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APPLICATION NUMBER

NDA 21-704

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDAs: 21-704 **Date of Submission:** December 19, 2003
July 19, 2004

Generic Name	Fexofenadine HCl (180 mg) and Pesudoephedrine HCl 240
Brand Name:	**Allegra-D 24®**
Formulations:	Extended-Release Tablets
Route of Administration:	Oral
Indication:	Seasonal Allergic Rhinitis and Nasal Congestion
Type of Submission:	NDA
Sponsor:	Aventis Pharmaceuticals
Type of Submission:	New Formulation
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.
Date of Submission:	December 19, 2003
Date Received:	January 12, 2004
Review Date:	August 25, 2004
First Draft	September 6, 2004
Second Draft	September 9, 2004
Briefing Draft	September 9, 2004
DFS Version:	September 24, 2004

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1. Executive Summary:

1.1 Recommendation:

The office of Clinical Pharmacology and Biopharmacetuics found this NDA acceptable.

1.2 Phase 4 Commitments

No Phase IV commitment is applicable for this application.

1.3 Summary of Clinical Pharmacology and Biopharmacetuics Findings

This NDA is for a new combination product containing immediate release FEX HCl **180 mg** and extended release pseudophedrine (PSE) HCl **240 mg** for once daily use (Allegra-D 24®).

What is the new Formulation?

The formulation consists of [ ] to effect the controlled release of the PSE (**Figure 1.3.1**). [ ]

Figure 1.3.1 Schematic Illustration of the New Allegra-D 24® Tablet

[ ]

Schematic not to scale;

What are the Main Findings?

From the submitted studies in this NDA the following conclusions can be made:

- Allegra –D 24 (FEX/PSE 180mg/240 mg) ER tablet is bioequivalent to the marketed individual components, Allegra® 180 mg and Sudafed® 24 hour, for FEX and PSE, respectively, following a single dose and at steady state conditions (**Figures 1.3.2 and 1.3.3**).

Mean FEX and PSE Plasma Concentration-Time Profiles Following a Single Doses of Allegra-D 24 (Treatment A) or Individual Components (Treatment B) (Study # 1001)

Figure 1.3.2 (FEX)

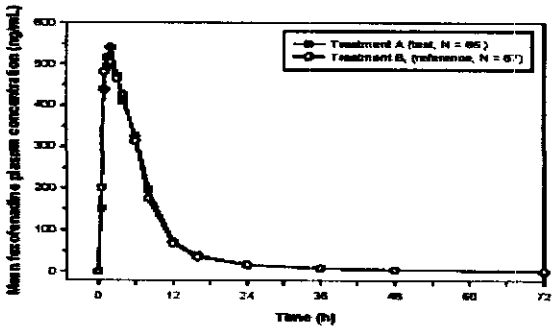
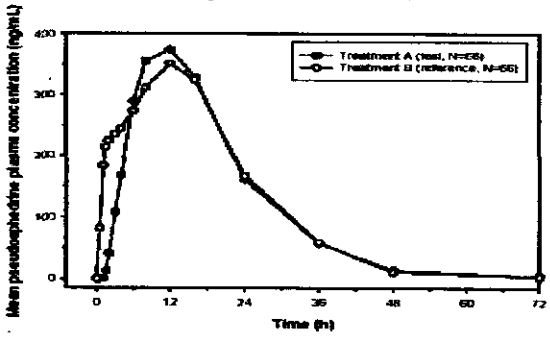


Figure 1.3.3 (PSE)



- Food with high fat content reduced FEX AUC by 42% and Cmax by 54%, when given at 30 min or 1.5 h after food ingestion (**Figures 1.3.4 and 1.3.5**)

Effect of Food on FEX (left) and PSE (right) Following at Fasting (A), 30 min (B), or 1.5 h (C) After High Fat Meals.

Figure 1.3.4

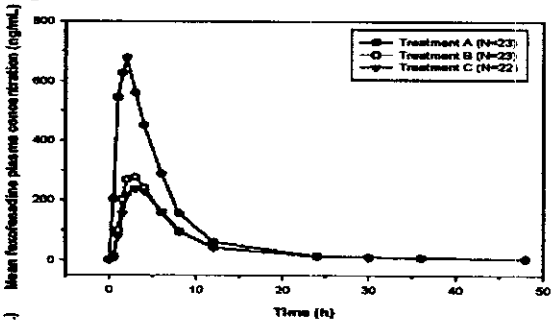
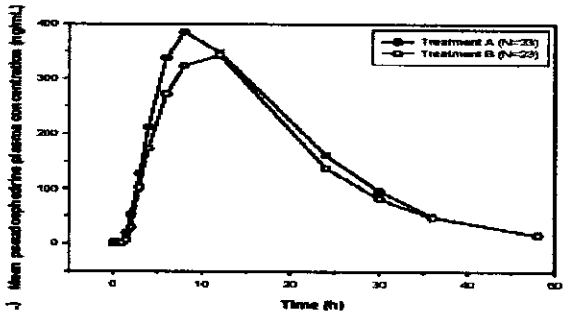


Figure 1.3.5



- The co-administration of grapefruit juice or orange juice reduced the efficacy of FEX as measured by the histamine induced skin wheals and flares (**Figures 1.3.6 and 1.3.7**). Also, based on the pop PK analysis of combined data from both fruit juice, the bioavailability of FEX appears to decrease by approximately 36% (**Table 1.3.1 and Figure 1.3.8**).
- However, these studies did not adequately address the effect of fruit juice on the exposure of FEX. Originally, at the end of Phase II meeting the Agency recommended to the sponsor to investigate the effect of grapefruit juice and apple juice on the bioavailability of FEX. The study protocols to investigate the effect of fruit juice on FEX using skin wheals and flares as

pharmacodynamic surrogate markers have never been submitted nor have been recommended by the Agency.

Mean (SD) Wheal and Flare Areas as Percentage of Baseline Value (n=20) (Study # 4141)

Figure 1.3. 6

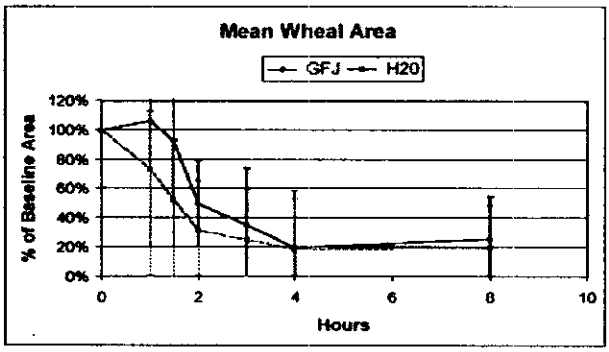


Figure 1.3.7

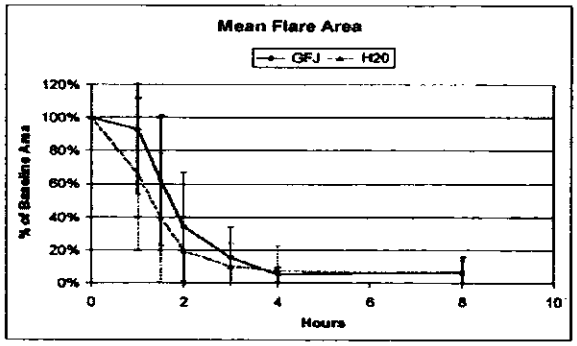
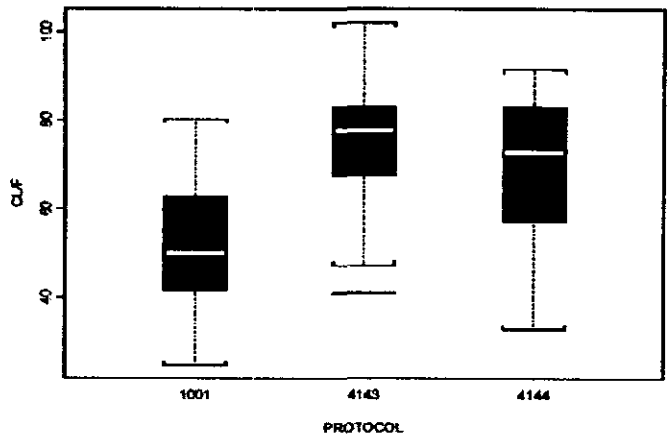


Table 1.3.1. Pop PK Parameters for Combined Data from Both Grapefruit Juice and Orange Juice

Summary of Fexofenadine NONMEM Population Parameter Estimates		
Parameter	**Estimate**	**95% Confidence Interval**
Apparent Clearance without juice effect (L/h)	47.4	(43.15, 51.65)
Apparent Volume of Distribution (L)	156	(134.64, 177.36)
Inter-compartmental Clearance (L/h)	11.2	(9.72, 12.68)
Peripheral Compartment Volume (L)	164	(137.74, 190.26)
Absorption Rate Constant (per h)	0.5 FIXED	.
Inter-Subject Variance on CL (ω^2)	0.084	
Residual Variance on CL (σ^2)	0.083	
Relative bioavailability (juice effect)	0.64	(0.52, 0.76)
Notes: 1. 95% confidence intervals calculated using the asymptotic approximation, Estimate ± 1.96 * SE(Estimate). 2. Population parameter estimates reported from the control stream, run.three4a.con, which includes F1, relative bioavailability due to the effect of juice. 3. The absorption rate constant (Ka) was fixed at a value of 0.5 based on the results of a previous analysis. This was because a sparse sampling scheme was used in protocols M016455A/4143 and M016455A/4144, which did not allow for adequate characterization of the absorption phase in these studies.		
Supporting Data: Table 7		

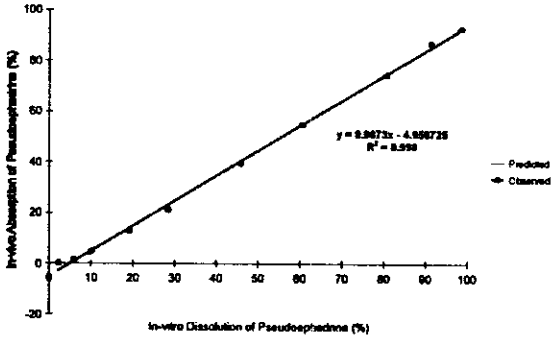
Figure 1.3.8. Pop PK Analysis (Pooled Clearance Estimate by treatment) (Studies # 1001 with water, 4143 with grapefruit juice and 4144 with orange juice)



- There was excellent *in vitro in vivo* correlation (IVIVC) for the dissolution data for PSE with r2 of 0.998 (**Figures 1.3.9 and 1.3.10**)
- The proposed *in vitro* dissolution data based on IVIVC relationship is acceptable to OCPB (**Table 1.3.2**)

Figures 1.3.9 and 1.3.10: IVIVC Data

1.3.9 Fraction of PSE Absorbed and Fraction Dissolved



1.3.10 Relationship Between Observed and Model Predicted Dissolution Profiles

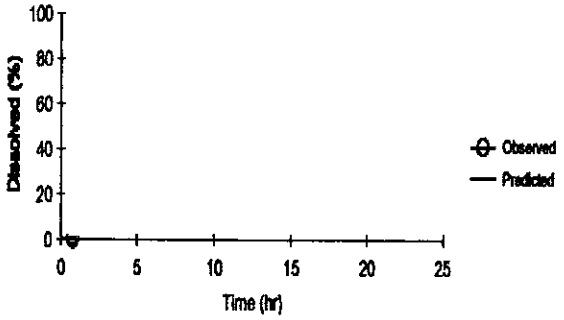


Table 1.3.2 Proposed BE Dissolution Limits for PSE

TIME (hr)	MINIMUM (%)	MAXIMUM (%)
3	[	]
7	[	]
23	Not less than [	]

What are the Specifications for Fexofenadine Component of Allegra-D 24?

The following are the sponsor's proposed method and specifications for fexofenadine:

USP Apparatus	II (Paddle)
Speed	50 RPM
Volume	900 ml
Media	[ ]
Specification	[ ] at 15 min
	[ ] at 45 min

From OCPB perspective, the method and the proposed specification are acceptable.

Are There any Safety Concerns For This Formulation?

Overall, there were no safety issues with this formulation. However, these safety observations are strictly limited to the summary data submitted to OCPB and should not be considered in anyway as final or complete. For complete safety assessment, please see the Medical Officer's review.

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On Original

Overall Summary and Conclusions:

Based on all the information submitted, the following main conclusions can be made:

- Based on the PK data, the exposure of FEX and PSE following the new Allegra-D 24 ER tablets justifies its use for once daily administration.
- The drug should be given on empty stomach or at least 4 hours after food. Food has a potential to reduce FEX absorption.
- The studies conducted by the sponsor to investigate the effect of fruit juices on the bioavailability of FEX are not adequate. Therefore, it is recommended that the sponsor conduct additional PK studies as a Phase IV commitment.
- From the submitted clinical studies on July 19, 2004, it appears that fruit juices such as grapefruit and orange may reduce FEX exposure and hence efficacy. Therefore, to maximize the exposure the drug should not be administered with these juices.
- There was excellent IVIVC correlation for PSE in Allegra-D 24.
- The proposed *in vitro* dissolution method and specifications are acceptable.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaulation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

2.0
Clinical Pharmacology and Biopharmaceutics Review (Question Based Review-QBR)

2.1 What are the General Attributes of Allegra-D 24

Originally, FEX was approved for seasonal allergic rhinitis in the US at a dose of 60 mg BID on July 25, 1996 (NDA # 20-625) and subsequently on February 25, 2000 was approved for the same indication at a dose of 180 mg QD (NDA# 20-872). In addition, the a fixed dose combination of FEX 60 mg and PSE 120 mg BID product was approved on December 24, 1997 as Allegra-D extended release tablet for the same indication (NDA #20-786). The list of all related NDA previously submitted by the sponsor for FEX is shown in **Table 2.1.1**.

Table 2.1.1. Previously submitted NDA for Fexofenadine

Table 3.2 – List of Aventis NDAs with pharmacokinetic information on fexofenadine HCl

NDA	Volume	Dosage Form	Date Submitted	Date Approved
NDA 20-625	S6–V1.21–P1	ALLEGRA capsules	31 July 1995	25 July 1996
NDA 20-872	S6–V1.28–P1	ALLEGRA tablets	17 July 1998	25 February 2000
NDA 20-786	S6–V1.15–P1	ALLEGRA-D tablets	20 December 1996	24 December 1997

Therefore, this NDA can be considered as an extension of the currently marketed Allegra-D fixed dose combination tablet. There are three main differences between the two products:

a) Allegra-D approved for twice daily administration, whereas Allegra-D 24 is proposed for once daily administration.

b) The total dose in the new product for each component (180 mg/240 mg) is 2-3 times higher than the currently approved dose for Allegra-D (60 mg/120 mg).

c) The formulation technology is different in each product. For Allegra-D 24, PSE component is slowly released from the tablet [redacted] while immediate release [redacted] technology is used for the release of FEX from the tablet – (see details below). This release technology was not used in the development of the currently approved Allegra-D formulation.

