packaging had, in fact, been tampered with. Although it is clear that no packaging is tamper-proof, it is in the public interest to facilitate the marketing of products with packaging that provides additional protection to consumers by enhancing tamper resistance. Therefore, the Center

Archival Copy

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Wellcome

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

AMENDMENT TO A PENDING SUPPLEMENT

March 14, 1991

Roger Williams, M.D., Director
Office of Generic Drugs, MPN II, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 73-585
SUDAFED® 12 Hour Caplets
(PSEUDOEPHEDRINE HYDROCHLORIDE)

Dear Dr. Williams:

Please refer to our Abbreviated New Drug Application of May 30, 1990 for Sudafed 12 Hour Caplets. We wish to amend this application to submit a bulk export label to provide for exporting of the 12 hour caplet. This label was not included in the original ANDA.

If you have any questions regarding this amendment, please call me at (919) 248-4453.

Sincerely,

J Greg Perkins

J. Greg Perkins, Ph.D.
Head, Department of Consumer Products
Drug Regulatory Affairs

TRZO/91/0259

RECEIVED
MAR 14 1991
GENERIC DRUGS

M E M O R A N D U M

Department of Health & Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 18, 1991

TO: Dr. Jerussi
Dr. Dighe
Kent Johnson

FROM: Roger L. Williams, M.D.

SUBJECT: Expedited Review of Selected OTC ANDAs

The Commissioner and the Center for Drug Evaluation and Research have agreed to expedite the review of selected ANDAs for OTC products when the proposed products are inherently more tamper resistent than currently marketed dosage forms (see attached memorandum). My understanding of important points relative to this memorandum are as follows:

1. Affected firms must be marketing a capsule dose form and must submit or have submitted an ANDA for a more tamper resistent formulation (tablet, caplet, one piece soft gelatin capsules) that is otherwise equivalent to the marketed product.

2. The affected firms must agree to discontinue marketing the capsule product on approval of the more tamper resistent formulation.

3. Reviews in both the Divisions of Chemistry and the Division of Bioequivalence will be expedited by moving the involved ANDA to the top of the reviewer's queue. Reviewers will not be asked to interrupt work in progress. When there is a conflict with any other expedited reviews, the Division director will establish priority.

4. Except for placement in the queue, usual procedures and criteria for OGD reviews will be followed. Relaxation of approval standards will not be permitted.

5. According to the criteria outlined in the attached memorandum, there appear to be only two ANDAs now in OGD that qualify for expedited review. One is Burroughs Wellcome's Pseudoephedrine 12-HR Caplet (ANDA 73-585) and one is KV Pharmaceuticals' Triprolidine 5 mg/Pseudoephedrine HCl 120 mg Controlled Release Caplet (ANDA 72-758).

I have asked Kent Johnson in the Office to coordinate implementation of the attached memorandum with you. Please let me know if you have any questions.

cc: Douglas Sporn
Robert Pollock
Don Hare
Yana Mille

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 3-25-91

ANDA NUMBER: 73585

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Pseudoephedrine HCl 12-hr caplet

FIRM NAME: Burroughs-Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr. Greg Perkins Director, Consumer Products

TELEPHONE NO.: 919-248-4453

Regarding ANDA 73585, Amendment of 3-13-91, the following information was requested:

1) single-dose study, p. 98. Sponsor shows 53 standard curves, reviewer found 54 curves and last page (183) is titled "run 54".

2) Analytical run #'s typed in upper left hand corner of pages do not agree with run #'s written in on the pages. which is correct?

3) What are the firm's criteria for data acceptance/rejection? What SOP applies to this study?

4) The lowest standard shows huge discrepancies in runs 39, 43, and 53. were these results used for calculation of subject samples?

5) multiple-dose study, p 165. Sponsor says 35 standard curves were used, but reviewer only found 31.

6) standard curve statistics on p. 194 (run 5), 196 (run 6), 200 (run 8) are missing.

7) standard curve statistics for runs 17 (p. 210), 19 (p. 212), and 21 (p. 216) are unreadable due to poor photocopying.

8) standard curve statistics table for run 7 (p. 199) was incomplete.

SIGNATURE: James P Henderson

DIVISION: Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND./NDA

U. S. GOVERNMENT PRINTING OFFICE: 1984-432-976: 7126

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 3-26-91

NDA NUMBER: 73-585

IND NUMBER:

TELECON/MEETING

INITIATED BY: [X] APPLICANT/SPONSOR [ ] FDA

MADE: [X] BY TELEPHONE [ ] IN PERSON

PRODUCT NAME: Pseudoephedrine HCl 12-hr caplet

FIRM NAME: Burroughs-Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr. Greg Perkins, Dr. John Findley, Jennifer Wagner et al.

TELEPHONE NO.:

Dr. Findley:

Discussion of questions from previous day: (study amendment 3-13-91)

1) there were 54 actual SC in the single-dose study.

2) the run # typed in the upper left-hand corner is correct

3) in cases where recalculations were done, recalculated data was used

4) rejection criteria

a) subject samples
measured conc. > 30 ng/ml (higher dilutions)
or < 1 ng/ml (lower dilutions)
CV of duplicates > 15 %

b) SC samples
% difference > 30 % for back-calculated standards

c) QC samples
4 spiked QC's + 3 pooled controls (1, 3, 30, 300 ng/ml) (A, B, C)
reject run if ≥ 3 of the 7 QC's differ by more than 15% from target values.

Question by Dr. Henderson: What are the target values for the pooled controls A, B, and C? Not in submission.
Answer: will fax you the info

5) 31 runs in multiple dose study

6) in runs 5, 6, and 8, no wave statistics were produced since a different control was used.

7) runs 17, 19, and 21 – values for CORSE + % diff read over phone

8) When large % differences occurred between prepared + determined SC values, the graph of the SC will indicate discontinuities where the after-run SC samples were not used.

SIGNATURE: James P Henderson

DIVISION: Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE - 1984-432-976/7126

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 3-27-91

NDA NUMBER: 73585

IND NUMBER:

TELECON/MEETING

INITIATED BY: [ ] APPLICANT/SPONSOR [X] FDA

MADE: [X] BY TELEPHONE [ ] IN PERSON

PRODUCT NAME: Pseudoephedrine 12-hr caplet

FIRM NAME: Burroughs-Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr. John Findlay

TELEPHONE NO.: 919-248-4280

Dr. Henderson's question: multiple-dose study. There are at least 15 instances of deviation >20% for the determined SC sample concentrations from their prepared values. However, the sc plots in the multiple-dose study do not show any discontinuities. Were all these SC samples used regardless of deviation?

3-28-91 Dr. Findlay's response:

in all but 5 of these instances, the problem is due to broken tubes or some other gross error. The counter is programmed to reject these samples and uses only the duplicate tube to fit the curve. Therefore, these large deviations (70-406%) were not used for final curve fitting.

However, in five cases Dr. Findlay can find no obvious explanation for the deviations ((b) (4)).

Run	Std (ng/ml)
2	0.195
14	0.390
19	1.56
24	1.56
27	6.25

SIGNATURE: James P Henderson

DIVISION: Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE: 1984-432-976/7126

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE
3-27-91

NDA NUMBER
73585

IND NUMBER

TELECON/MEETING

INITIATED BY
☒ APPLICANT/SPONSOR
☐ FDA

MADE
☒ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
Pseudoephedrine 12 hr caplet

FIRM NAME
Burroughs-Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. Greg Perkins

TELEPHONE NO.