2.1.1 What is the Relevant Communication to the NDA?

A. End-of-Phase II Meeting:

An End of Phase II meeting was held with the sponsor on January 29, 2002 (IND# 48,486). From the clinical pharmacology perspective, the following main comments were conveyed to the sponsor at that meeting:

- The inclusion of female subjects in the proposed studies (the sponsor proposed exclusion of females).
- The sponsor was advised to use the final to-be-marketed formulation in the proposed studies, otherwise a link would be necessary.
- Collecting blood samples for the determination of C_{min}.
- Monitoring appropriate safety endpoints.
- Optimizing the dissolution method with specifications for each component.
- The sponsor was advised to conduct the BE study following a single and multiple doses and the food effect study after a single dose.
- The 90% CI for Cmax in the effect of food study should be set to 80%-125%.
- It was recommended to the sponsor to study the effect of grapefruit juice and apple juice on the bioavailability of fexofenadine.
- The sponsor was advised to open a new IND for Allegra-D 24. This is because the drug release technology in the new formulation is different from that of the currently approved Allegra-D. Therefore, in early 2003, the sponsor opened a new IND with a pivotal bioequivalence study (#66,289, N000)

B. Pre-NDA Meeting

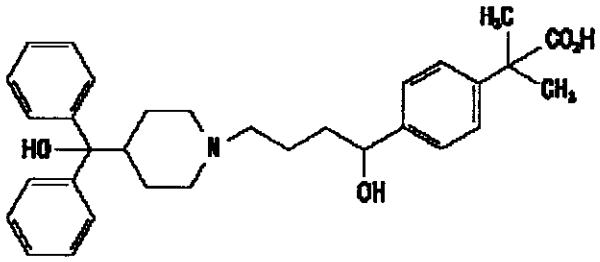
The Pre-NDA meeting was held with the sponsor on August 27, 2003. From OCPB perspective, here are the main comments:

- In addition to other PK parameters listed in the proposed format, the sponsor was requested to also include Tmax and T ½ for each component following a single dose and at steady state (C_{av}), and degree of fluctuation (C_{max}–C_{min} /C_{av}) for each component.
- IVIVC should be validated before it can be used to set dissolution specifications.

2.2 What is the General Clinical Pharmacology?

What is FEX as Drug Substance?

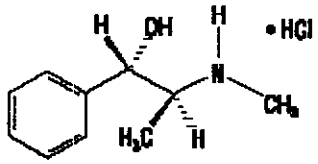
FEX is the only active ingredient in Allegra marketed products. Pharmacologically it is classified as histamine H1-receptor antagonist. FEX is the major active metabolite of terfenadine. It has a molecular weight 538.13. Its chemical structure is as follows:



FEX HCl

What is PSE as Drug Substance?

PSE is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. PSE is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. PSE produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. The molecular weight of PSE is 201.70 and its chemical structure is as follows:



PSE HCl

2.2.1 What are the PK Characteristics of FEX and PSE?

In the current NDA, no new efficacy or safety studies have been conducted with Allegra-D 24 formulation. The PK and bioavailability (BA) of FEX have been evaluated in 21 clinical studies in NDA 20-625 and 15 clinical studies in NDA 20-872 (**Table 2.2.1.1**). The absorption and drug-drug interaction information derived with the combination of 60 mg FEX and 120 mg PSE have been also evaluated in 5 clinical studies in NDA 20-786.

Table. 2.2.1.1 List of Sponsor's NDAs with Relevant PK Information to FEX

NDA	Volume	Dosage Form	Date Submitted	Date Approved
NDA 20-625	56-V1 21-P1	ALLEGRA capsules	31 July 1995	25 July 1996
NDA 20-872	56-V1 28-P1	ALLEGRA tablets	17 July 1998	25 February 2000
NDA 20-786	56-V1.16-P1	ALLEGRA-D tablets	20 December 1996	24 December 1997

The relevant PK results and conclusions from the previous NDAs are summarized below:

A. FEX

- The PK in patients with seasonal allergic rhinitis is similar to those in healthy subjects.
- Tmax occur with 1 to 3 hours
- Mean half life is 14.4 hours.
- Percent binding to plasma proteins range from 62-70%.
- Exhibits linear PK over the dose of 120 mg BID. A slight departure from dose proportionality with respect to single dose and steady state Cmax and single dose AUC was observed for the 240 mg dose.
- Excretion: 80 % and 11.5 % excreted in the feces and urine, respectively. Biliary and renal excretions are considered to be the principal routes of elimination.
- As expected, FEX Cmax in patients with severe renal impairment increases by 111%.
- The drug undergoes minimal metabolism. Therefore, hepatic impairment has little effect on the disposition and/or exposure of FEX.
- Exists in a racemic mixture of two enantiomers (R(+)/S(-) isomers) with a ratio of 62:38. This ratio is independent of time or dose.
- Ketoconazole and erythromycin increase the systemic bioavailability of FEX by approximately 159% and 103%, respectively.

B. PSE

- One compartment PK
- Percent of plasma protein binding is unknown.
- Extensively distributed into extravascular sites (apparent volume of distribution between 2.6 and 3.5 L/kg).
- Minimal hepatic metabolism (less than 1%)
- Mainly undergo N-demethylation to the active metabolite norpseudoephedrine.
- Excreted mainly unchanged in urine (43% to 96%).
- Half life depends on urine pH as follows. The half life range from approximately 2 hours at a pH 5 to 20 hours at pH 8.

2.2.2 What is the Rational for the Combination Drug Products?

Allegra-D is an antihistamine/decongestant for the relieve of seasonal allergic rhinitis (SAR) and idiopathic urticaria in adult and children >12 years of age. The sponsor is seeking approval of Allegra-D 24 (QD) for the same indication as for Allegra-D (BID).

It should be noted that, FEX (NDA 20-625, NDA 20-872) and PSE (Final Monograph for Combination Drug Products; Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use) as well as the combination of FEX 60 mg + 120 mg PSE (NDA 20-786) have been reviewed and found to be safe and efficacious at doses including those recommended for the current FEX 180 mg + PSE 240 mg extended release tablet. As a result, no nonclinical toxicology/safety studies were performed with this new extended release tablet.

2.2.3 What Studies are submitted in the Current NDA?

A. PK Studies

The sponsor submitted three main PK studies and IVIVC analysis. These studies are listed and summarized in **Tables 2.2.3.1 and 2.2.3.2.**

From the BE perspective, there were two main studies: a pivotal BE study comparing Allegra-D 24 to its individual components after a single and multiple doses until steady state (study # 1001) and the other is effect of food study (Study # 1002). There was also a pilot BE study (Study # KA467). These studies will be summarized in the subsequent sections.

Table 2.2.3.1 List of Studies Submitted in this NDA

IND No. (Sponsor IND No.) Protocol No. Report No.	Route	Study Design	Dosage Form(s)	Drug Name Dose	Plant Lot No. Date of Manufacture	Number of Subjects Exposed	Applicant Conclusion
KA467 *KA467*	Oral	Pilot Bioavailability A comparative, single-dose two-way randomized crossover design with a drug-free washout period of 7 days	Test: fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg extended release tablet References: Allegra® (fexofenadine HCl) tablet 180 mg Sudafed® (pseudoephedrine HCl) 24 Hour tablet 240 mg	Fexofenadine HCl 180 mg Pseudoephedrine HCl 240 mg	Test: UB 0000D January 2001 References: Allegra® Marketed product 1000407 Sudafed® 24 Hour Marketed product 9902255	12 Healthy males	No statistically significant differences in pharmacokinetic parameters between the test and reference treatments for fexofenadine or pseudoephedrine Cmax ratio. 1.07 and 1.11 AUC ratio. 1.1 and 1.16 for fexofenadine and pseudoephedrine, respectively.
MD16455 SH001 *SH001*	Oral	Pivotal Bioequivalence Open-label, randomized, two-treatment, two-period, crossover design administered as single dose followed by once daily dosing for 9 days under fasting conditions with a drug-free washout period of at least 8 days.	Test: fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg extended release tablet References: Allegra® (fexofenadine HCl) tablet 180 mg Sudafed® (pseudoephedrine HCl) 24 Hour tablet 240 mg	Fexofenadine HCl 180 mg Pseudoephedrine HCl 240 mg	Test: UB Aventis KCIO 1054547 September 2002 References: Allegra® Marketed product 1053229 Sudafed® 24 Hour Marketed product 0116002	70 Healthy males and females	Fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg extended release tablet is bioequivalent to the marketed individual components Allegra® 180 mg and Sudafed® 24 Hour tablets under single dose and steady-state conditions.
MD16455 SH002 *SH002*	Oral	Pivotal Food Effect Open-label, single-dose, randomized, 3-period, 3-treatment, crossover design with a washout period of at least 6 days between each dose. Treatment A: Product administered under fasted conditions. Treatment B: Product coadministered with high fat meal. Treatment C: Product administered 1 hour after high fat meal.	Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet	Fexofenadine HCl 180 mg Pseudoephedrine HCl 240 mg	Test: UB Aventis KCIO 1054547 September 2002	24 Healthy males and females	Food decreased fexofenadine Cmax and AUC by 54% and 42%, respectively, similar magnitude of decrease when administered 1 hour after meal. Pseudoephedrine bioequivalent between fasted and fed conditions.

Table 2.2.3.2 Summary of PK Data in this NDA

Protocol No. Report No.	Route	Administration Schedule	Population Sex/Age Mean/range	Dosage Forms	Dose	C_{max} ng/mL	t_{max} h	AUC h•ng/mL	$t_{1/2}$ h	C_{trough} ng/mL	Applicant Conclusions
KA467 *KA467*	Oral	FBE bioavailability Single dose, fasted	Healthy male 31.2 (18-42) years	Test: fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg extended release tablet References: Allegra® (Fexofenadine HCl) tablet Sudafed® (Pseudoephedrine HCl) 24 Hour tablet	180 mg 240 mg 180 mg 240 mg	488 267 456 242	2.3 13.2 2.1 13.6	3056 6359 2834 5570	15.0 8.2 12.9 8.2	Not applicable	No statistically significant differences in pharmacokinetic parameters between the test and reference treatments for fexofenadine or pseudoephedrine. Cmax ratio: 1.07 and 1.11 AUC ratio: 1.1 and 1.16 for fexofenadine and pseudoephedrine, respectively.
MD16435 S/1001 *S/1001*	Oral	Pivotal Bioequivalence Single dose plus 72 hour blood sampling followed by 6 once-daily doses of each treatment.	Healthy male and female 23.8 (18-44) years	Test: Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet References: Allegra® (Fexofenadine HCl) tablet Sudafed® 24 Hour (Pseudoephedrine HCl) tablet	180 mg 240 mg 180 mg 240 mg	Day 1/9 634 / 674 384 / 495 624 / 630 370 / 477	Day 1/9 2.0 / 1.8 12.0 / 12.0 2.0 / 2.0 12.0 / 8.0	Day 1/9 4316 / 4019 8138 / 8688 4115 / 3865 8564 / 9072	Day 1 14.6 7.1 14.9 6.8	Day 9 16.5 171.9 17.4 178.6	Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet is bioequivalent to the marketed individual components Allegra® 180 mg and Sudafed® 24 Hour tablets under single dose and steady-state conditions.
MD16435 S/1002 *S/1002*	Oral	Pivotal Food effect. Single dose, fasted and fed	Healthy male and female 28.1 (18-44) years	Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet	180 mg Fasted Fed Fed (1 h prior to dose) 240 mg Fasted Fed	795 302 283 394 366	2.0 2.5 3.0 8.0 12.0	4401 2404 2219 7839 7095	14.9 18.8 18.6 7.0 7.8	Not applicable	Food decreased fexofenadine Cmax and AUC by 54% and 42%, respectively; similar magnitude of decrease when administered 1 hour after meal Pseudoephedrine bioequivalent between fasted and fed conditions.

B. Clinical Studies:

Effect of Grapefruit and Orange Juice

In July 19, 2004, the sponsor submitted additional studies related to the effect of grapefruit juice and apple juice on the PK of FEX (**Table 2.2.3.3**). These studies were originally requested from the sponsor at the End of Phase II meeting held in January 29, 2002. Therefore, the sponsor was reminded after the 45 Day filing meeting with a letter dated March 2, 2004. As shown in **Table 2.2.3.3** the sponsor submitted studies to evaluate the effect grapefruit juice and orange juice on the phamacodynamic-PD (as measured via skin wheal and flare) rather than exposure as measure by the classical PK parameters (Cmax or AUC). Also the sponsor did not provide information on the effect of apple juice, but rather used orange juice instead.

Table 2.2.3.3 List of Studies Submitted in July 19, 2004 fort the Effect of Juice of the PK of FEX

Study #	Design	Monitored Parameters
4141	•Single dose, crossover PD study •Grapefruit juice vs water •N=20 healthy subjects	•Skin wheal and flare •No PK samples
4143	•Double-blind, single dose, crossover PD study, placebo controlled •Grapefruit juice vs water •N=23 healthy subjects	•Skin wheal and flare •Sparse blood samples for Pop PK
4144	•Double-blind, single dose, crossover PD study, placebo controlled •Orange juice vs placebo •N=34 healthy subjects	•Skin wheal and flare •Sparse blood samples for
Pop PK	Analysis of spares PK samples	
Literature	Review of relevant literature	

C. Crossed Referenced Studies

- Study# M106455B/3081: This study was completed as part of the previous NDA 20-872 to support the approval of FEX 180 mg QD. It was a double blind, randomized, placebo controlled, parallel group study comparing the efficacy and safety of FEX 120 mg and 180 mg QD in the treatment of allergic rhinitis.
- The sponsor also included summaries of relevant studies previously submitted under NDAs # 20-625, 20-972, and 20-786.
- Long term safety from the previously submitted clinical study # PJPR0027.

For these studies, please see medical Officer's review

2.2.4 Does this Drug Prolong the QT or QTc Interval?

No signals for prolongation in QTc intervals were noted in this submission (see also the Medical Officer's Review). All QTc issues were addressed in the previous submissions.

2.3 Are there any Intrinsic Factors?

Severe renal impairment may affect the disposition of FEX (see below).

2.3.1. Are there any Intrinsic Factor Affecting Exposure?

There is a potential increase of FEX exposure in patients with renal impairment. These studies information were reviewed in the original NDA # 20-972.

2.4 Are there any Extrinsic Factors?

- High fat meals may reduce the absorption of FEX, but has little effect on PSE. The AUC and Cmax reduced by 42% and 54%, respectively.
- Fruit juices such as grapefruit and orange may reduce the efficacy and possibly FEX exposure. From the Pop PK analysis of the recent studies submitted by the sponsor in July 19, 2004, the bioavailability of FEX appears to be reduced by 36% based on the meta analysis of the combined data from both grapefruit and orange juice. In addition, the efficacy of FEX appears to reduce as measured by histamine induced skin wheals and flares.
- By contrast, ketoconazole and erythromycin increase the systemic bioavailability of FEX by 159 and 103%, respectively.

Studies related to drug-drug interactions were reviewed in the original NDA # 20-972. The effect of food and fruit juices studies will be discussed in the biopharmaceutics section.

2.5 Biopharmaceutics Issues

2.5.1 What is the Drug Product/Formulation?

The formulation consists of [redacted]

Figure 2.5.1.1 Schematic Illustration of the New Allegra-D 24®

[redacted]

Schematic not to scale;

2.5.2 What is the Mechanism of Drug Release?

[tablet includes the active ingredient PSE HCl, USP and sodium chloride (NaCl)] (**Figure 2.5.1.1**).

]

The detail description of the formulation used in this NDA is shown in **Tables 2.5.2.1 and 2.5.2.2**

Table 2.5.2.1 Formulation used in the NDA

Protocol No. *Report No.*	*Lot No*	*Dosage Form and Strength*	*Batch Size* *Date of Manufacture*	*Effect of Change* *Or* *Formulation or Significant Manufacturing Change (if any) and Reason for Change*
KA467 – Pilot Bioavailability *KA467*	25080 1020407 B002065	Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet Allegra® (Fexofenadine HCl) tablet 180 mg Sudafed® (Pseudoephedrine HCl) 24 Hour tablet 240 mg	Test: 6 kg January 2001 References: Allegra® Marketed product Sudafed® 24 Hour Marketed product	Prototype formulation No statistically significant differences between the test and reference treatments for fexofenadine HCl or pseudoephedrine HCl pharmacokinetic parameters.
MD164555/1001 – Pivotal Bioequivalence *S/1001*	1054547 1053229 01H082	Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet Allegra® (Fexofenadine HCl) tablet 180 mg Sudafed® (Pseudoephedrine HCl) 24 Hour tablet 240 mg	Test: 134.5 kg September 2002 References: Allegra® Marketed product Sudafed® 24 Hour Marketed product	[ ] Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet is bioequivalent to the individual components, Allegra® and Sudafed® 24 hour for fexofenadine and pseudoephedrine, respectively.
MD164555/1002 – Pivotal Food effect *S/1002*	1054547	Fexofenadine HCl 180 mg and Pseudoephedrine HCl 240 mg extended release tablet	Test: 134.5 kg September 2002	To-be marketed formulation. Food decreased fexofenadine C_{max} and AUC by 54% and 42%, respectively; similar magnitude of decrease when administered 1 hour after meal. Pseudoephedrine bioequivalent between fasted and fed conditions.

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

2.5.3 What is the Relative Bioavailability of the Proposed to-be-marketed Formulation Following a Single Dose Administration Compared to the Reference Products?

The sponsor conducted two BE studies, one pivotal (Study # 1001) and one pilot (Study # 1002). Only the pivotal study will be briefly discussed below. However, for the pilot study (# 1002), please see individual study section.

Study # M106455S/1001:

This is a pivotal, single and multiple dose (steady-state) BE study in healthy subjects. This was two-way crossover study in approximately 70 subjects. Each subject received the following treatments:

Treatment A (Test): The final to-be-marketed formulation of Allegra-D 24 (fexofenadine 180 mg/pseudoephedrine 240 mg ER) tablet as a single dose followed by once daily dosing for 6 days under fasting conditions.

Treatment B (Reference): Fexofenadine 180 mg IR (Allegra) tablet and 240 mg pseudoephedrine (Sudafed® 24 hour, Warner-Lambert) ER tablet coadministered as a single dose followed by once daily for 6 days.

Blood samples were collected over 72 hours and 24 hours following a single dose administration and after the last dose on Day 9, respectively. In addition, trough levels were monitored during the multiple dose phase of the study on Days 4-9. The plasma concentration of each component was determined in this study.

What are the Main Findings from Study # 1001:

- The 90% CI for Cmax and AUC was within 80% to 125% **(Table 2.5.3.1)**
- The plasma concentration-time profiles for FEX and PSE were very similar following all treatments **(Figures 2.5.3.1 and 2.5.3.1)**.
- From this study it can be concluded that Allegra-D 24 hour is interchangeable with Allegra 180 mg and Sudafed 24 hour 240 mg tablets taken individually.

Table 2.5.3.1 Summary of BE Parameters for FEX and PSE (study # 1001).

	Geometric LS Mean		Treatment Comparisons	
Parameter (units)	Test [a] Trt A	Reference [a] Trt B	Mean Ratio [b] (%)	90% CI
Fexofenadine				
$AUC(0-\infty)_{,1}$ (ng·h/mL)	4052.5	3956.3	102.4	(94.5 – 111.1)
$C_{max,1}$ (ng/mL)	569.4	561.6	101.4	(89.6 – 114.8)
$AUC(0-24)_{,7}$ (ng·h/mL)	3831.0	3725.5	102.8	(94.5 –112.0)
$C_{max,7}$ (ng/ml)	631.3	584.6	108.0	(96.7 –120.7)
$C_{min,7}$ (ng/mL)	15.2	16.4	92.6	(84.3 –101.7)
Pseudoephedrine				
$AUC(0-\infty)_{,1}$ (ng·h/mL)	7988.1	8536.9	93.6	(89.8 – 97.5)
$C_{max,1}$ (ng/mL)	393.7	370.0	106.4	(102.1 – 110.9)
$AUC(0-24)_{,7}$ (ng·h/mL)	8490.0	8930.4	95.1	(90.2 – 100.2)
$C_{max,7}$ (ng/ml)	488.0	472.1	103.4	(97.9 – 109.1)
$C_{min,7}$ (ng/mL)	157.3	162.8	96.6	(86.3 – 108.2)

[a] Test (Trt A) = fexofenadine HCl 180 mg - pseudoephedrine HCl 240 mg extended-release tablet.
Reference (Trt B) = marketed fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg tablets.
[b] Ratio = Geometric LS mean test/ geometric LS mean reference (A/B).

FEX Plasma Concentration-Time profiles on Day 1 (Single Dose) and Day 9 (Multiple Dose)

Figure 2.5.3.1 (single Dose)

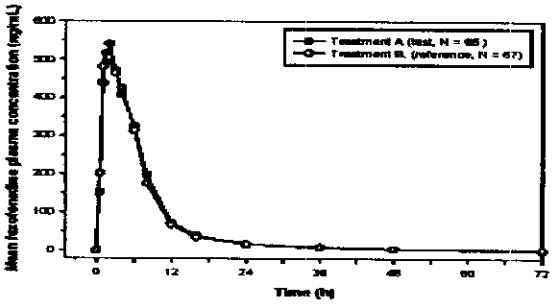
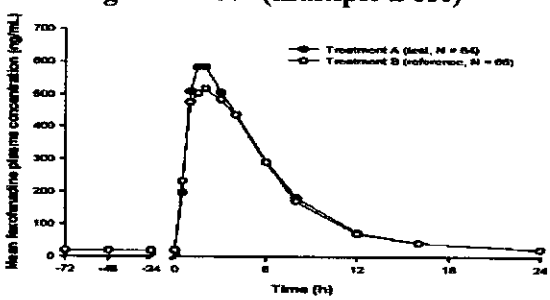


Figure 2.5.3.2 (multiple Dose)



PSE Plasma Concentration-Time profiles on Day 1 (Single Dose) and Day 9 (Multiple Dose)

Figure 2.5.3.3 (single dose)

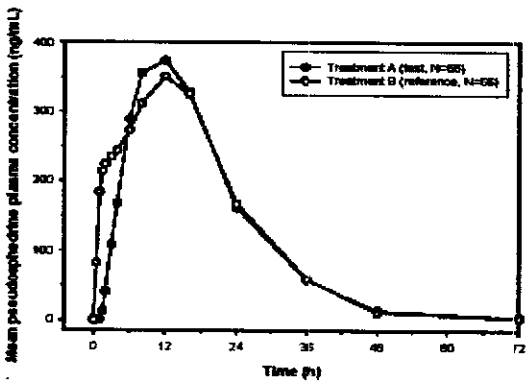
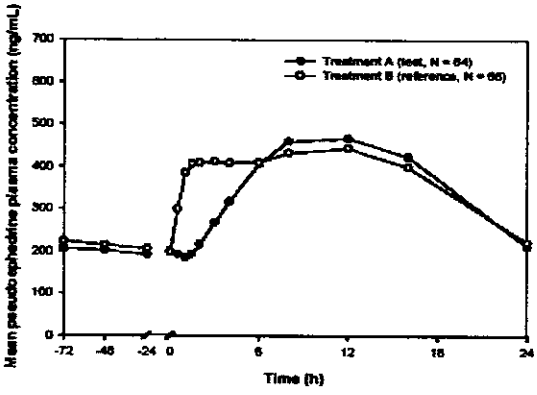


Figure 2.5.3.4 (multiple dose)



2.5.4 What is the Effect of Food on the Bioavailability of the Proposed to-be-marketed Formulation?

Study # M106455S/1002:

This was an open label, three-way crossover, three-way treatment, randomized study to assess the effect of food on the PK of Allegra-D 24 in 24 healthy subjects. This was conducted using the final-to-be marketed formulation. All subjects received the following treatments with at least 6 days washout period:

Treatment A: A single dose of Allegra-D 24 under fasting condition.

Treatment B: A single dose of Allegra-D 24 administered 30 minutes after start of a high fat breakfast and according to the FDA guidance.

Treatment C: A single dose of Allegra-D 24 administered 1.5 hour after the start of a high-fat breakfast.

What are the Main Findings from Study # 1002?

- Food reduced the absorption of FEX by 50% (42% for AUC and 54 % for Cmax), regardless of timing of food ingestion as described in this study (**Table 2.5.4.1**).
- However, food had no effect on PSE component of the Allegra-D 24 (**Table 2.5.4.1**)
- The plasma concentration-time profiles for FEX and PSE with and without food clearly demonstrate the dramatic effect of food on FEX, but not on PSE (**Figures 2.5.4.1 and 2.5.4.2**)

Table 2.5.4.1 Effect of food on FEX and PSE (Treatments: A=fasting, B= 30 min after food, and C: 1.5 h after food) (study # 1002).

	Geometric LS Mean			Treatment Comparisons	
Parameter (units)	Reference Trt A [a]	Test Trt B [a]	Test Trt C [a]	Mean Ratio [b](%)	90% CI
Fexofenadine					
AUC(0-∞) (ng·h/mL)	3930.4	2296.9	2178.2	B/A = 58.4 C/A = 55.4	(51.0 – 66.9) (48. 3 – 63.6)
AUC(0-last) (ng·h/mL)	3812.0	2131.9	1995.8	B/A = 55.9 C/A = 52.4	(48.9 – 63.4) (45.8 – 59.9)
C_{max} (ng/mL)	625.7	286.8	267.0	B/A = 45.8 C/A = 42.7	(37.9 – 55.4) (35.3 – 51.6)
t_{max} [c] (h)	2.0	2.5	3.0	-	-
Pseudoephedrine					
AUC(0-∞) (ng·h/mL)	7683.1	6972.0	[d]	B/A = 90.7	(87.8 – 93.8)
AUC(0-last) (ng·h/mL)	7521.0	6768.2	[d]	B/A = 90.0	(87.1 – 93.0)
C_{max} (ng/mL)	384.6	351.0	[d]	B/A = 91.2	(86.2 – 96.6)
t_{max} [c] (h)	8.0	12.0	[d]	-	-

[a] Trt A: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered under fasting conditions.
Trt B: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 30 min after start of a high-fat breakfast.
Trt C: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 1.5 h after start of a high-fat breakfast.
[b] Ratio = Geometric LS mean test/ geometric LS mean reference.
[c] tmax presented as median and range
[d] No data, pseudoephedrine for Trt C was not quantitated.

Effect of Food on FEX (left) and PSE (right) Following at Fasting (A), 30 min (B), or 1.5 h (C) After High Fat Meals.

Figure 2.5.4.1

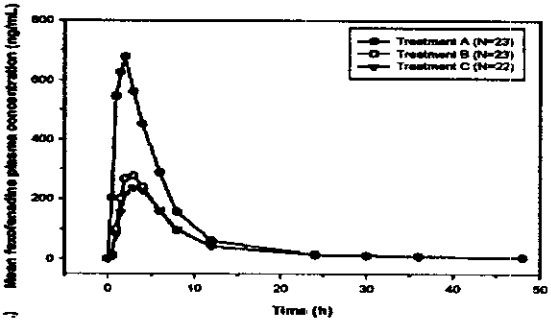
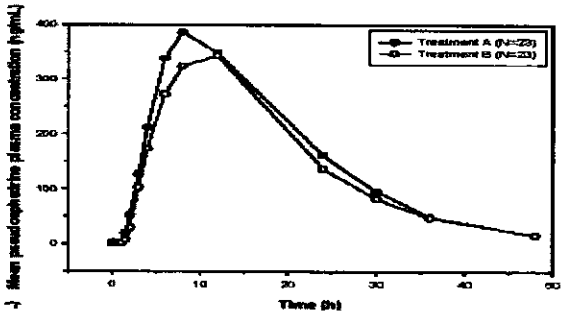


Figure 2.5.4.2



2.5.5 Are there Any Other Food Products that May Potentially Affect the Bioavailability of FEX?

Yes. Based on literature reports, fruit juices such as grapefruit, organ, and apple juice appear to reduce the bioavailability of FEX. Therefore, at the end-of Phase II meeting, the Agency recommended to the sponsor to conduct a PK study to investigate the effect of grapefruit juice and apple juice on FEX. The sponsor did not submit these studies with this NDA in December 19, 2003 submission. Therefore, the sponsor was reminded again with a memo dated March 2, 2004 after the 45 days filing meeting. Thus, on July 19, 2004, the sponsor submitted the three studies and one Pop PK analysis report. These studies are briefly summarized below:

2.5.5.1 Study # 4141

What is the Main Objective?

The primary objective of the study was to investigate if there was an effect of grapefruit juice on fexofenadine hydrochloride (HCl) inhibition of induced wheal and flare.

How the Study Was Designed?

This was a randomized, open-label, single-dose, single-center, crossover study in 20 healthy volunteers. There were two treatments with a washout period of 7 days as follows:

Treatment Group	Period 1	Washout	Period 2
A	Fexofenadine 180 mg with 8 oz. of water	→	Fexofenadine 180 mg with 8 oz. of grapefruit juice
B	Fexofenadine 180 mg with 8 oz. of grapefruit juice	→	Fexofenadine 180 mg with 8 oz. of water

What Parameters were Monitored?

- No PK samples were collected in this study.
- Skin wheal and flare measurements were performed.

What are the Main Findings from Study 4141?

- Wheal areas were significantly larger after the administration of grapefruit juice ($p = 0.046$)
- The geometric mean area under the effect curve (AUEC) for wheal was 0.988 cm2 with administration of grapefruit juice and 0.687 cm2 without grapefruit juice (**Table 2.5.5.1.1 and Figures 2.5.5.1.1 and 2.5.5.1.2**).

Table 2.5.5.1.1 Comparison of AUEC Following FEX With Grapefruit Juice or Water (Study # 4141)

Variable	Geometric Mean Area				
	Grapefruit Juice (cm^2)	H2I (cm^2)	GMR	95% Confidence Interval	P value
Flare	13.954	11.710	1.19	0.77-1.85	0.421
Wheal	0.988	0.687	1.44	1.01- 2.05	0.046

Mean (SD) Wheal and Flare Areas as Percentage of Baseline Value (n=20) (Study # 4141)

Figure 2.5.5.1.1

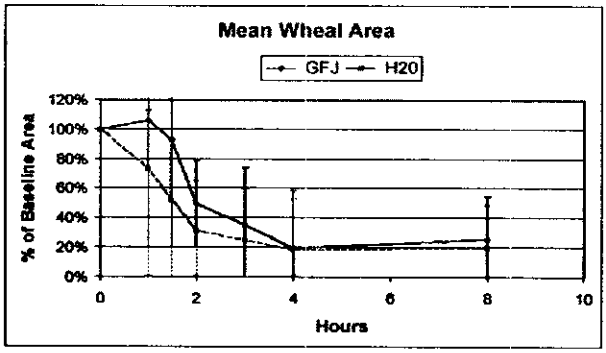
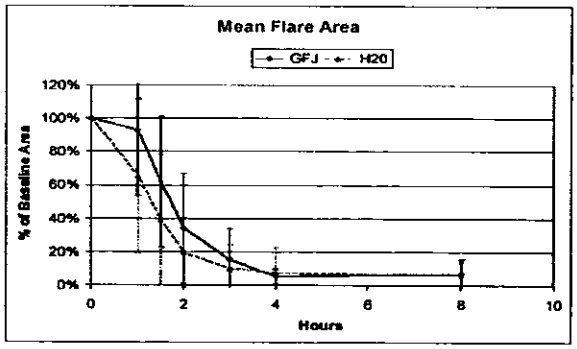


Figure 2.5.5.1.2



Conclusions from Study #4141:

- It appears that grapefruit juice increases the wheal and flare areas when administered with FEX .
- Thus, grapefruit juice may increases the histamine release and therefore reduces the effect of FEX.
- There was a wide variability in the data.