Dr. Findberg says that the pooled controls A, B, & C do not have predetermined concentrations and, therefore, should only be used for precision and not for QC.

SIGNATURE
James P Hardeman

DIVISION
Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 3-28-91

ANDA NUMBER: 73585

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Pseudoephedrine 12-hr caplet

FIRM NAME: Burroughs-Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr Greg Perkins

TELEPHONE NO.: 919-248-4453

Expir dates for
Sudafed 12 hr capsule
batch 7V2153 : 10/89
Sudafed Liquid 7V2154: 2/89

Amendment 3-13-91

p. 230 – SD study
runs 47 → subj 17, 18, 22, 23
49 → subj: 2, 3

p 232 – MD study
runs 1 → subj none
9 → 7
21 → 22
36 → 5, 6, 7, 10, 12

SD

subj	Trt	run
17	A	47
18	D	
22	D	
23	B	
2	D	49
3	B	

MD

run	subj	trt
1	none	–
9	7	
21	22	

SIGNATURE: James P Hardeman

DIVISION: Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE
4-4-91

ANDA NUMBER
73585

IND NUMBER

TELECON/MEETING

INITIATED BY
☐ APPLICANT/SPONSOR
☒ FDA

MADE
☒ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
Pseudoephedrine HCl 12-Hour Caplet

FIRM NAME
Burroughs-Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. John Findlay

TELEPHONE NO.
919-248-4280

In the original ANDA, the sensitivity limit was set at 1 ng/ml. However, the sponsor is using standards at concentrations of 0.195, 0.390, and 0.780 ng/ml.

Dr. John Findlay had the following explanations:

1) this procedure was developed several years ago and the original limit of 1 ng/ml was probably too conservative.

2) Since the great majority of plasma levels from study subjects are well in excess of 1 ng/ml, there was no need to claim a lower limit.

3) The subject samples excluded from this study (values < 1 ng/ml) were very few in number and occurred mainly at 20 minutes post dose and so would not be expected to have any impact on the study outcome.

4) When this study was done several years ago, it was not an accepted practice that the lowest standard had to be the limit of quantitation, and this issue for ANDA is still unresolved.

The reviewer directly asked Dr. Findlay if he would affirmatively state that the LOQ for this study was 0.195 ng/ml. Dr. Findlay would not make this statement.

SIGNATURE
James P Hayslett

DIVISION
Bioequivalence

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE - 1984-432-976/7126

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date April 11, 1991

From Acting District Director, (HFR-SE150)

Subject ANDA #73-585, Pseudoephedrine Hydrochloride 12 Hour Caplets
Burroughs Wellcome Co., Greenville, NC

To Michael F. Karpers, Acting Chief
Compliance Evaluation Staff (HFD-320)

The purpose of this memorandum is to bring a situation to your attention to avoid any possible confusion or misunderstanding.

You recently faxed an inquiry to Richard Davis concerning the status of several ANDA's, including 73-585.

We covered 73-585 during an inspection of Burroughs Wellcome Company, Greenville, NC on 7/23-26/90. Inspection uncovered a difference in particle size of the active drug substance with only in vitro (and no in-vivo) dissolution data to support their contention that this change will not impact on the bio-availability of the drug. We classified this EIR "BP" and endorsed it on 9/19/90, to Jackie Queen, HFD-320 for review and evaluation of the particle size issue. I have attached a copy of that endorsement. We have received no feedback or further requests concerning this ANDA.

If the in-vitro dissolution data submitted is adequate, Atlanta District would recommend approval of this ANDA.

Roger E. Kline

Roger E. Kline

Attachment

cc: Medical Products Quality Assurance Staff (HFC-120)
Richard J. Davis, Regional Food and Drug Director
Mid-Atlantic Region (HFR-MA1)
(Chairman, Field Drug Committee)

4/12/91

Diane Walker called & stated Chemist said particle size not important due to extreme solubility of product & they were approving based on that & this memo

DATE ASSGND: 06/90 CS#: 39771 PRIORITY: DATE INSPD: 7/23-26/90
CENTRAL FILE NO.: 1018495 JD/TA: 54 CNTY: 147 PHONE: (919) 758-3436 GRP: 8/6-9,16/90
NME: BURROUGHS WELLCOME COMPANY EMPL NO: 304
CITY: GREENVILLE STATE: NC ZIP: 278351887 STREET: U S HWY 13/STATE HWY 1590 DISTRICT:

Page 1 of 2 Pages ENDORSEMENT

Inspection of this large pharmaceutical manufacturer was initiated in response to Atlanta District's scheduling of GMP coverage of profile classes ADM, CRU, MIS and POW. Additionally, Compliance Evaluation Staff, CDER, HFD-320, requested an inspection in conjunction with the review of ANDA #73-585, which provides for the firm to manufacture, perform analytical testing and package Pseudoephedrine Hydrochloride 12-Hour Caplets. Profile coverage for (b) (4) was requested while the inspection was in progress in conjunction with a pending government contract.

The current inspection has documented deficiencies in significant areas of control to include: (b) (4)

Additionally, written investigation reports were lacking for several other product failures identified during this inspection, indicating a significant lack of control, since the firm has no assurance that processes are still validated when the causative factor(s) are not identified.

Annual Review reports were not completed for 1989 and the reports for 1988 failed to adequately identify and address repeat failures for (b) (4) batches during that year.

Several times during the inspection, managers responsible for internal auditing admitted that they had previously identified several of the same problem areas as this FDA inspection. The firm had already planned some corrective actions prior to the inspection including: the hire of an employee to coordinate product failure investigations;

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST.COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE David J Sutter DATE: 9/19/90

DISTRIBUTION: O: Atl Compliance, w/encl; cc: Pitt Co RP, w/encl; cc: Ral; cc: DJS; cc: DPU
cc: HFV-142/Mary Ledbetter, w/483; cc: C. Mullikin (+profile);
cc: HFD-336, W/Exhib 40-48+483; cc: HFD-320/J. Queen, w/Exhib 39-39+483

FDA 461(2)-CE (09/83)

procedural changes for conducting annual reviews, and the preparation of protocols for cleaning validation in the Chemical Manufacturing Division.

The written response to the FDA-483, dated 8/28/90, which was received after the completion of this report, promised extensive changes to validation and process change control programs. They promised adequate corrections to the other observations with the primary exception of observation #7 dealing with release of new product prior to completion of 3 consecutive validation batches.

The review of ANDA #73-585 identified differences between the clinical and planned production batches, with the most significant change being a difference in particle size of the active drug substance. The firm provided in vitro dissolution data to support their contention that this change will not impact on the bioavailability of the drug.

F/U: The original EIR is being sent to Atlanta Compliance Branch for their response to Burrough's Wellcome 8/28/90 reply-to-the-483 letter, primarily with respect to the firm's variance from conducting 3 batch validation work prior to release of new product. As currently written we were able to demonstrate that the firm's exception to 3 batch validation procedures have been employed in situations where sufficient material had been available for 3 batch validation. Our response should be coordinated with CDER to reflect current FDA policy for limited situations such as the production of orphan drugs where infrequent manufacturing becomes a factor.