Reviewers Comments on Study # 4141:

- From the OCPB point of view, this study was irrelevant to the original request that was made at the End-of-Phase 2 meeting.
- See also the overall comments at the end of this section related to the effect of grapefruit juice series of studies.

2.5.5.2 Study # 4143

What is the Main Objective?

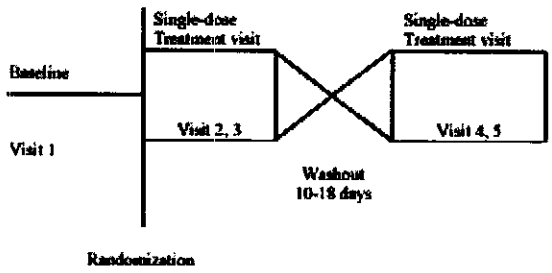
The primary objective of the study was to compare the effect of a single dose of FEX 180 mg plus grapefruit juice versus placebo plus grapefruit juice on the change from baseline (pre-dose) in histamine skin flares at 20, 40, and 60 minutes post-dose; then hourly through the first 12 hours post-dose; and 23 and 24 hours post-dose.

What is the Study Design?

This was a randomized, single-dose, single-center, crossover, placebo controlled study in 34 healthy volunteers (**Figure 2.5.5.2.1**). There were two treatments with a washout period of 14 days as follows.

Treatment A: FEX 180 mg tablet with 8 oz regular strength grapefruit juice
Treatment B: Placebo tablet (matching FEX) with 8 oz regular strength grapefruit juice

Figure 2.5.5.2.1 Scheme of Study Design (Study # 4143)



What Parameters were Monitored?

- Skin wheal and flare measurements were performed at pre-dose, 20 min, 40 min, 60 min, and hourly through 12 hours with an additional 2 time points obtained at Hours 23 and 24.
- 4 plasma samples per subjects were collected for pop PK analysis at the following time points:
    - One sample between 0.5 and 6 hours post-dose during Visit 2.
    - One sample at 22-24 hours post-dose on Visit 3
    - One sample between 0.5 and 6 hours post-dose during Visit 4
    - One sample at 22-24 hours post-dose on Visit 5

What are the Main Findings from Study 4143?

- FEX plus grapefruit juice had significantly greater suppression of histamine induced wheals and flares than placebo plus grapefruit juice at all time points.
- Pop PK analysis will be discussed in a separate section below.

Conclusions from Study #4143:

- FEX with grapefruit juice suppress wheals and flares in a greater extent than placebo with grapefruit juice.

2.5.5.3 Study # 4144

This is almost a duplicate study as that of study # 4143.

The objective and design of this study was exactly the same as the above study # 4143, except that orange juice was administered with FEX or its match placebo tablet, instead of grapefruit juice. The number of subjects was also the same (i.e., 34). Efficacy end points (wheals and flares) and PK spares sampling time points were also the same as study # 4143. The main results and conclusions were of similar trend as that of study #4143. Therefore for detail, please see individual study reports.

Reviewers Comments on Studies # 4143 and 4144:

- The observed effects are due to FEX alone rather than grapefruit juice or orange juice.
- Specifically for these studies, the sponsor did not adequately test the effect of juices on the formation of wheals and flares.
- The bottom line is that, in these studies, the sponsor tested the effect of FEX on the suppression of wheals and flares compared to placebo. Therefore, the addition of juices was of little value in these studies, unless the sponsor included a third arm with water as a comparator for the juices.

2.5.5.4 Pop PK Report

What Was the Objective?

The main objective of this analysis was to obtain an estimate of the change in FEX exposure when concurrently administered with grapefruit and orange juice.

How the Analysis were Performed?

The data from the above two clinical studies (# 4143 and 4144) were used for this population PK analysis. The data from the BE study # 1001 were included in the pooled analysis as control dataset to provide PK information in a similar population given concurrently with water.

It is important to note that the Pop PK analysis was performed on a combined juice dataset without regard to type of juice used in the individual study. The reason for this approach is that the sample size is too small in each study as well as the data was comparable following both juices.

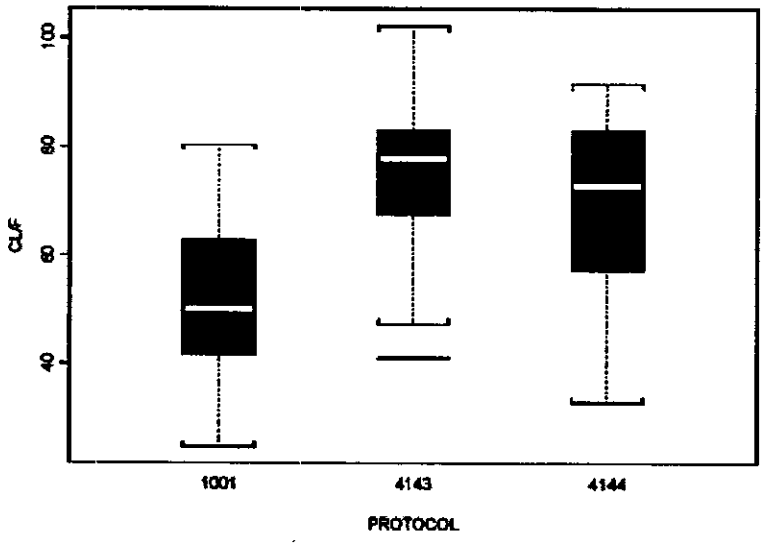
What are the Main Findings from the Pop PK Analysis?

Overall, the relative bioavailability of FEX was reduced by a mean of 36% in the presence of grapefruit or orange juice (**Table 2.5.5.4.1 and Figure 2.5.5.4.1**).

Table 2.5.5.4.1 Pop PK Parameters

Summary of Fexofenadine NONMEM Population Parameter Estimates		
Parameter	**Estimate**	**95% Confidence Interval**
Apparent Clearance without juice effect (L/h)	47.4	(43.15, 51.65)
Apparent Volume of Distribution (L)	156	(134.64, 177.36)
Inter-compartmental Clearance (L/h)	11.2	(9.72, 12.68)
Peripheral Compartment Volume (L)	164	(137.74, 190.26)
Absorption Rate Constant (per h)	0.5 FIXED	.
Inter-Subject Variance on CL (ω^2)	0.084	
Residual Variance on CL (σ^2)	0.083	
Relative bioavailability (juice effect)	0.64	(0.52, 0.76)
Notes: 1. 95% confidence intervals calculated using the asymptotic approximation, Estimate $\pm$ 1.96 * SE(Estimate). 2. Population parameter estimates reported from the control stream, nm.threeda.con, which includes F1, relative bioavailability due to the effect of juice. 3. The absorption rate constant (Ka) was fixed at a value of 0.5 based on the results of a previous analysis. This was because a sparse sampling scheme was used in protocols M016455A/4143 and M016455A/4144, which did not allow for adequate characterization of the absorption phase in these studies.		
Supporting Data: Table 7		

Figure 2.5.5.4.2 Pooled Clearance estimate by treatment (Studies # 1001 with water, 4143 with grapefruit juice and 4144 with orange juice)



Overall Conclusions and Comments on all Effect of Juices Studies.

- Based on three studies, it appears that grapefruit juice and organ juice reduce the effect of FEX.
- Both grapefruit juice and orange juice appears to have comparable effects.
- Based on Pop PK meta analysis of the combined data from grapefruit and orange juices, the exposure to FEX appears to be reduced by approximately 36% with both grapefruit juice and orange juice.

- The meta analysis of the combined data from both grapefruit juice and orange juice is not optimal to make adequate determination of the magnitude of the effect from each juice.
- The sponsor did not adequately study the effect of grapefruit juice and apple juice on the PK of FEX as originally recommended by the Agency.
- The data from grapefruit juice and orange juice can not be extrapolated to apple juice, unless the sponsor provides adequate supportive information.
- From OCPB and PK perspective, the studies provided by the sponsor on the effect of juices are considered insufficient to conclude adequate effect on FEX exposure.

2.5.5 Is there *In vitro In Vivo* Correlation (IVIVC) for PSE Dissolution Data?

The sponsor conducted IVIVC analysis for PSE component of Allegra-D 24 for the following reasons:

- To describe the relationship between the *in vitro* dissolution and *in vivo* absorption profiles of PSE from the Allegra-D 24 tablet.
- To assess the internal and external predictability of the *in vivo* behavior of PSE from the extended release tablet.
- To determine the control limits of dissolution specifications for PSE from the extended release tablet.

Based on OCPB comments at the pre-NDA meeting, the sponsor has validated the IVIVC method. IVIVC will be used by the sponsor as a tool to determine *in-vivo* performance from *in-vitro* dissolution. For IVIVC analysis the sponsor used the *in vivo* absorption data from the above described pivotal BE study (#M016455S/1001).

How the IVIVC was Performed?

The sponsor followed the Agency's guidelines to establish the IVIVC. Hence, it is briefly described below (for more detail, please see individual study section).

- This was carried out using *in-vitro* dissolution and *in vivo* absorption data from the test lot used in the pivotal bioequivalence study #1001. This lot used in this stud was the to-be-marketed product manufactured at production scale in the commercial product manufacturing facilities.
- For Level A correlation, a deconvolution method was applied to the PK data followed by comparison of the fraction of drug absorbed *in-vivo* to the fraction of drug dissolved *in-vitro* (i.e., two-stage procedure).
- *In-vitro* dissolution data were fitted to a cumulative Weibull distribution function. The percent of drug released relative to the amount released at infinity was interpolated at each PK sampling time point in study M016455S/1001.
- The *in-vivo* absorption profile of PSE (percent absorbed-time curve) was calculated from the mean plasma concentration-time curve according to Wagner-Nelson method, which assumes a one-compartment model with first order elimination rate. A direct linear (1:1) relationship

was then explored between the *in-vitro* fractional dissolution rate and the in-vivo absorption rate.

What are the Main Findings of IVIVC Analysis?

- There was a linear relationship between the fraction of PSE absorbed and the fraction of drug dissolved with r2 = 0.998 and slope of 0.9873 (**Figure 2.5.5.1**). This is consistent with level A correlation (point-to-point relationship).
- There was excellent relationship between observed *in vitro* dissolution data and model predicted fit (**Figure 2.5.5.2**).
- The average absolute percent prediction error (%PE) for Cmax and AUC(0-∞) was less than 6% when evaluated against internal or external data (**Table 2.5.5.1**).
- Based on these observations the sponsor proposed BE dissolution limits for PSE as shown in **Table 2.5.4.2.**

Figure 2.5.5.1 Fraction of PSE Absorbed Fraction Dissolved

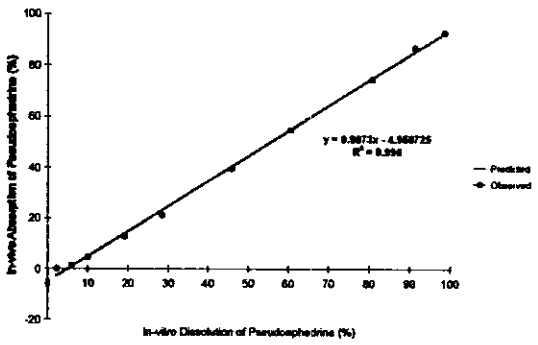


Figure 2.5.5.2 Observed and Model and Predicted Dissolution Profiles

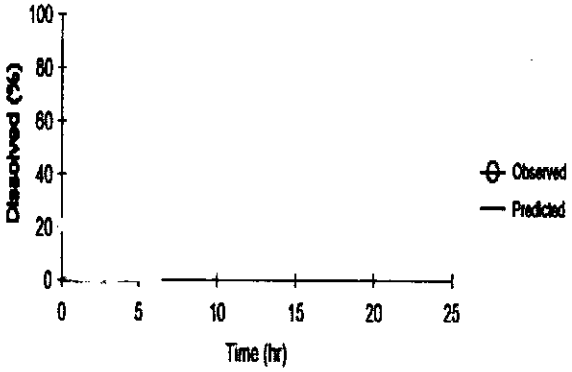


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Table 2.5.5.1 Internal and External Predictability of the IVIVC Model

Parameter	Internal Data (M016455S/1001)	Internal Predictability (%PE)	External Data (M016455S/1002)	External Predictability (%PE)
		C_{max} (ng/mL)		
Geometric LSM	378.4	-0.22%	383.2	1.05%
Arithmetic	393.6	3.65%	393.7	3.68%
Mean Profile	373.6	-1.50%	385.7	1.69%
		$AUC_{(0-\infty)}$ (ng*h/mL)		
Geometric LSM	7826.6	-3.25%	7646.0	-5.69%
Arithmetic	8220.4	1.69%	7855.3	-2.88%
Mean Profile	8191.9	1.35%	7846.0	-3.00%

Prediction Errors (%PE) Calculated for Predicted vs. Observed Parameters
LSM- Least squares mean
Internal predictability evaluated using data from the test lot of study M016455S/1001
External predictability evaluated using data from the fasted arm of study M016455S/1002

Table 2.5.5.2 Proposed BE Dissolution Limits for PSE

TIME (hr)	MINIMUM (%)	MAXIMUM (%)
3	[redacted]	[redacted]
7	[redacted]	[redacted]
23	Not less than [redacted]	

What are the sponsor's Justifications for the Proposed Specification?

- The sponsor provided analysis based on the Agency's guidance with Level A correlation. This type of correlation allows the prediction of the entire time course of the plasma concentration-time profile of PSE.
- The dissolution method was demonstrated to be robust and independent of experimental conditions such as pH, agitation and medium.
- The IVIVC was used was evaluated using internal and external predictability assessments.
- Control limits for dissolution specifications were derived based on the IVIVC model and inter-individual variability information from the pivotal bioequivalence study (#1001).

Conclusions from IVIVC Analysis:

- Based on the submitted data it can be concluded that IVIVC may be used as a surrogate for bioequivalence.
- IVIVC can be used to set the dissolution specifications for PSE proposed formulation in this NDA.
- The dissolution specifications proposed by the sponsor are acceptable.

2.5.6 What are the Specifications for Fexofenadine Component of Allegra-D 24?

The method and specifications for *in vitro* dissolution for fexofenadine were discussed at the pre-NDA meeting held in August 27, 2003. In addition, a detailed description of the dissolution method was submitted in September 26, 2003. The following is a summary of the sponsor's proposed *in vitro* dissolution method and specifications for fexofenadine **(Figure 2.5.6.1 and Table 2.5.6.1)**

USP Apparatus	II (Paddle)
Speed	50 RPM
Volume	900 ml
Media	[ ]
Specification	[ ] at 15 min
	[ ] at 45 min

Figure 2.5.6.1 Mean Fexofenadine Dissolution Profile for Fresh (0) and 12 Months Old to-be-Marketed Tablets (n=6 tablets). (Batch # 1054547/L0002204). (Source: CMC section Page 922)

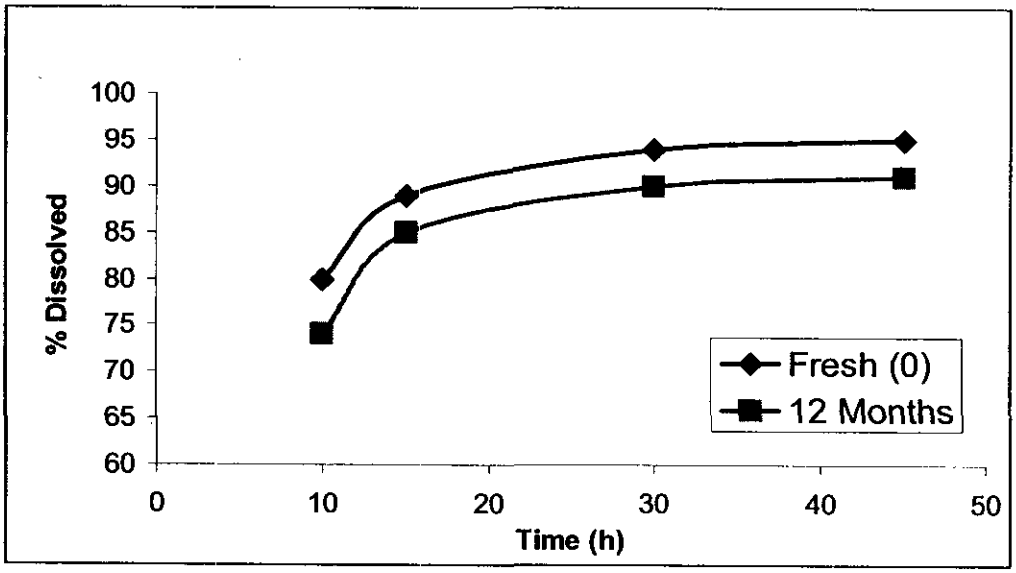


Table 2.5.6.1 Mean (Range) Fexofenadine Dissolution Time Points for to-be-Marketed Tablets At Different Shelf Time Points (n=6 tablets). (Batch # 1054547/L0002204). (Source: CMC section Page 922)

Time (min)	Fresh (0)	6 Months	12 Months
10	80	92	74
15	89	93	85
30	94	93	90
45	95	93	91

It should be noted that there is consistent decrease in % dissolved with shelf life time at all time points (**Figure 2.5.6.1 and Table 2.5.6.1**). No information is available on the dissolution beyond 12 months. Therefore, it is unknown what would be the profiles for 24 months or older tablets. For further detail, please CMC review in reference to stability data.

Conclusion:

Based on the above data, from OCPB perspective, the method and the proposed specifications are acceptable.

2.6 Are there any Analytical issues?

Since the original NDA, no changes have been made to the analytical methodology for the determination of FEX and PSE. In the current submission, no analytical issues have been observed.

For the determination of FEX plasma concentrations, an LC-MS/MS method was used. This method was well validated with a lower limit of quantitation of – ng/mL. In terms of precision, the %CV for inter and intra-batch analysis range from [redacted] For PSE, an [redacted] was used. The assay's lower limit of quantitation was – ng/mL. The inter and intra-batch %CV range from [redacted]

3. Detail Labeling Recommendation

From OCPB perspective, the following statements or similar language should be included in the labels of ALL Fexofenadine containing products. Additional comments will be made directly into the sponsor's proposed label jointly with the Medical Officer's comments. In addition, the sponsor should consider one of the following options for all fexofenadine products:

1. A single label for all fexofenadine containing products and/or
2. Standardize the format and the contents of all fexofenadine products' labels.

At the present time, there are inconsistencies in the format and contents among all fexofenadine labels. The following are edits to OCPB related sections of the proposed Allegra-D 24 hour label (new information is in red and double underlined and deleted information is strikethrough):

[

]

9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4.2 Individual Study Review

4.2.1 Study # M106455S/1001:

This is a pivotal, single and multiple dose (steady-state) BE study in healthy subjects. This was two-way crossover study in approximately 70 subjects. Each subject received the following treatments:

Treatment A (Test): The final to-be-marketed formulation of Allegra-D 24 (fexofenadine 180 mg/pseudoephedrine 240 mg ER) tablet as a single dose followed by once daily dosing for 6 days under fasting conditions.

Treatment B (Reference): Fexofenadine 180 mg IR (Allegra) tablet and 240 mg pseudoephedrine (Sudafed® 24 hour, Warner-Lambert) ER tablet coadministered as a single dose followed by once daily for 6 days.

Subjects received their first (Day 1) and last (Day 9) doses in each treatment period after a 10-hour fast, and all food was withheld for at least 4 hours after dose administration. The drug products used in this study are listed in **Table 4.2.1.1**.

When Blood Samples Were Collected?

Blood samples were collected over 72 hours and 24 hours following a single dose administration and for 48 hours after the last dose on Day 9, respectively (**Table 4.2.1.2**). In addition, trough levels were monitored during the multiple dose phase of the study on Days 4-9. The plasma concentration of each component was determined in this study.

How Safety Was Monitored?

Safety evaluations, including physical examinations, vital signs, ECG, and clinical laboratory tests, were conducted at screening and end of study.

Table 4.2.1.1. Drug Products Administered in Study # 1001

Drug Code:	M016455	M016455	
INN[a]:	fexofenadine HCl	fexofenadine HCl	pseudoephedrine HCl
Treatment:	A	B	B
Formulation:	Extended-release tablet containing fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg	Marketed tablet containing fexofenadine HCl 180 mg (ALLEGRA®)	Marketed tablet containing pseudoephedrine HCl 240 mg (Sudafed® 24 Hour)
Manufacturer:	Aventis	Aventis	Pfizer
Batch/lot number:	PR: B0261	1053229 RR:B0261	0116052

[a] INN: International nonproprietary name

Table 4.2.1.2. Study Schedule

Events	Pre Study	Treatment Periods 1 and 2 [a]						Post Study [b]
Day	-21 to -2	-1 Check-in	1	2	3	4 to 8 [c]	9	10	10 to 13
Subjects in clinic [d]		X	X	X	X		X	X	
Informed consent [e]	X	X							
Urine drug screen	X	X							
Urine pregnancy	X	X							X
Modified physical exam	X								X
ECG/vital signs/clinical labs [f]	X								X
HIV/Hepatitis B & C test	X								
Demographics & medical history	X								
Drug administration [g]			0700			0700 (Daily)	0700		
Pharmacokinetic samples [h]			Predose (0 h) 0730 (0.5h) 0800 (1 h) 0830 [1.5 h] 0900 (2 h) 1000 (3 h) 1100 (4 h) 1300 (6 h) 1500 (8 h) 1900 (12 h) 2300 (16 h)	0700 (24 h) 1900 (36 h)	0700 (48 h)	0700 (Daily)	Predose (0 h) 0730 (0.5 h) 0800 (1 h) 830 (1.5 h) 0900 (2 h) 1000 (3 h) 1100 (4 h) 1300 (6 h) 1500 (8 h) 1900 (12 h) 2300 (16 h)	0700 (24 h)	

Events	Pre Study	Treatment Periods 1 and 2 [a]						Post Study [b]
Day	-21 to -2	-1 Check-in	1	2	3	4 to 8 [c]	9	10	10 to 13
Breakfast		-	-	-	-	-	-	-	
Lunch		-	1200				1200		
Dinner		1800	1800				1800		
Snack		2100	2100				2100		
Adverse events	X	X	X	X	X	X	X	X	X

[a] Period 2 started after an 8-day washout period following the last dose (Day 9) in Period 1.
[b] Completed within 3 days after the last pharmacokinetic sample (Day 10) in Period 2.
[c] Outpatient visits.
[d] On Days 3 and 10 of each Treatment Period, subjects were discharged from the clinic after the morning procedures.
[e] Informed consent obtained at Treatment Period 1 check-in only.
[f] Clinical labs included hematology, serum chemistry, and urinalysis; BP, HR, and respiratory rate done after 5 min supine with oral temperature.
[g] Medication given with 240 mL water (water ad libitum 2 h after dose); subjects remained upright until 4 h after dose. Early morning dose was given under fasting conditions once daily from Day 4 until Day 8.
[h] Predose sample collected within 1 h of dose on Day 1; early morning pharmacokinetic samples were taken every morning prior to dosing from Day 4 until Day 8.

What are the Main Findings from Study # 1001:

- The main data from this study are shown in **Table 4.2.1.3 and Figures 4.2.1.1-4.2.1.6)**
- The 90% CI for Cmax and AUC was within 80% to 125% (**Table 4.2.1.3**)
- The plasma concentration-time profiles for FEX and PSE were very similar following all treatments (**Figures 4.2.1.1-4.2.1.6**).
- From this study it can be concluded that Allegra-D 24 hour is interchangeable with Allegra 180 mg and Sudafed 24 hour 240 mg tablets taken individually.

Table 4.2.1.3 Summary of BE Parameters for FEX and PSE (study # 1001).

	Geometric LS Mean		Treatment Comparisons	
Parameter (units)	Test [a] Trt A	Reference [a] Trt B	Mean Ratio [b] (%)	90% CI
Fexofenadine				
$AUC(0-\infty)_{,1}$ (ng·h/mL)	4052.5	3956.3	102.4	(94.5 – 111.1)
$C_{max,1}$ (ng/mL)	569.4	561.6	101.4	(89.6 – 114.8)
$AUC(0-24)_{,7}$ (ng·h/mL)	3831.0	3725.5	102.8	(94.5 –112.0)
$C_{max,7}$ (ng/ml)	631.3	584.6	108.0	(96.7 –120.7)
$C_{min,7}$ (ng/mL)	15.2	16.4	92.6	(84.3 –101.7)
Pseudoephedrine				
$AUC(0-\infty)_{,1}$ (ng·h/mL)	7988.1	8536.9	93.6	(89.8 – 97.5)
$C_{max,1}$ (ng/mL)	393.7	370.0	106.4	(102.1 – 110.9)
$AUC(0-24)_{,7}$ (ng·h/mL)	8490.0	8930.4	95.1	(90.2 – 100.2)
$C_{max,7}$ (ng/ml)	488.0	472.1	103.4	(97.9 – 109.1)
$C_{min,7}$ (ng/mL)	157.3	162.8	96.6	(86.3 – 108.2)

[a] Test (Trt A) = fexofenadine HCl 180 mg - pseudoephedrine HCl 240 mg extended-release tablet.
Reference (Trt B) = marketed fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg tablets.
[b] Ratio = Geometric LS mean test/ geometric LS mean reference (A/B).

FEX Plasma Concentration-Time profiles Following on Day 1 (Single Dose) and on Day 9 (Multiple Dose)

Figure 4.2.1.1 (Single Dose)

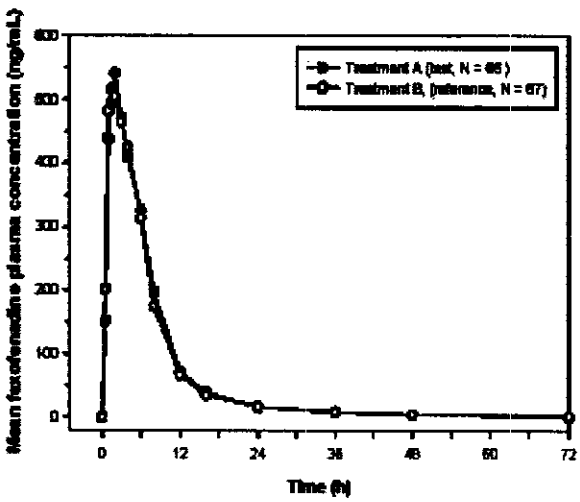
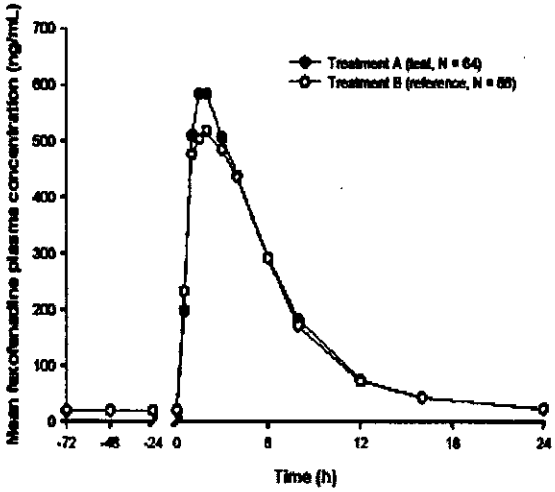


Figure 4.2.1.2 (Multiple Dose)



PSE Plasma Concentration-Time profiles on Day 1 (Single Dose) and on Day 9 (Multiple Dose)

Figure 4.2.1.3 (Single Dose)

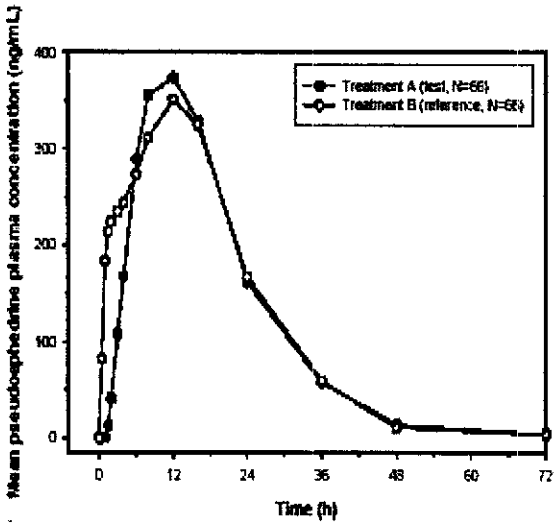
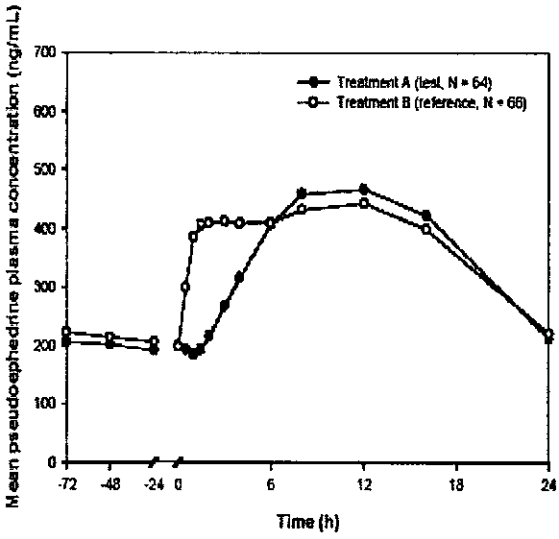


Figure 4.2.1.4 (Multiple Dose)



FEX and PSE Plasma Concentration-Time profiles from Day 1 Through Day 9

Figure 4.2.1.5 FEX

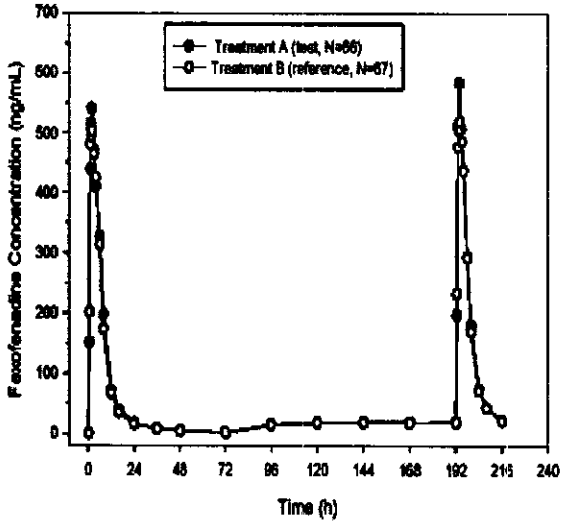
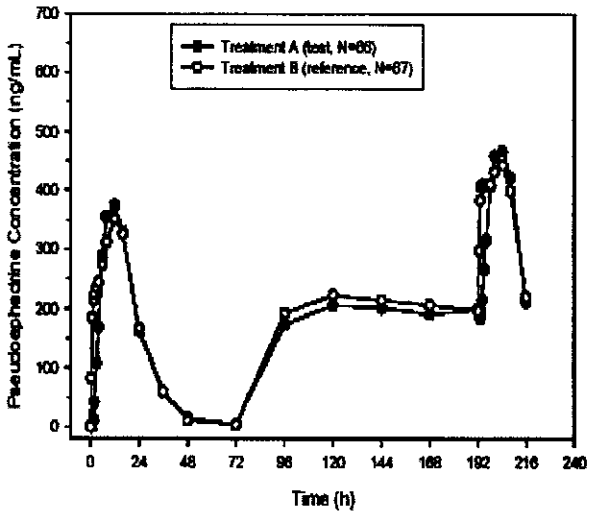


Figure 4.2.1.6 PSE



4.2.2 Study # M106455S/1002:

This was an open label, three-way crossover, three-way treatment, randomized study to assess the effect of food on the PK of Allegra-D 24 in 24 healthy subjects. This was conducted using the final-to-be marketed formulation. All subjects received the following treatments with at least 6 days washout period:

Treatment A: A single dose of Allegra-D 24 under fasting condition (over night fasting)

Treatment B: A single dose of Allegra-D 24 administered 30 minutes after the start of a high fat breakfast and according to the FDA guidance.