With respect to our coverage of GMP's for timed release pseudoephedrine hydrochloride caplets filed under ANDA 73-585 we are forwarding a copy of this report to HFD-320, ATTN: Jackie Queen for evaluation, final classification (temporarily classified B, P), and determination of the approvability of the application. As outlined in our report we are particularly concerned about the change in particle size of the active drug substance for which the firm has no in-vivo data available. They have provided a report at our request, which details in-vitro dissolution data. They contend that the data supports equivalency of two products containing (b) (4) or (b) (4) drug substance.

Daniel J. Sitko
Supervisory Investigator,
Raleigh-RP/Atlanta DO

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service — 740

Shirley Brown,

Memorandum

~~6-7-90~~ 4-4-91 Pre Approval Update

Division of Generic Drugs — HFD- 632

Requestor's Name Valerie Vaskio — Phone 4430193

Subject: ESTABLISHMENT EVALUATION REQUEST

To: Division of Manufacturing & Product Quality (HFD-320)

Sterile Product ______ Non Sterile Product ✓

Application and Supplement No. 73-585

Brand Name (if any) *

Establishment Name, Dosage Form and Strength Pseudoephedrine Hydrochloride 12 Hour (Caplet)

Profile Class Code: TTR

Priority Classification: ______ (See SMG BD-4820.3)

Applicant's Name: ~~Burroughs Wellcome~~ Co

Address: 3030 Cornwallis Road Research Triangle Park, NC 27709

Facilities to be Evaluated: (Name, full Address, DMF No., and responsibility) — **For HFD 320 Use** Status & Date of Inspection:

(b) (4)

WC mnfctr of finished product, analytical testing and packaging — AC-OK per ATL-DO memo of 4/11/91 - Dev - 4/12/91

1. Applicant, P.O. Box 1887, Greenville NC 27834 — OK 7/23/90

(b) (4)

[redacted]

2. [redacted]

3. [redacted]

4. ______

5. ______

Other Information or Special Requests: ______

****

APR 4 19

For HFD-320 Use Only: Date Received: 6-18-90

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: Carl Broadway — Date Completed: 1/9/91

Acceptable
M Harper 4/12/91

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

~~EIRTS~~ 70UT.

N+320
BN

FORM FDA 3274 (3/90)

APR 18 1991

ANDA 73-585

Burroughs Wellcome Co.
Attention: Mr. Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Sir:

Reference is made to your abbreviated new drug application dated June 12, 1990, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for SUDAFED (Pseudoephedrine Hydrochloride Extended-release Tablet), 120 mg (Caplet).

In order for our laboratory to validate your submitted methods please retain the following materials for collection by a field investigator who will be instructed to procure samples of the bioequivalence batch and a copy of your methods validation package, in the near future.

Please include:

1. At least 100 caplets of SUDAFED (Pseudoephedrine Hydrochloride 12-Hour Extended-release tablets), 120 mg (preferably 10 packages of the proposed size for marketing) of batch # 9S6005 and 7U2752.
2. Internal and reference standards.
3. Impurity standard.
4. At least 500 mg of drug substance from every supplier you intend to use for the manufacture of the drug product.
5. A copy of the methods validation package, filed in your application.
6. A copy of the batch formula and record used to make the bioequivalence batch # 9S6005 and 7U2752.
7. A copy of your report of analysis of the bioequivalence batch and include all chromatograms and spectra if available.
8. A Material Safety Data Sheet (OSHA form 174) or equivalent information.

Within five days of receipt of this letter please inform the home district office that you will be able to comply fully with the above instructions. If you cannot, then please inform them of this fact so that they may schedule the assignment at the proper time.

Under no circumstances are you to send samples to a district laboratory for analysis, unless instructed otherwise by the home district.

Sincerely yours,

4/18/91

Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-585
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File
~~HFD-638/labeling reviewer~~
HFD-634/RPatel/MShaikh/04/16/91 Mujahid Shaikh 4-17-91
HFD-634/VVashio/04/17/91 Washio 4/17/91
R/D initialed by RPatel
cls/04/16/91/b:73-585.LTR
F/T by cls/04/17/91
Information Request
RPatel 4/17/91

ANDA 73-585

APR 18 1991

Burroughs Wellcome Co.
Attention: Mr. Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Sir:

Please refer to your abbreviated new drug application dated June 12, 1990, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for SUDAFED (Pseudoephedrine Hydrochloride Extended-release Tablet), 120 mg (Caplet).

Reference is also made to your communications dated August 7, 1990, March 13, 1991 and March 14, 1991, amending this application.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. (b) (4)

2.

3.

4.

5. [redacted] (b) (4)

6.

7.

8.

9.

10.

11.

4/18/91

12. Label and labeling are the subject of the following comments:

Carton: Not Satisfactory

FRONT:

A. We would recommend that the phrase "[redacted] (b) (4)" be replaced with "Extended-release". This term is currently used in the USP.

B. Define "Caplets" (capsule-shaped tablet).

C. Separate the statement of identity (Nasal Decongestant) from the established name. In addition, revise the established name and strength to read:

Pseudoephedrine Hydrochloride Extended-release Caplets, 120 mg.

BACK:

A. Revise to read:

Each coated Extended-release caplet...

B. The labeling for this product should be updated to follow the tentative final monograph for OTC nasal decongestant drug products (January 15, 1985; 50 FR 2220). However, if you elect to retain your current labeling you will be expected to conform to the "final monograph", when issued.

In any case, the Drug-Interaction Precaution must be updated to read:

> Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your physician.

Please revise your carton labeling, then prepare and submit a draft copy of the revised carton labeling.

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. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be ~~considered a minor amendment~~ and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

for expedited review Rent 4/18/91

Sincerely yours,

4/18/91

Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-585
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File
HFD-638/JPhillips
HFD-634/RPatel/MShaikh/04/16/91
HFD-634/VVashio/04/07/91
R/D initialed by RPatel
cls/04/17/91/b:73-585.LTR
F/T by cls/04/17/91
Not Approvable

APR 18 1991

ANDA 73-585

FDA
Attention: Mr. M. Lawrence
60 Eighth Street, N.E
Atlanta, GA 30309

Dear Mr. Lawrence:

The in vivo bioequivalence study requirements have been met for the subject ANDA. We must request the analytical methods be validated based on the two batches: 9S6005 and 7U2752.

As instructed under the new PRE-APPROVAL INSPECTION/INVESTIGATIONS program (7346.832) you are requested to collect samples from the applicant's laboratory at the address given below:

Burroughs Wellcome Co.
Attention: Mr. Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, NC 27709

Phone: (919) 248-3000

In addition, included is a copy of the methods validation package for this drug product as instructed in Part IV of the compliance program.

Upon completion of the district's portion of the methods validation, please send worksheets, all attachments, conclusions, and recommendations directly to the review chemist Mr. Mujahid L. Shaikh (MPN II/OGD, HFD-634, Room 222) within five days of completion.

Sincerely yours,

4/18/91

Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures

cc: ANDA #73-034
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File
HFD-634/RPatel/MShaikh/04/16/91 Mujahid Shaikh 4-17-91
HFD-634/VVashio/04/17/91 Vashio 4/17/91
R/D initialed by RPermisohn
cls/04/17/91/b:73-585
F/T by cls/04/14/91
Expedite

Patel 4/17/91

Wrdwd 5/13/91

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Wellcome

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

April 24, 1991

Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
MPN II, HFD-600
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

ORIG NEW CORRES

Re: ANDA 73-585
SUDAFED® (pseudoephedrine hydrochloride) 120 mg Extended Release Caplets

Dear Dr. Williams:

Reference is made to a letter received from FDA dated April 18, 1991, concerning our Abbreviated New Drug Application filed on June 12, 1990, for SUDAFED Extended Release Caplets.