Treatment C: A single dose of Allegra-D 24 administered 1.5 hour after the start of a high-fat breakfast.

The food was consumed within 25 minutes after start of meals in each arm of the study. Blood samples were collected over 48 hours post-dose in each treatment period for the determination of FEX and PSE concentrations in plasma. The drug products used in this study and the blood samples collection time points are listed in **Tables 4.2.2.1 and 4.2.2.2.**

Table 4.2.2.1. Drug Products used in this study

Drug Code:	M016455
Treatments:	A, B, C
INN [a]:	fexofenadine HCl
Dosage Form:	fexofenadine HCl 180 mg - pseudoephedrine HCl 240 mg extended-release tablet
Manufacturer:	Aventis Pharma
Lot number:	L0002204

[a] International nonproprietary name

Table 4.2.2.2. Study Schedule

Events	Screening		Treatment Period		End of Study [g]	
	-21 to -2 [a]	Day -1 check in	Day 1	Day 2	Day 2 discharge	
Subjects in clinic		X	X	X	X	X
Informed consent	X	X				
Urine drug screen	X	X				
Pregnancy test [b]	X	X				X
Modified physical exam	X					X
ECG/Vital signs/clinical labs [c]	X					X
HIV/Hepatitis B & C test	X					
Demographics & medical history	X					
Drug administration [d]			0700			
PK samples [e]			0700 (0 h) 0730 (0.5 h) 0800 (1.0 h) 0815 (1.5 h) 0900 (2 h) 1000 (4 h) 1100 (6 h) 1300 (8 h) 1500 (10 h) 1900 (12 h)	0700 (24 h) 1100 (28 h) 1300 (30 h)	0700 (48 h)	
Breakfast			[f]	0830		
Lunch		-	1200	1230		
Dinner		1800	1800	1800		
Snack		2100	2100	2100		
Adverse events		X	X	X	X	X

Notes: Overall schedule was shifted, and the timing of individual subjects was staggered to accommodate clinic schedule requirements.

[a] Prestudy screening conducted no more than 3 weeks (21 days) before study start and completed by Day -1 of Treatment Period 1.

[b] Female subjects of child bearing potential only. Serum pregnancy test performed at screening; urine pregnancy test performed at check-in to each treatment period.

[c] Clinical laboratories performed following a 4 h fast and included hematology, serum chemistry and urinalysis; vital signs included blood pressure, heart rate, respiratory rate, and oral temperature.

[d] All study medication given with 240 mL water; water allowed ad libitum 2 h after dose; subjects remained upright until 4 h after dose.

[e] Predose (0 h) samples were collected up to 1 h before dose on Day 1.

[f] Subjects given Treatment A fasted from 10 h before dose until lunch on Day 1; subjects given Treatment B were given a high-fat breakfast on Day 1 at 0810 (10 min before the dose); subjects given Treatment C were given a high-fat breakfast on Day 1 at 0510 (1.5 h before the dose).

[g] Performed within 3 days of study completion (Day 4 of Treatment Period 1).

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What are the Main Findings from Study # 1002:

- Food reduced the absorption of FEX by approximately 50 % (42% for AUC and 54% for Cmax), regardless of timing of food ingestion as described in this study (**Table 4.2.2.3 and Figure 4.2.2.1**).
- However, food had no effect on PSE component of Allegra-D 24 (**Table 4.2.2.3 and Figure 4.2.2.2**)

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Table 4.2.2.3. Effect of food on FEX and PSE (Treatments: A=fasting, B= 30 min after food, and C: 1.5 h after food) (study # 1002).

	Geometric LS Mean			Treatment Comparisons	
Parameter (units)	Reference Trt A [a]	Test Trt B [a]	Test Trt C [a]	Mean Ratio [b](%)	90% CI
Fexofenadine					
AUC(0-∞) (ng·h/mL)	3930.4	2296.9	2178.2	B/A = 58.4 C/A = 55.4	(51.0 – 66.9) (48.3 – 63.6)
AUC(0-last) (ng·h/mL)	3812.0	2131.9	1995.8	B/A = 55.9 C/A = 52.4	(48.9 – 63.4) (45.8 – 59.9)
Cmax (ng/mL)	625.7	286.8	267.0	B/A = 45.8 C/A = 42.7	(37.9 – 55.4) (35.3 – 51.6)
tmax [c] (h)	2.0	2.5	3.0	-	-
Pseudoephedrine					
AUC(0-∞) (ng·h/mL)	7683.1	6972.0	[d]	B/A = 90.7	(87.8 – 93.8)
AUC(0-last) (ng·h/mL)	7521.0	6768.2	[d]	B/A = 90.0	(87.1 – 93.0)
Cmax (ng/mL)	384.6	351.0	[d]	B/A = 91.2	(86.2 – 96.6)
tmax [c] (h)	8.0	12.0	[d]	-	-

[a] Trt A: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered under fasting conditions.
Trt B: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 30 min after start of a high-fat breakfast.
Trt C: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 1.5 h after start of a high-fat breakfast.
[b] Ratio = Geometric LS mean test/ geometric LS mean reference.
[c] tmax presented as median and range
[d] No data, pseudoephedrine for Trt C was not quantitated.

FEX and PSE Plasma Concentration-Time Profiles (study # 1002)
(Note blood samples for treatment C were not quantified)

Figure 4.2.2.1 (FEX)

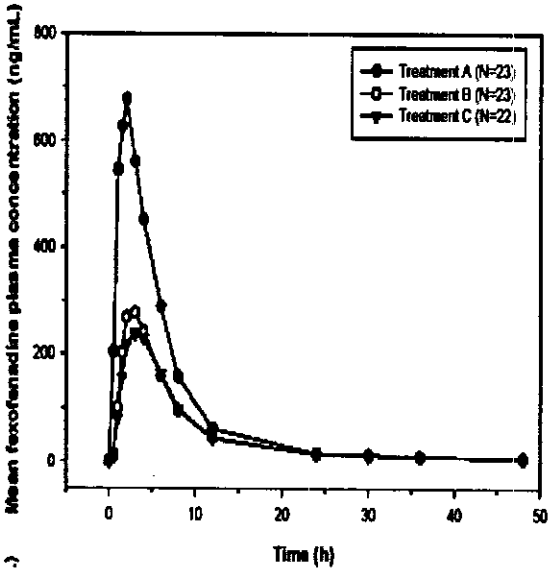
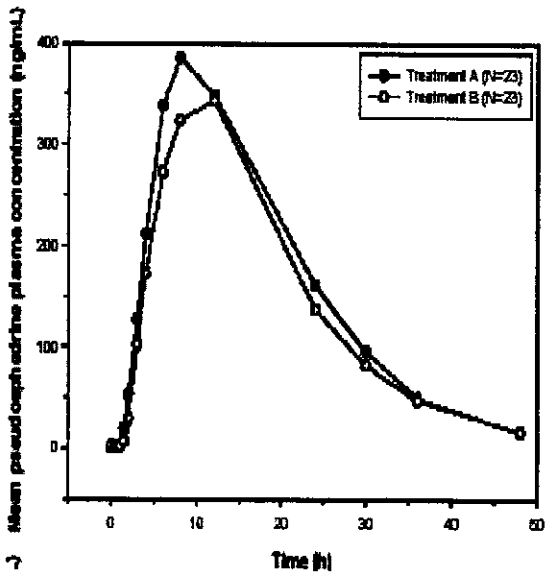


Figure 4.2.2.2 PSE



4.2.3 Study # KA467:

This is a pilot BE/BA study conducted as a single dose two-way crossover in 12 healthy male subjects. In this study a prototype formulation for Allegra-D 24 was used. Subjects received the following treatments with 7 days washout period:

Treatment A (Test): A single dose of Allegra-D 24.

Treatment B (Reference): Fexofenadine 180 mg IR (Allegra) tablet and 240 mg pseudoephedrine (Sudafed® 24 hour, Warner-Lambert) ER tablet co-administered as a single dose.

This study was similar to the single dose arm of the pivotal BE study described above (#M106455S/1001). Therefore, this study will not be extensively reviewed. Blood samples were collected over 96 hours.

What are the Main Findings in Study # KA467?

- The upper limits of the 90% CI for Cmax and AUC of both FEX and PSE were above the BE limits of 125% (**Tables 4.2.3.1 and 4.2.3.2**)
- In terms of the plasma concentration-time profiles, it appears that the FEX levels for the test and reference formulation are comparable (**Figure 4.2.3.1**), whereas for the PSE is consistently higher than the reference (**Figure 4.2.3.2**).

Table 4.2.3.1 Summary of PK Data for FEX (study # KA467)

Parameter	Least-Squares Means [1]		Ratio [2]	Power [3]	90% Confidence Interval [4]	
	Test	Reference			Lower	Upper
AUC 0-t (ng-hr/ml)	3009	2797	1.076	0.58	0.924	1.228
AUCinf (ng-hr/ml)	3056	2834	1.078	0.60	0.930	1.226
Cmax (ng/ml)	488	456	1.070	0.47	0.895	1.245
Tmax (hour)	2.33	2.08	1.120	0.11	-	-
Ke (1/hour)	0.0535	0.0577	0.928	0.35	-	-
T½ (hour)	15.0	12.9	1.166	0.18	-	-
Log-Transformed:						
AUC 0-t (ng-hr/ml)	2891	2635	1.097	0.65	0.938	1.283
AUCinf (ng-hr/ml)	2938	2673	1.099	0.67	0.944	1.280
Cmax (ng/ml)	458	427	1.072	0.51	0.892	1.288

1. Least-squares geometric means for log-transformed data.
2. *Ratio calculated as Test least-squares mean divided by the Reference least-squares mean. None of* the comparisons was detected as statistically significant by ANOVA (α=0.05).
3. Power to detect a difference of 20% of the Reference mean or a ratio of 1.25 (log-transformed results).
4. Confidence interval on the ratio.

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Table 4.2.3.2 Summary of PK Data for PSE (study # KA467)

Parameter	Least-Squares Means [1]		Ratio [2]	Power [3]	90% Confidence Interval [4]	
	Test	Reference			Lower	Upper
AUC 0-t (ng-hr/ml)	6029	5391	1.118	0.72	0.989	1.247
AUCinf (ng-hr/ml)	6359	5570	1.142	0.71	1.011	1.272
Cmax (ng/ml)	267	242	1.101	0.82	0.987	1.215
Tmax (hour)	13.2	13.6	0.969	0.32	-	-
Ke (1/hour)	0.0867	0.0868	0.999	0.61	-	-
T½ (hour)	8.19	8.18	1.002	0.68	-	-
Log-Transformed:						
AUC 0-t (ng-hr/ml)	5823	5143	1.132	0.79	0.992	1.292
AUCinf (ng-hr/ml)	6179	5336	1.158	0.77	1.012	1.325
Cmax (ng/ml)	259	233	1.110	0.97	1.012	1.218

1. Least-squares geometric means for log-transformed data.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean. None of the comparisons was detected as statistically significant by ANOVA (α=0.05).
3. Power to detect a difference of 20% of the Reference mean or a ratio of 1.25 (log-transformed results).
4. Confidence interval on the ratio.

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Figure 4.2.3.1 Mean FEX Plasma Concentration-Time Profile (Study # KA467)

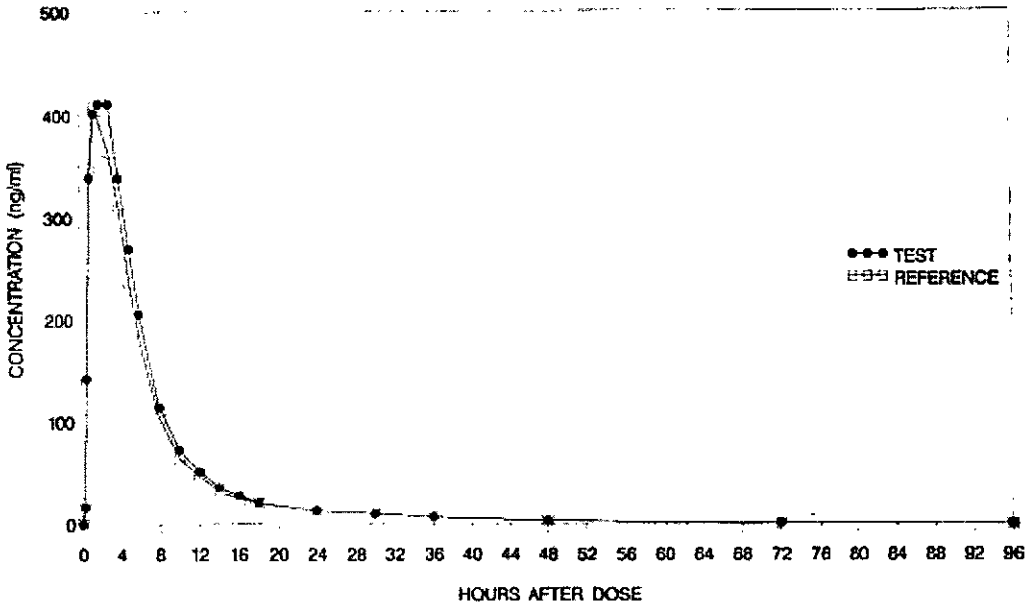
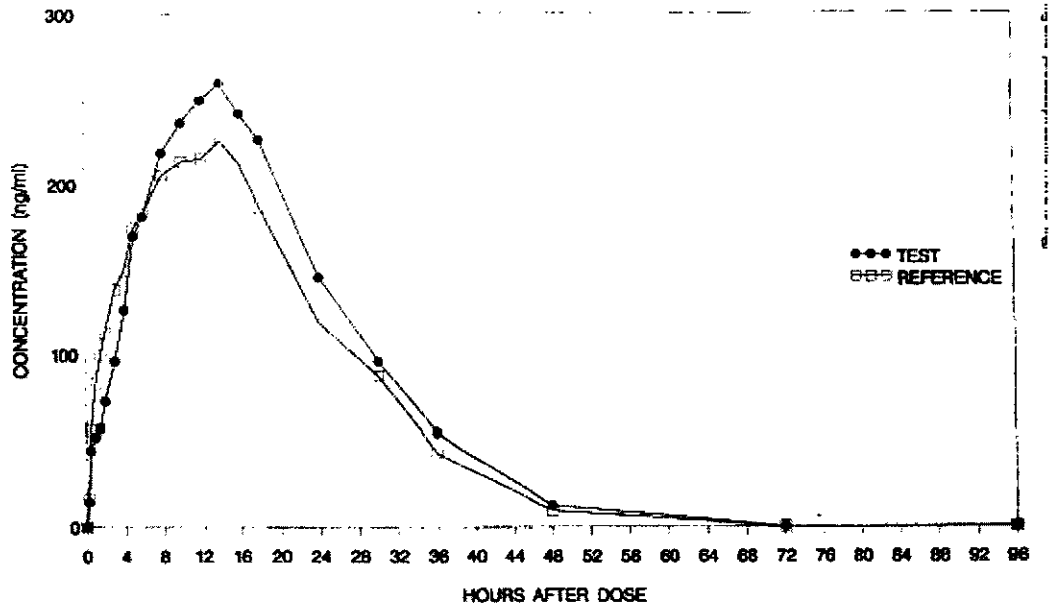


Figure 4.2.3.2 Mean PSE Plasma Concentration-Time Profile (Study # KA467)



4.2.4 *In vitro In Vivo* Correlation (IVIVC) Analysis/Report.