Please be advised that we will be amending the application in the near future to respond to the chemistry and labeling comments contained in your letter of April 18, 1991.

Sincerely,

J. Greg Perkins, Ph.D.
Head, Department of Consumer Products
Drug Regulatory Affairs

TRZO/91/0357/4-23-91/*tg
GP/SUDAFED Caplets

RECEIVED
APR 30 1991
GENERIC DRUGS

ORIG

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

Dup to Bio

Draft labeling is satisfactory & I have requested FPL per telephone.
6-10-91
Tom Parker

May 3, 1991

Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
MPN II, HFD-600
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT
A/C

BIOAVAILABILITY MATERIAL
J/S

Re: ANDA 73-585
SUDAFED® (pseudoephedrine hydrochloride, 120 mg) 12 Hour Caplets

Dear Dr. Williams:

Reference is made to a letter received from your division, dated April 18, 1991, concerning our Abbreviated New Drug Application for SUDAFED 12 Hour Caplets submitted on May 30, 1990.

The enclosed data are in response to questions outlined in the April 18, 1991 letter.

If there are any additional comments concerning this submission, please do not hesitate to contact Mr. Richard Kiernan at (919) 248-3193, or Dr. Greg Perkins, at (919) 248-4453.

Sincerely,

Anne McKay

Anne F. McKay
Head, Department of
Compliance & Registration
Drug Regulatory Affairs

Desk Copy: Dr. R. Williams

RECEIVED
MAY 3 1991
GENERIC DRUGS

GRZO/91/0018

10 MAY 91
0 M.

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 6-10-91

NDA NUMBER: 93-585

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: SUDAFED - 12 hr CAPLET

FIRM NAME: BURROUGHS WELLCOME

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

GREG PERKINS
DIANE BURNE
JENIFER WAGNER

10AM

TELEPHONE NO.

919-248-3634

I EXPRESSED CONCERNS THAT THE FIRM WAS ELIMINATED THE (b) (4) THAT USED TO BE ON THE CAPSULE CARTON. BY REGULATION, A TABLET DOSAGE FORM NEEDS ONLY ONE TAMPER RESISTANT DEVICE WHICH IN THIS CASE IS THE IMPRINTED FOIL BACKING OF THE BLISTER UNIT. THE FIRM DOES NOT WANT TO INCLUDE THE (b) (4) (b) (4).

- FAX REQUESTED & RECEIVED OF THE BACKING. THIS IS ACCEPTABLE (WILL SAY CAPLET INSTEAD OF CAPSULE).

- ~~WILL~~ REQUESTED FPL FOR ALL LABELS/LABELING & TO BE NOTIFIED WHEN IT COMES INTO THE BUILDING.

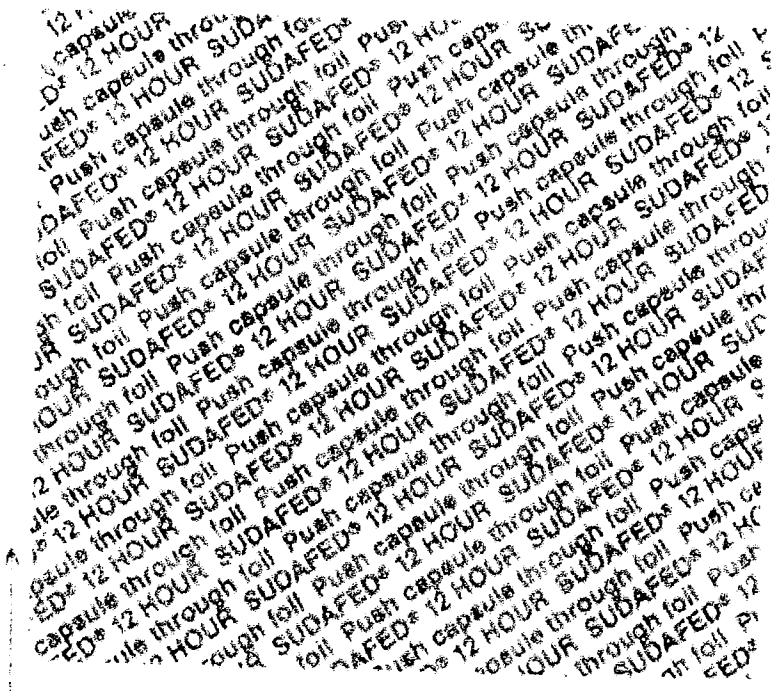
SIGNATURE: Jerry Phillips 6/10/91

DIVISION: OGD

ORIGINATOR

FORM FD 2587 (11/77)

Example of type of printing that will be used for foil backing of Sudafed 12 Hour Caplets



(No printing in these areas)

ORIG
3.1

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

Roger Williams, M.D., Director
Office of Generic Drugs, MPN II, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 14, 1991

ORIG NEW CORRES

Re: ANDA 73-585
SUDAFED® 12 Hour Caplets
(pseudoephedrine hydrochloride
120 mg)

Dear Dr. Williams:

Reference is made to a visit from Ms. Amy Hobgood of the Atlanta District of FDA Compliance, and Mr. George Sazba, of the Atlanta Regional Laboratory, to our plant on June 5, 1991.

As requested during this inspection, samples of pseudoephedrine hydrochloride, SUDAFED 12-Hour Caplets and reference materials were provided for methods validation purposes. Samples of these materials were originally provided to Ms. Hobgood during a visit to our plant on April 30, 1991. However, due to a change in FDA sampling procedures for methods validation samples, it was necessary to resample the materials and have the sampling witnessed by Ms. Hobgood and Mr. Sazba.

If there are any questions concerning this submission, please do not hesitate to contact Mr. Richard Kiernan at (919) 248-3193.

Sincerely,

Anne F. McKay
Head, Department of
Compliance & Registration
Drug Regulatory Affairs

RECEIVED
JUN 18 1991
GENERIC DRUGS

GRZO/91/0023

ORIGINAL

ARCHIVAL COPY

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

FPL for labeling
carton is Satisfactory
7-8-91
Jerry Phillips

FINAL PRINTED LABELING

FPL

June 25, 1991

RECEIVED
JUN 25 1991
GENERIC DRUGS

NDA ORIG AMENDMENT
O/A-MA

Roger Williams, M.D., Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
MPN II, HFD-600
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 73-585
SUDAFED® 12 Hour Caplets
(pseudoephedrine hydrochloride 120 mg)

Dear Dr. Williams:

We are submitting herewith 12 copies of final printed labeling in anticipation of approval of our Abbreviated New Drug Application for SUDAFED 12 Hour Caplets submitted on May 30, 1990.

The labeling has been revised in accordance with your letter of April 18, 1991. Please also refer to conversations of June 6 and 12, 1991 between Jerry Phillips of your staff and Richard Kiernan, Diana Byrne, Jennifer Wegener and myself of Burroughs Wellcome Co. regarding tamper-resistant features of the package, and final printed labeling.

If you have any questions regarding the enclosed labeling, please contact Jennifer Wegener, Pharm.D. at (919) 248-8499.