The objectives of the IVIVC analysis were:

- To describe the relationship between the *in vitro* dissolution and in vivo absorption profiles of psedudoephedrine from the Allegra-D 24 tablet.
- To assess the internal and external predictability of the *in vivo* behavior of PSE from the extended release tablet.
- To determine the control limits of dissolution specifications for PSE from the extended release tablet.

Based on OCPB comments at the pre-NDA meeting, the sponsor has validated the IVIVC method. IVIVC was used by the sponsor as a tool to determine *in-vivo* performance from *in-vitro* dissolution. For IVIVC analysis the sponsor used the *in vivo* absorption data from the above described pivotal BE study (#M016455S/1001).

How the IVIVC Was Performed?

The sponsor followed the Agency's guidelines to establish the IVIVC. Hence, it is briefly described below.

- This was carried out using *in-vitro* dissolution and *in vivo* absorption data from the test lot used in the pivotal bioequivalence study #1001. This lot was the to-be-marketed product manufactured at production scale in the commercial product manufacturing facilities.
- For Level A correlation, a deconvolution method was applied to the PK data followed by comparison of the fraction of drug absorbed *in-vivo* to the fraction of drug dissolved *in-vitro* (i.e., two-stage procedure).
- *In-vitro* dissolution data were fitted to a cumulative Weibull distribution function. The percent of drug released relative to the amount released at infinity was interpolated at each PK sampling time point in study M016455S/1001.
- The *in-vivo* absorption profile of PSE (percent absorbed-time curve) was calculated from the mean plasma concentration-time curve according to Wagner-Nelson method, which assumes a one-compartment model with first order elimination rate. A direct linear (1:1) relationship was then explored between the *in-vitro* fractional dissolution rate and the in-vivo absorption rate.
- The internal predictability of the model, calculated as percent prediction error (%PE), was evaluated by comparing the model predicted parameters (Cmax and AUC0-∞) with those from study #1001, which was used to define the IVIVC.
- The external predictability of the model was evaluated by comparing the model predicted parameters with those from an independent test data set that was not used to define the IVIVC. The PK data from the fasted arm of the food effect study #1002, was used for this purpose.
- A simple PK model based on a one-compartment model with the absorption rate calculated using the Weibull function was developed in order to describe the individual and average plasma concentration-time profile of PSE. Dissolution specifications were determined using

an iterative simulation approach based on the premise that the lots exhibiting dissolution profiles at the upper and lower dissolution limits would be bioequivalent (90% CI for treatment ratios within 80.00% to 125.00%) to the reference lot (Sudafed 24 Hour Tablets) used in the pivotal bioequivalence (Study # 1001).

- The rationale for the selection of Sudafed 24 Hour as the reference was based on the fact that it has a similar drug delivery mechanism, [redacted] as the to-be-marketed formulation.

What are the Main Findings of IVIVC Analysis?

- For the tested lot (#1054547), the *in vitro* dissolution data showed almost a complete dissolution (96%) by 23 hours (**Table 4.2.3.1**).
- There was a linear relationship between the fraction of PSE absorbed and the fraction of drug dissolved with r2 = 0.998 and slope of 0.9873 (**Figure 4.2.3.1**). This is consistent with level A correlation (point-to-point relationship).
- The negative y intercept was due to the absorption lag time (1 hour) following oral administration of the extended release tablet. No time scaling factors were necessary.
- The cumulative *in vivo* % absorbed and *in vitro* % dissolved were 92.66% and 96.62% by 24 hours, respectively (**Table 4.2.3.2**).
- There was excellent relationship between observed *in vitro* dissolution data and model predicted fit (**Figure 4.2.3.2**).
- In addition, there was a good relationship between observed *in vivo* plasma concentration-time profiles obtained form study # 1001 and predicted *in vitro* data (**Table 4.2.3.3 and Figure 4.2.3.3**).
- The simulated concentrations for the lower and upper dissolution limits are shown in **Table 4.2.3.4 .** For Cmax, the lower and upper limit is 357 ng/ml for the reference, 325 ng/ml and 422 ng/ml for the test respectively (**Table 4.2.3.5**).
- The average absolute percent prediction error (%PE) for Cmax and AUC(0-∞) was less than 6% when evaluated against internal or external data (**Table 4.2.3.6**).
- Based on these observations the sponsor proposed BE dissolution limits for PSE as shown in **Table 4.2.3.7.**

Table 4.2.3.1. *In vitro* Dissolution Data for Lot # 1054547

	Time (hr)					
Tablet	0.75	3	7	11	15	23
1	[					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						]
12						
Mean	0.2	20.0	52.7	76.3	88.0	96.1
SD	NA	1.8	3.3	3.0	2.0	1.4
Min	[					]
Median	0.0	20.0	53.0	76.5	88.0	96.0
Max	[					]
CV%	NA	9.0	6.3	3.9	2.2	1.4

SD- Standard deviation; Min- Minimum; Max- Maximum; CV% - Coefficient of variation

Figure 4.2.3.1. Fraction of PSE Absorbed and Fraction dissolved

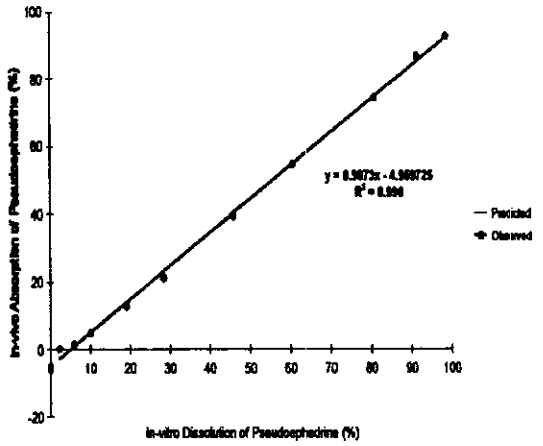


Figure 4.2.3.2. Observed and Model Predicted Dissolution Profiles

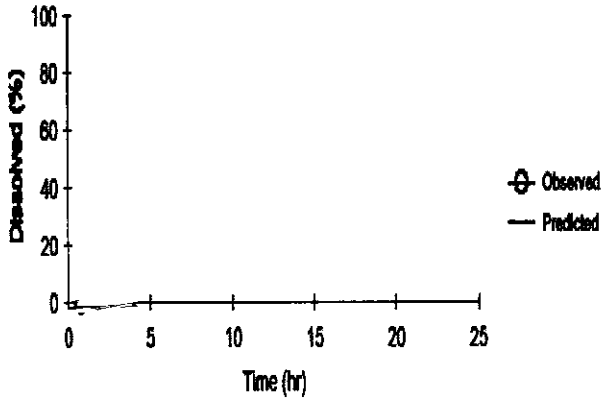


Table 4.2.3.2 Cumulative Absorption *in vivo* and Dissolved Fraction *in vitro*

Time (hr)	In-vivo % Absorbed	In-vitro % Dissolved
0.0	0.00	0.00
0.5	0.00	0.00
1.0	0.03	2.15
1.5	1.42	5.93
2.0	4.62	10.23
3.0	12.75	19.46
4.0	21.04	28.77
6.0	39.61	45.98
8.0	54.57	60.22
12.0	74.44	79.57
16.0	86.82	89.72
24.0	92.66	96.62

- In-vivo data % were obtained from Wagner-Nelson analysis
- In-vitro data % were obtained from fitting dissolution data to Weibull function and the percent of drug released was interpolated at each pharmacokinetic sampling time point in study M016455S/1001

Table 4.2.3.3 Model Predicted and Observed Plasma Concentrations from Study # 1001

Time (hr)	Concentration ± S.D. (ng/mL)	
	Observed	Predicted
0.0	0.0 ± 0.0	0.0 ± 0.0
0.5	0.0 ± 0.0	0.0 ± 0.0
1.0	0.3 ± 1.4	0.8 ± 2.3
1.5	12.8 ± 9.3	10.9 ± 11.1
2.0	40.8 ± 19.5	36.3 ± 20.3
3.0	107.5 ± 36.9	103.9 ± 34.1
4.0	168.5 ± 48.4	173.5 ± 46.5
6.0	288.4 ± 69.1	286.9 ± 71.1
8.0	354.1 ± 93.8	355.3 ± 88.8
12.0	373.6 ± 108.8	379.2 ± 101.1
16.0	329.4 ± 105.0	320.4 ± 95.1
24.0	161.8 ± 65.2	168.9 ± 68.7
36.0	57.9 ± 35.3	50.5 ± 34.5
48.0	14.4 ± 14.5	15.1 ± 15.6
72.0	4.5 ± 10.4	1.7 ± 2.9

Observed data obtained from averaging the individual data in study M016455S/1001
Predicted data obtained from averaging the model predictions from individual fits

Figure 4.2.3.3. PK Fit of the Predicated and Observed Data From Study # 1001

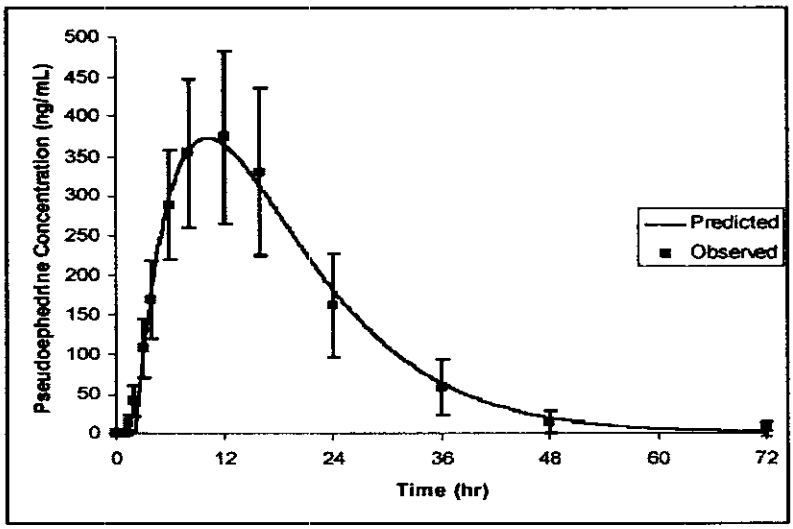


Table 4.2.3.4 Simulated Concentrations for the Lower and Upper Dissolution Limits

Time (hr)	Concentration (ng/mL) Mean ± SD	
	Lower (n=66)	Upper (n=66)
0	0.0 ± 0.0	0.0 ± 0.0
0.5	0.0 ± 0.0	0.0 ± 0.0
1	0.3 ± 1.4	1.2 ± 2.8
1.5	6.1 ± 7.2	22.9 ± 16.2
2	18.3 ± 12.7	68.4 ± 31.4
3	51.1 ± 22.5	166.0 ± 52.4
4	84.4 ± 30.0	243.9 ± 64.9
6	180.5 ± 45.0	370.1 ± 88.3
8	251.6 ± 69.6	419.7 ± 110.5
12	316.3 ± 91.4	393.6 ± 116.9
16	313.7 ± 94.7	322.0 ± 108.2
24	171.0 ± 62.1	145.9 ± 64.4
36	61.2 ± 35.3	52.3 ± 33.7
48	15.1 ± 14.5	13.1 ± 13.6
72	4.6 ± 10.4	4.5 ± 10.3

Individual plasma concentration-time profiles were simulated using the IVIVC model; individual residuals were obtained from individual compartmental analysis of the test lot used in the pivotal bioequivalence study, M016455S/1001.

Table 4.2.3.5 PSE PK Parameters Based on Simulated Lower and Upper Dissolution Profiles

Parameter	Units	Reference	Test	Ratio	90% Confidence Interval
			Lower Limit		
C_{max}	ng/mL	357.3	325.3	91.05	87.15 - 95.12
AUC_{0-t}	ng*h/mL	8068.8	6895.3	85.46	81.66 - 89.43
$AUC_{0-\infty}$	ng*h/mL	8253.1	6971.3	84.47	80.68 - 88.44
			Upper Limit		
C_{max}	ng/mL	357.3	422.0	118.11	113.27 - 123.14
AUC_{0-t}	ng*h/mL	8068.8	7976.9	98.86	94.46 - 103.47
$AUC_{0-\infty}$	ng*h/mL	8253.1	8158.3	98.85	94.44 - 103.46

Table 4.2.3.6 Internal and External Predictability of the IVIVC Model

Parameter	Internal Data (M016455S/1001)	Internal Predictability (%PE)	External Data (M016455S/1002)	External Predictability (%PE)
		C_{max} (ng/mL)		
Geometric LSM	378.4	-0.22%	383.2	1.05%
Arithmetic	393.6	3.65%	393.7	3.68%
Mean Profile	373.6	-1.50%	385.7	1.69%
		$AUC_{(0-\infty)}$ (ng*h/mL)		
Geometric LSM	7826.6	-3.25%	7646.0	-5.69%
Arithmetic	8220.4	1.69%	7855.3	-2.88%
Mean Profile	8191.9	1.35%	7846.0	-3.00%

Prediction Errors (%PE) Calculated for Predicted vs. Observed Parameters
LSM- Least squares mean
Internal predictability evaluated using data from the test lot of study M016455S/1001
External predictability evaluated using data from the fasted arm of study M016455S/1002

Table 4.2.3.7 Proposed BE Dissolution Limits for PSE

TIME (hr)	MINIMUM (%)	MAXIMUM (%)
3	[	]
7	[	]
23	Not less than [	]

Appears This Way
On Original

Conclusions from IVIVC Analysis:

- Based on the submitted data it can be concluded that IVIVC may be used be used as a surrogate for bioequivalence.
- IVIVC can be used to set the dissolution specifications for PSE proposed formulation in this NDA.
- The dissolution specifications proposed by the sponsor are acceptable.

4.2.5 Clinical Reports:

4.2.5.1 Effect of Grapefruit and Orange Juice

In July 19, 2004, the sponsor submitted additional studies related to the effect of grapefruit juice and apple juice on the PK of FEX (**Table 2.7.3.1**). These studies were originally requested from the sponsor at the End of Phase II meeting held in January 29, 2002. Therefore, the sponsor was reminded after the 45 Day filing meeting with a letter dated March 2, 2004. As shown in **Table 2.7.3**, the sponsor submitted studies to evaluate the effect grapefruit juice and orange juice on the phamacodynamic-PD (as measured via skin whale and flare) rather than exposure as measure by the classical PK parameters (Cmax or AUC). Also the sponsor did not provide information on the effect of apple juice, but rather used orange juice instead.