Sincerely,

J. Greg Perkins, Ph.D.
Head, Department of Consumer Products
Drug Regulatory Affairs

JGP/mg*
TRZO/91/0634
Enclosure

DEADLINE
DUE 7/25 - REK

JUL 16 1991

TO: Director, Atlanta District Office (HFR-SE100)

FROM: Acting Chief, Compliance Evaluation Staff, HFD-320

SUBJ: NDA/ANDA Notification
ANDA 73-585
Pseudoephedrine
Hydrochloride 12 Hrs.
Ext. Release Caplet

Applicant:
Burroughs Wellcome Company
3030 Cornwallis Road
Research Triangle Park,
North Carolina 27709

PROFILE: TTR

Establishment:
Burroughs Wellcome Company
P.O. Box 1887
Greenville, NC 27834

CFN#: 11018495

The subject application, involving activities at the establishment(s) in your District as specified above, is nearing the approval stage in the Center for Drug Evaluation and Research. Based upon the current Quality Assurance Profile, CDER does not intend to assign a pre-approval inspection, and knows of no reason why approval of the application should be withheld.

However, we will delay or withhold approval if warranted by ongoing inspection activities as provided in the memo of February 14, 1990 from the Director, Office of Compliance, CDER to all Districts, subject to "Procedure to request evaluations from Districts for all NDA/ANDAs".

Within 10 days, please advise the undersigned by fax (8/295-8202) or EMS whether or not approval should be withheld or delayed. Your reply should be in the format prescribed in the memo referenced above.

Thank you for your attention.

Michael F. Karpers

Priority: ANDA Pending
Target Completion: JUL 26 1991

cc:
HFD-320 CES R/F
HFD-320
HFD-632 Shaikh/Doleski
7/16/91:sdf
SHIRNETTE'S DISK
4005.10d:July 16, 1991

RECEIVED
JUL 16 1991
ATLANTA DD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date July 24, 1991

From Acting Director of Chemistry, Southeast Regional Laboratory
(HFR-SE660)

Subject ANDA 73-585, Sudafed 12 Hour Caplets

To Mujahid Shaikh, Review Chemist
Office of Generic Drugs (HFD-600)

As instructed by Atlanta District I am forwarding the validation study for your review.

Perry S. Wilkes

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 7-24-9

NDA NUMBER: ANDA 73-585

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☐ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Sudafed 12 Hr. Ext. Release caplet

FIRM NAME:

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Kermit Floyd (Contact Person for Atlanta District)

TELEPHONE NO.: 8-257-4003

15 Am.

I Called Kermit to find out the Status of MR Package and when he or District ~~District~~ Director is going to send me. He asked me to Call John Turner 8-257-4344. Then I called John Turner to find out the Status. I told me that he will get back to me in a short while. Then instead of John, Mr. Perry called me and find out the Zip address of ~~[illegible]~~ so that he can send me and requested him to send me by Federal Express. He agreed to that: and That was the end of talk

SIGNATURE: Snaikh

DIVISION: Chemistry IV

587 (11/77)

DIVISION FILE

U. S. GOVERNMENT PRINTING OFFICE: 1981—361-976/7726

DEPARTMENT OF HEALTH & HUMAN SERVICES 1673 Public Health Service

Memorandum

Pre-Approval EER

7-10-91

From Division of Generic Drugs. HFD- 632

Requestor's Name M.SHAIKH / D. Doleski Phone 295-8365

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product ✓

Application and Supplement No. 73-685

Brand Name *(if any)* SUDAFED

Establishment Name, Dosage Form and Strength Pseudoephedrine Hydrochloride 12 Hrs. Ext. release Caplet Profile Class Code: TTR

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: Burroughs Wellcome Co

Address: 3030 Cornwallis Road, Research Triangle Park NC 27709

Facilities to be Evaluated: *(Name, full Address, DMF No., and responsibility)* For HFD 320 Use Status & Date of Inspection:

(4005)

1. The Applicant, P.O. Box 1887, Greenville NC 27834 AC 7/23/90

2. [Manufacturing Site for finished Product + testing]

3. (b) (4)

Other Information or Special Requests: _____

********Product specific inspection already completed ms 7/16/91

JUL 11 1991

For HFD-320 Use Only: Date Received: _____

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: _____ Date Completed: 7/25/91

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90)

ANDA 73-585

Burroughs Wellcome Co.
Attention: Mr. Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, NC 27709

JUL 31 1991

Dear Sir:

Please refer to your abbreviated new drug application dated June 12, 1990, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for SUDAFED (Pseudoephedrine Hydrochloride Extended-release Tablet), 120 mg (Caplet).

Reference is also made to your communications dated May 3, June 14, and June 25, 1991, amending this application.

Please be advised that our analysts have completed validation of the method submitted in this ANDA and have following comments:

I. Analyst's comments regarding method validation:

(b) (4)

[redacted]

Following this page, 2 pages withheld in full (b)(4)-CCI/TS

III. Our Regional Director's comments regarding method validation are as follows:

"A. Dissolution testing

1. [redacted] (b) (4)

2.

3.

4.

B. Assay/Content Uniformity

1. [redacted] (b) (4)

2.

3.

You are required to take an action by submitting all the information considering all the problems pointed out by our analysts and Regional Laboratory Director so that we can forward your response in this matter for their comments.

Sincerely yours,

Robert A. Jewson 7/30/91

Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-585
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File
HFD-638/
HFD-634/RPatel/MShaikh/07/26/91 Mujahid Shaikh 7-29-91
HFD-634/VVashio/ Vashio 7/29/91
HFR-SE 600/KFloyd/SWBellman
HFR-SE 100/JHTurner
HFR-MA 460/PLGable
R/D initialed by RPatel RP 1rd 7/31/91
cls/07/26/91/d:73-585.LTR
F/T by cls/date
Information Request

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 31 July 91

NDA NUMBER: 73-585

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☒ APPLICANT/SPONSOR ☐ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Sudafed Caplet

FIRM NAME: BW

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr. Greg Perkins

TELEPHONE NO.: 919-248-4453

NA letter issued 7-31-91 was faxed to Dr. Greg Perkins 7/30/91 (with signature). The contents of the letter were based on the Atlanta District Lab NV analysis.

Dr Patel suggested that the firm contact the lab directly to resolve these outstanding issues.

Dr Perkins' staff is working promptly on the response

Paul Gable CIN-DO
Kermit Floyd ATL REG OFF
points of contact, as agreed to by field.
copy of letter was faxed to the above field offices

SIGNATURE: Washco C&S

DIVISION: Generic Drugs

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 11 Aug 91

NDA NUMBER: 73-585

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☑ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Sudafed Caplets

FIRM NAME: Burroughs Wellcome

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr Greg Perkins

TELEPHONE NO.: 919 248-4453

(Paul Gable CIN-DO 8-684-3501)

Follow up call to Dr. Greg Perkins BW on the progress of their response with the lab, to letter dated 7-31-91.

The persons at BW are working on the response and will contact FDA labs for additional inquiries.

26 Aug 91 -
Follow up:
Dr. Perkins is no longer with BW Jennifer Wagner is new point of contact.
BW intends to submit a response at the end of Sept 91. A fax copy will be sent when they submit their document.

Washco C&O

SIGNATURE: Washco C&O

DIVISION: Generics

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

FOR THE RECORD
ANDA 73-585

Reference is made to our Not-approvable letter dated July 31, 1991 that included comments from the Atlanta and Cincinnati District Offices.

Follow-up calls were made to Burroughs Wellcome Co. (BW) 919 248-4453 and to the Atlanta and Cincinnati FDA laboratories to monitor the progress of this ANDA. Conversation with Ms. Jennifer Wegener, BW, on September 19, 1991 indicated that the firm would be submitting a response to our NA letter dated July 31, 1991 and would send copies to the field offices if needed. The progress was discussed with Gordon Johnston, Review Support Staff, and it was concluded that the most efficient manner in which to resolve the outstanding issues was to collectively involve FDA field offices, OGD and BW.

Phone calls were made to Mr. Kermit Floyd, ATL-DO, FTS 257-4003 and Mr. Ken Scholz and Ms. Womack, CIN-DO, FTS 684-3501 for briefing on the progress with this ANDA and that copies of the amendment would be sent to the field offices for their review.

Conversation with Ms. Wegener, September 23, 1991, clarified the amendment would be submitted within a few days, and copies would be sent to the Atlanta and Cincinnati FDA offices. After receiving the amendment we will contact her if additional information is required, or if OGD, FDA field offices and BW will need to discuss issues in a conference call.

This ANDA was authorized EXPEDITED REVIEW through Office of the Commissioner, FDA, (see Memorandum dated March 18, 1991, attached) in response to the abrupt withdrawal of Sudafed capsules, initiated by the tampering of Sudafed capsules in Washington state.

V Vashio CSO
Valerie Vashio, CSO
September 23, 1991

ORIGINAL

2.1

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

September 25, 1991

NDA ORIG AMENDMENT
AC

Roger Williams, M.D., Director
Office of Generic Drugs, MPN II, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: ANDA 73-585
SUDAFED® 12 Hour (pseudoephedrine hydrochloride extended-release caplets, 120 mg)

Dear Dr. Williams:

Reference is made to the letter received from Dr. Robert Jerussi, of your division on July 30, 1991, concerning the analytical methods validation data for SUDAFED 12-Hour Caplets originally submitted in our Abbreviated New Drug Application of May 30, 1990.

Enclosed is our response to the comments contained in Dr. Jerussi's letter of July 30, 1991.

Should you require any additional information, please do not hesitate to call Mr. Richard Kiernan at (919) 248-3193.

Sincerely,

Anne F. McKay
Head, Department of
Regulatory Compliance and Registration
Drug Regulatory Affairs

Desk Copies: Mr. P. Gable
Cincinnati Regional Laboratory

Mr. K. Floyd
Southeast Regional Laboratory

GRZO/91/0035

RECEIVED
OCT 1 19
GENERIC DRUGS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date October 8, 1991

From Acting Director of Chemistry, Southeast Regional Laboratory (HFR-SE660)

Subject ANDA 73-585. Comments on Firm's Response
Firm: Burroughs Wellcome Co.
Research Triangle Park, N.C.

To Mujahid Shaikh, Review Chemist
Office of Generic Drugs/HFD 634 CDER

As requested by Valerie Vashio on 10/7/91, we have reviewed the firm's comments under their letter dated 09/25/91 (Rec'd 10/1/91) relative to the subject ANDA. Chemist George Salem has summarized our comments in the attached memo.

We are also attaching the Cincinnati Lab's comments on the automated dissolution procedure they evaluated.

We leave the final decision on the dissolution methods as well as the other comments to you, as the reviewing chemist.

Perry S. Wilkes

PSW:pas

Attachment

cc: HFR-SE600
HFR-SE660
KMF
GWS

Following this page, 3 pages withheld in full (b)(4)-CCI/TS

FOR THE RECORD
ANDA 73-585

Telephone call was made to Burroughs Wellcome Co. to Anne Mckay (919)248-4453 by me and Ms. Valerie Vashio, CSO to let her know that our chemists at Atlanta and Cincinnati FDA District Laboratories have responded to your amendment dated 9-25-91 and they raised minor issue regarding MV and dissolution studies. We requested her a commitment that you work with us expeditiously to resolve these issues before you market this subject drug product and we will process this ANDA toward approval. She asked us the nature of these minor issues and suggested us to write them a letter listing all the minor issues and then they will submit a required commitment. That was the end of conversation.

Mujahid L. Shaikh
Review Chemist, OGD
10-9-91

Mujahid Shaikh
10/9/91

ANDA 73-585

Burroughs Wellcome Co.
Attention: Ms. Anne F. McKay
3030 Cornwallis Road
Research Triangle Park, NC 27709

OCT 15 1991

Dear Madam:

Please refer to your abbreviated new drug application dated June 12, 1990, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for SUDAFED (Pseudoephedrine Hydrochloride Extended-release Tablet), 120 mg (Caplet).

Reference is also made to your amendment dated September 25, 1991, and the phone conversation between Anne McKay of the firm and Valerie Vashio and Mujahid Shaikh of the Agency on October 9, 1991.

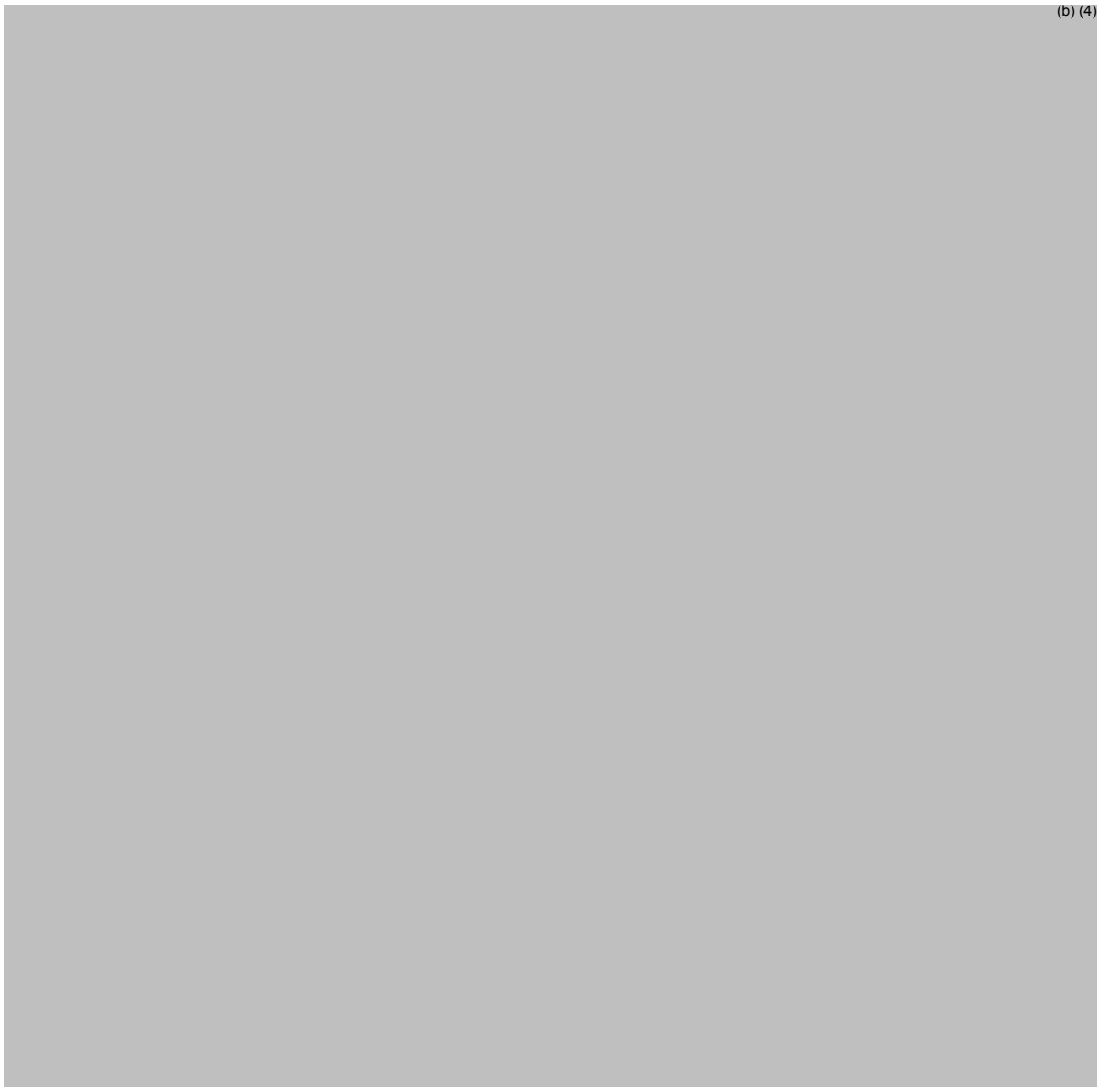
Please be advised that our chemists at Southeast Regional Laboratory and Cincinnati District Laboratory have forwarded the following responses to your amendment dated September 25, 1991:

I. Chemist, Southeast Regional Laboratory's comment regarding method validation:

(b) (4)

Following this page, 1 page withheld in full (b)(4)-CCI/TS

(b) (4)



You are requested to take an action by submitting a commitment that you will work with us expeditiously to resolve above mentioned minor issues, which will enable us to continue processing this application toward approval. Please reply to this letter within ten days.

Sincerely yours,

RKPatel 10/15/91

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

cc: ANDA #73-585
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File
HFD-634/MSmela/MShaikh/10/10/91 Mujahid Shaikh 10/14/91
HFD-634/VVashio/10/11/91 Washio 10/13/91
R/D initialed by MSmela M. Smela 10/15/91
cls/10/11/91/d:73-585.LTR
F/T by cls/10/11/91
Information Request

FOR THE RECORD
ANDA 73-585

Telephone call was made by Burroughs Wellcome as scheduled during conversation held on 10-16-91 to clarify some of the issues listed in our correspondence dated 10-15-91 so that they prepare response more precisely or if they decide to submit commitment, they would be sure what they are committing for. The peoples joined in this telecon includes myself, Valerie Vashio from OGD, and (b) (6) (b) (6), Mr. Johnson and Ms. Skinner from BW. (b) (6) showed concern regarding comments listed by Chemist, FDA SE Regional Labs. in our letter section I but he agreed, with some reservation, to submit some validation data to show (b) (4) (b) (4). Secondly (b) (6) showed some concern to accommodate (b) (4) (b) (4) but he agreed to do so. Mr. (b) (6) showed a lot of concern regarding comments of Chemist from, Cincinnati District Labs., His concern includes (b) (4) . I mentioned to him if he has a concern regarding the (b) (4) and if he has other ideas to accommodate Chemist's comments. He mentioned they might make some kind of modification in their method to accommodate Chemist's request. I told him that he is most welcomed to do so. Ms. Skinner told me and Ms. Valerie Vashio that they will prepare a response to this and will fax to us within two days for our review. That was the end of our conversation.

Mujahid Shaikh 10/17/91

Mujahid L. Shaikh
Review Chemist
OGD/CDER
10-17-91

[redacted] 9/19/91 Memorandum

Division of Generic Drugs HFD- 632

Requestor's Name M. SHAIKH / D. Doleski Phone 295-8365

Subject ESTABLISHMENT EVALUATION REQUEST 10/11/91 updat

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product ✓

Application and Supplement No. [redacted] 73-585

Brand Name *(if any)* SUDAFED

Establishment Name, Dosage Form and Strength Pseudoephedrine Hydrochloride 12 Hrs. Ext. release Caplet Profile Class Code: TTR

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: Burroughs Wellcome Co

Address: 3030 Cornwallis Road, Research Triangle Park NC 27709

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*) For HFD 320 Use Status & Date of Inspection:

1. The Applicant, P.O. Box 1887, Greenville NC 27834 AC 7/23/91

X [Manufacturing Site for finished Product + testing]

2. [redacted] (b) (4)

3.

Other [illegible] Special Requests: _____

*******Product specific inspection already conducted 7/16/91

For HFD-320 Use Only: Date Received: 9/25/91

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: Melissa Cruz Date Completed: 10/21/91

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90)

FOR THE RECORD
ANDA 73-585

Telephone call was made to Mr. George Salem, Chemist of Southeast Regional Labs. Atlanta to discuss the Burroughs Wellcome's response dated 10-22-91 which was submitted to reply his comments included in his letter dated 10-8-91. First two comments of his letter, which were of major concern, were discussed and I read the BW's response to him and he concured with me. Then I also brought other three comments of his letter to his attention and he was not very concerned about them. That was the end of the conversation.

Mujahid Shaikh 10/23/91
Mujahid L. shaikh
Review Chemist, OGD
10-23-91.

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX 5109270915
tel. 919 248-3000

October 23, 1991 SUPPL NEW CORRES

Rashmikant M. Patel, Ph.D., Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: ANDA 73-585
SUDAFED® 12 Hour (pseudoephedrine hydrochloride extended-release caplets, 120 mg)

Dear Dr. Patel:

Reference is made to your letter dated October 15, 1991, concerning our Abbreviated New Drug Application for SUDAFED 12 Hour Caplets.

As requested in your letter, we commit to working expeditiously with you on resolving the minor issues relating to the methods validation for SUDAFED 12 Hour Caplets.

As discussed in a telephone conversation on October 17, 1991 between Ms. Valerie Vashio and Dr. Mujahid Shaikh, of FDA, and Mr. [redacted] (b) (6) and Ms. Susan Skinner, of Burroughs Wellcome Co., the attached information are provided to respond to the letter of October 15, 1991.

We look forward to resolving all outstanding issues to continue towards approval of this application. Should you require any additional information, please do not hesitate to call me at (919) 248-4950.

Sincerely,

Anne F. McKay
Head, Department of
Compliance & Registration
Drug Regulatory Affairs

Enclosure

RECEIVED
OCT 24 1991
GENERIC DRUGS

GRZO/91/0055

FOR THE RECORD
ANDA 73-585

Telephone call was made to Mr. Kenneth L. Scholz, Chemist from Cincinnati District to discuss the Burroughs Wellcome's response dated 10-22-91 which was submitted to reply his comments included in his letter dated 10-7-91. I discussed each and every issue listed his letter. He concurred with me except one major issue which is the validation data for revised method (AutoAnalyzer) should be provided with complete carryover studies and method should be able to do quantitate (b)(4) of the listed strength as he mentioned in his comment regarding this issue.

Telephone call was made to Burroughs Wellcome (Ann Mckay) by Ms. Valerie Vashio and me to rely this message and ask them to provide this data to us. That was the end of the conversation.

Ann Mckay from Burroughs Wellcome call, ed back to Valerie Vashio and me to let us know their response. He mentioned that they do not have validation data which we requested and it will take them two weeks to generate it and if they give us commitment to provide us the validation data and we give them an approval of this ANDA. I told her that I cannot make decision myself and I have to consult our Division Director and I will let her know as soon as I have the answer in this regard.

Dr. R. Patel was consulted in this matter and he suggested that I should call Kenneth Scholz and get his opinion and if he concurs with me that a commitment from BW should be enough for the approval. I called Ken Scholz to discuss the whole situation. He concurred with me if BW's gives us the comittment containing validation data including carryover studies and the method should be able to quantitate (b)(4) of the listed strength.

Telephone call was made again to Ann McKay of Burroughs Wellcome by Valerie Vashio and me to request her to submit us the commitment for the validation data including carryover studies and show us the method should be able to quantitate (b)(4) of the listed strength. The validation data should be supported by laboratory results. She concurred with us and she is going to sent us today. That was the end of conservation.

Mujahid Shaikh 10-24-91

Mujahid L. Shaikh
Review Chemist
Division of Chemistry I
OGD/CDER
10-24-91

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

October 24, 1991

Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
MPN II, HFD-600
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NEW CORRESP

Re: ANDA 73-585
SUDAFED® 12 Hour (pseudoephedrine hydrochloride extended-release caplets, 120 mg)

Dear Dr. Williams:

Reference is made to several telephone conversations held between Mr. Valerie Vashio, and Mr. Mujahid Shaikh, of FDA, and Burroughs Wellcome Co. personnel concerning the methods validation of SUDAFED 12 Hour Caplets.

As discussed in our phone conversation of October 18, 1991, we have adopted the Chemist's original recommendation (page 4, of the letter dated July 30, 1991) of using standards prepared at concentrations near the midpoint of the expected sample concentrations. Additional standard preparations at 35% and 70% of the labeled strength have been included and samples are quantitated using standards near the expected labeled strength dissolved for that hourly interval.

These changes are expected to have no impact on the method linearity or carryover previously demonstrated. However, we will provide additional validation data for the AutoAnalyzer determination for drug release using multiple standard concentrations within ten working days. The data will include linearity, carryover, and demonstrate accuracy within (b) (4) of actual label strength over the specified range.

Should you require any additional information, please do not hesitate to me at (919) 248-4950.

Sincerely,

Anne McKay

Anne F. McKay
Head, Department of
Compliance and Registration
Drug Regulatory Affairs

ORIGINAL

RECEIVED

OCT 25 19

GENERIC DRUGS

ANDA Approval Summary

7 85 — NDA number
Burroughs Wellcome Co — Applicant Name

Sustained Extended-release Tablets — Established Name of Drug
Tablet (Caplet) — Dosage Form
120mg — Strength
Blisterpack of 10 Coated Caplets — Container size(s)

	Date Found Satisfactory	Comment
Labeling	7-9-91	OK Jean Phillips
Chemistry, Manufacturing, and Controls	10-23-91	Mujahid Siddiqi
CMC's updated submitted 10-17-91		
Manufacturer - Finished Dosage Form		OK 10/21/91
Outside Facilities		
Manufacturer(s) - Active Ingredient(s)		

Mujahid Siddiqi — Chemist Reviewer — 10-23-91 — Date
Michael Smeltz Jr. — Branch Chief — 10/28/91 — Date

Petition Required (No / ✓ Yes)	11/3/87 petition	87P-0297/CP petition Approval
Listed Drug Information 505(j)(2)(A)	6/13/90	sec fmis 5/30/90 submission
Patent Certification 505(j)(2)(B)	6/13/90	PI
Date Patent/Exclusivity Expires (if applicable)	N/A	
Bioequivalence Section		
Dissolution Required? (No / ✓ Yes : ✓ DB / DGD)		see 4/9/91 - Bio review
In vivo study(s) required? (No / ✓ Yes)		
Study(s) Found Acceptable	see 4/9/91	Bio review
Waiver Request Granted		
Total Bioequivalence Requirement Met	4/9/91	

Robert Pollock — Administrative Reviewer — 10/28/91 — Date

Approved _____
Disapproved _____
Director, Division of Generic Drugs — Date

Comments:

OHPA

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: ANDA 73-585

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM: [X] Bureau of Drugs [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [ ] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [X] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY: [X] HUMAN [ ] VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG:
SUDAFED Extended-release Tablet

DOSAGE FORM: Caplet

HOW DISPENSED: [ ] Rx [X] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s). If amount is declared on label.)

Pseudoephedrine Hydrochloride ~~120~~ 120 mg

NAME OF APPLICANT (Include City and State)

Burrough Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Nasal Decongestant

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: MUJAHID L. SHAIKH (HFD-634) DATE: 10-23-91

FORM APPROVED BY

Michael Smela Jr. DATE: 10/28/91

FD 1442 (1/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

ANDA ACTION LETTER ROUTING RECORD

ANDA # 73-585
AADA #
Drug Pseudoephedrine HCL ~~ER~~
Dosage Form Ext. Rel TAB
Strength 120mg
Applicant Burroughs Wellcome
Manufacturing Site(s) Applicant at Greenville N.C.
Proposed Action (AP) AE

Original Rec'd Date 7/9/90
Amendment Date(s) ~~7/9/90~~ 3/13/91, 3/14/91, 6/14/
Chemistry Reviewer M. Saaith 6/25/
Supervisor M. Smela 9/25/
Bio Reviewer J. Henderson
Supervisor R. Putnam 10/24
Patent Certification IP I

REVIEWER:	RECEIPT	ACTION
1. R. Pollock, M.S Chief, Program Support Staff Comments:	Date 10/28/91 Initials RP	Date 10/28/91 Initials
2. S. Dighe, Ph.D. Director, Bioequivalence Comments: The firm has conducted crossover studies comparing the test- caplet formulation with the approved, marketed capsule formulat. The single dose studies under fasting and fed conditions demonstrated bioequivalence of the two products. The multiple dose study also demonstrates the bioequivalence of the two products. From the bioequivalence point of view the applicant is approvable.	Date 10/28/91 Initials SD	Date 10/29/91 Initials SD
3. K. Johnson, M.S. Associate Director Office of Generic Drugs Comments: Labeling is satisfactory.	Date 10-29-91 Initials RJ	Date 10-29-91 Initials RJ
4. Director of Chem. I ~~or II~~ Office of Generic Drugs Comments: With the commitment provided by B-W as concurred by our lab staff and the review chemist, the CMC portions of this ANDA is considered satisfactory. Recommended approval of the caplet dosage form	Date 10/30/91 Initials DRC	Date 10/30/91 Initials DRC
5. R. Jerussi, Ph.D. Office Level OGD Review (if necessary) Comments:	Date Initials	Date Initials
6. D. Hare Office of Generic Drugs Comments: Patent and exclusivity provisions are OK	Date Initials	Date 10/30/91 Initials DRH
7. Office Level Bio Review Comments:	Date Initials	Date 10/31 Initials
8. R. Williams, M.D. Director Office of Generic Drugs Comments:	Date Initials	Date 10/31/91 Initials

LETTER SIGNED: (Date)

(revision date 9-23-91)
(C:Forms)