Table 4.2.5.1.1 List of Studies Submitted in July 19, 2004 fort the Effect of Juice of the PK of FEX

Study #	Design	Monitored Parameters
4141	•Single dose, crossover PD study •Grapefruit juice vs water •N=20 healthy subjects	•Skin wheal and flare •No PK samples
4143	•Double-blind, single dose, crossover PD study, placebo controlled •Grapefruit juice vs water •N=23 healthy subjects	•Skin wheal and flare •Sparse blood samples for Pop PK
4144	•Double-blind, single dose, crossover PD study, placebo controlled •Orange juice vs placebo •N=34 healthy subjects	•Skin wheal and flare •Sparse blood samples for
Pop PK	Analysis of spares PK samples	
Literature	Review of relevant literature	

4.2.5.1.1 Study # 4141

What is the Main Objective?

The primary objective of the study was to investigate if there was an effect of grapefruit juice on FEX inhibition of induced wheals and flares.

What is the Study Design?

This was a randomized, open-label, single-dose, single-center, crossover study in 20 healthy volunteers. There were two treatments with a washout period of 7 days as follows:

Treatment Group	Period 1	Washout	Period 2
A	Fexofenadine 180 mg with 8 oz. of water	→	Fexofenadine 180 mg with 8 oz. of grapefruit juice
B	Fexofenadine 180 mg with 8 oz. of grapefruit juice	→	Fexofenadine 180 mg with 8 oz. of water

How Histamine Induced Wheals and Flares Test Was Performed?

- Epicutaneous tests were performed with 10 mg/mL histamine phosphate administered by the prick test method.
- The tests for wheal and flare were performed at 1, 1.5, 2, 3, 4, and 8 hours after dosing.
- A different site on the volar surfaces of the forearm was used for each test, with the sequence of sites being the same for each subject.
- Wheal and flare areas were measured using a tape applied to the skin surface over the affected area on which a tracing was made. Each tape was removed and applied to a clear, solid plastic surface for analysis. After being scanned into the computer, each traced wheal and flare area was analyzed by computer software designed for these analyses.

What Parameters were Monitored?

- No PK samples were collected in this study.
- Skin wheal and flare measurements were performed.

How the Data was Analyzed?

The area under the percent suppression and time curve (AUEC 0-8) was analyzed by analysis of variance (ANOVA). Data were log transformed before analysis to support the maintenance of a normal distribution. Treatments were considered equivalent if geometric mean ratios of FEX with grapefruit juice/FEX alone fell within 80% to 120%.

What are the Main Findings from Study 4141?

- It appears that grapefruit juice increases the wheal and flare areas when administered with FEX (**Figures 4.2.5.1.1.1 and 4.2.5.1.1.2 and Table 4.2.5.1.1.1**).
- Thus, grapefruit juice may increases the histamine release and therefore reduces the effect of FEX.
- The geometric mean area under the effect curve (AUEC) for wheal was 0.988 cm2 with administration of grapefruit juice and 0.687 cm2 without grapefruit juice (**Table 4.2.5.1.1.1**).
- Wheal areas were significantly larger after the administration of grapefruit juice ($p = 0.046$).
- A total of 12/20 (60%) of subjects with coadministration of grapefruit juice and 14/20 (70%) with no grapefruit juice reached total suppression for wheal, defined as 95% suppression compared with baseline. For both wheal and flare, predose areas were used as baseline values.
- Mean time to total suppression of wheal for subjects receiving grapefruit juice was 3.75 hours compared with 2.46 hours for those who did not receive grapefruit juice.
- Mean time to suppression for flare was 3.8 hours for subjects who received grapefruit juice and 3.04 hours for those who did not.
- There is a wide variability in the data (**Figures 4.2.5.1.1.1 and 4.2.5.1.1.2**).

Mean (SD) Wheal and Flare Areas as a Percentage of Baseline Value (n=20) (Study # 4141)

Figure 4.2.5.1.1.1 (Wheal)

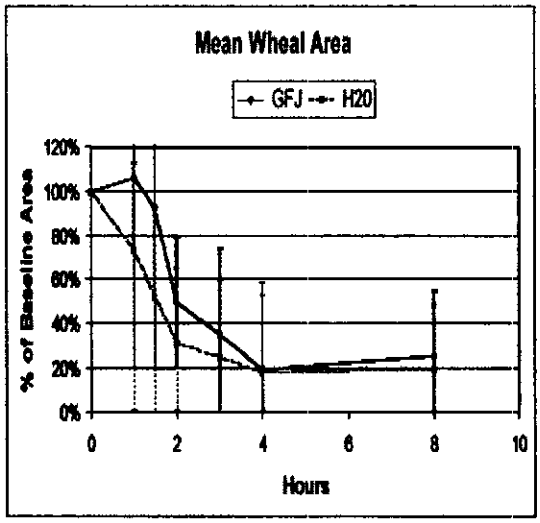


Figure 4.2.5.1.1.2 (Flare)

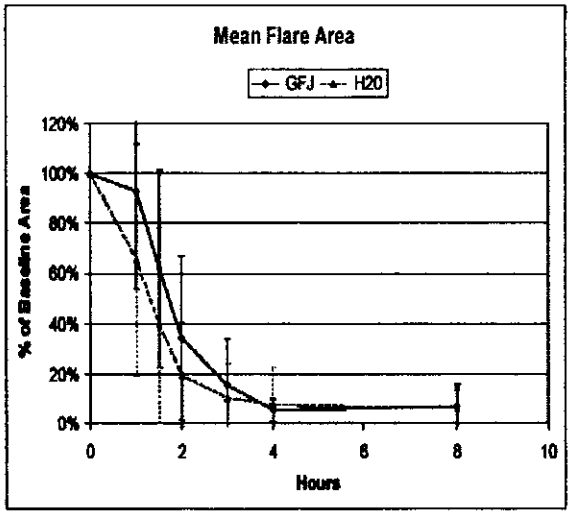


Table 4.2.5.1.1.1 Comparison of AUEC Following FEX With Grapefruit Juice or Water (Study # 4141)

Variable	Geometric Mean Area				
	Grapefruit Juice (cm^2)	H20 (cm^2)	GMR	95% Confidence Interval	P value
Flare	13.954	11.710	1.19	0.77-1.85	0.421
Wheal	0.988	0.687	1.44	1.01- 2.05	0.046

Conclusions from Study #4141:

- It appears that grapefruit juice increases the wheal and flare areas when administered with FEX.
- Thus, grapefruit juice may increases the histamine release and therefore reduces the effect of FEX.

Reviewers Comments on Study # 4141:

- From the OCPB point of view, this study was irrelevant to the original request that was made at the End-of-Phase 2 meeting.
- See also the overall comments at the end of this section related to the effect of grapefruit juice series of studies.

4.2.5.1.2 Study # 4143

What is the Main Objective?

The primary objective of the study was to compare the effect of a single dose of FEX 180 mg plus grapefruit juice versus placebo plus grapefruit juice on the change from baseline (pre-dose) in histamine skin wheals and flares at 20, 40, and 60 minutes post-dose; then hourly through the first 12 hours post-dose; and 23 and 24 hours post-dose.

What is the Study Design?

This was a randomized, single-dose, single-center, crossover, placebo controlled study in 34 healthy volunteers. The procedures for the determination of skin tests for wheals and flares are the similar to that described in the above study (#4141). There were two treatments with a washout period of 14 days as follows.

Treatment A: FEX 180 mg tablet with 8 oz regular strength grapefruit juice
Treatment B: Placebo tablet (matching FEX) with 8 oz regular strength grapefruit juice

What Parameters were Monitored?

- Skin wheal and flare measurements were performed at pre-dose, 20 min, 40 min, 60 min, and hourly through 12 hours with an additional 2 time points obtained at Hours 23 and 24.
- 4 plasma samples per subjects were collected for Pop PK analysis at the following time points:
    - One sample between 0.5 and 6 hours post-dose during Visit 2.
    - One sample at 22-24 hours post-dose on Visit 3
    - One sample between 0.5 and 6 hours post-dose during Visit 4
    - One sample at 22-24 hours post-dose on Visit 5

What are the Main Findings from Study 4143?

- FEX plus grapefruit juice had significantly greater suppression of histamine induced wheals and flares than placebo plus grapefruit juice at almost all time points.
- Pop PK analysis will be discussed in a separate section below (**see section 4.2.5.1.4**)

Conclusions from Study #4143:

FEX with grapefruit juice suppress wheals and flares in a greater extent than placebo with grapefruit juice.

4.2.5.1.3 Study # 4144

This is almost a duplicate study as that of study # 4143.

The objective and design of this study was exactly the same as the above study # 4143, except that orange juice was administered with FEX or its match placebo tablet, instead of grapefruit juice. The number of subjects was also the same (i.e., 34). Efficacy end points (wheals and flares) and PK spares sampling time points were also the same as study # 4143. The main results and conclusions are of similar trend as that of study #4143.

Reviewers Comments on Study # 4144:

- The observed effects are due to FEX alone rather than grapefruit juice or orange juice.
- Specifically for this study and the previous study # 4143, the sponsor did not adequately test the effect of juices on the formation of wheals and flares.
- The bottom line is that, in these studies, the sponsor tested the effect of FEX on the suppression of wheals and flares compared to placebo. Therefore, the addition of juices was of little value in these studies, unless the sponsor included a third arm with water as a comparator for the juices.

4.2.5.1.4 Pop PK Report

What Was the Objective?

The main objective of this analysis is to obtain an estimate of the change in FEX exposure when concurrently administered with grapefruit and orange juice.

How the Analysis were Performed?

This is a meta-analysis to estimate the effect of fruit juice on FEX exposure. This analysis was based on the data from the above two clinical studies (# 4143 and 4144). The data from the BE study # 1001 were included in the pooled analysis as control dataset to provide PK information in a similar population given concurrently with water.

It is important to note that the Pop PK analysis was performed on a combined juice dataset without regard to type of juice used in the individual study. The reason for this approach is that the sample size is too small in each study as well as the data was comparable following both juices. There were a total of 112 subjects in this analysis with 1194 concentration observations.

What are the Main Findings from the Pop PK Analysis?

- The individual observed plasma concentration-time data points from the three clinical studies are shown in **Figure 4.2.5.1.4.1.**
- Overall, the relative bioavailability of FEX was reduced by a mean of 36% in the presence of grapefruit or orange juice (**Table 4.2.5.1.4.1**).
- FEX apparent clearance appears to be higher following grapefruit juice (56%) and orange juice (72%) compared to water (50%) (**Table 4.2.5.1.4.2 and Figure 4.2.5.1.4.2**).
- The sponsor believes that the differences observed in exposure may be due to inter-study factors other than juice since data were not available on test and reference treatments within a single study, or within each individual.

Figure 4.2.5.1.4.1. Individual Observed Plasma of FEX Concentration-time Points

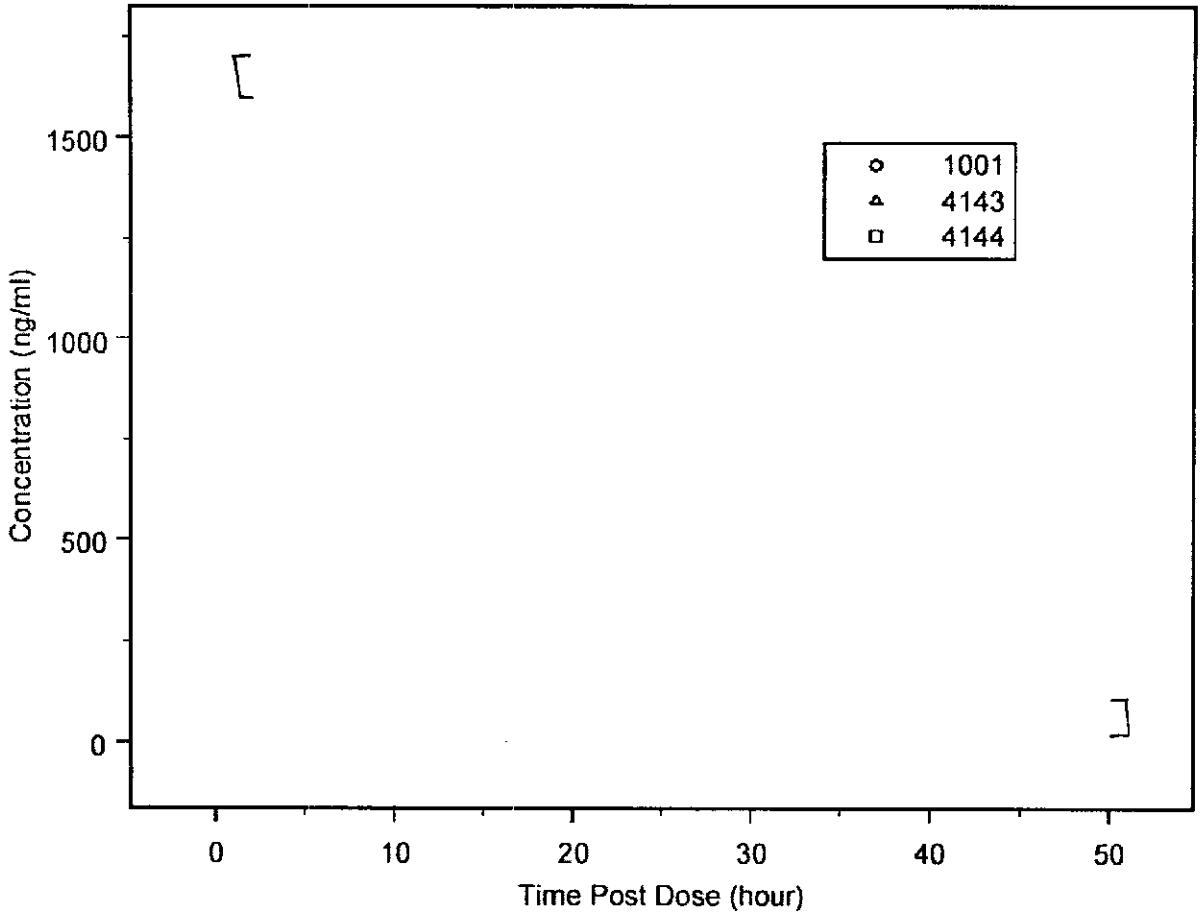


Table 4.2.5.1.4.1. Pop PK Parameters

Summary of Fexofenadine NONMEM Population Parameter Estimates		
Parameter	**Estimate**	**95% Confidence Interval**
Apparent Clearance without juice effect (L/h)	47.4	(43.15, 51.65)
Apparent Volume of Distribution (L)	156	(134.64, 177.36)
Inter-compartmental Clearance (L/h)	11.2	(9.72, 12.68)
Peripheral Compartment Volume (L)	164	(137.74, 190.26)
Absorption Rate Constant (per h)	0.5 FIXED	.
Inter-Subject Variance on CL (ω^2)	0.084	
Residual Variance on CL (σ^2)	0.083	
Relative bioavailability (juice effect)	0.64	(0.52, 0.76)
Notes: 1. 95% confidence intervals calculated using the asymptotic approximation, Estimate ± 1.96 * SE(Estimate). 2. Population parameter estimates reported from the control stream, run three4a.con, which includes F1, relative bioavailability due to the effect of juice. 3. The absorption rate constant (Ka) was fixed at a value of 0.5 based on the results of a previous analysis. This was because a sparse sampling scheme was used in protocols M016455A/4143 and M016455A/4144, which did not allow for adequate characterization of the absorption phase in these studies.		
Supporting Data: Table 7		

Figure 4.2.5.1.4.2. Pooled Clearance estimate by treatment (Studies # 1001 with water, 4143 with grapefruit juice and 4144 with orange juice)

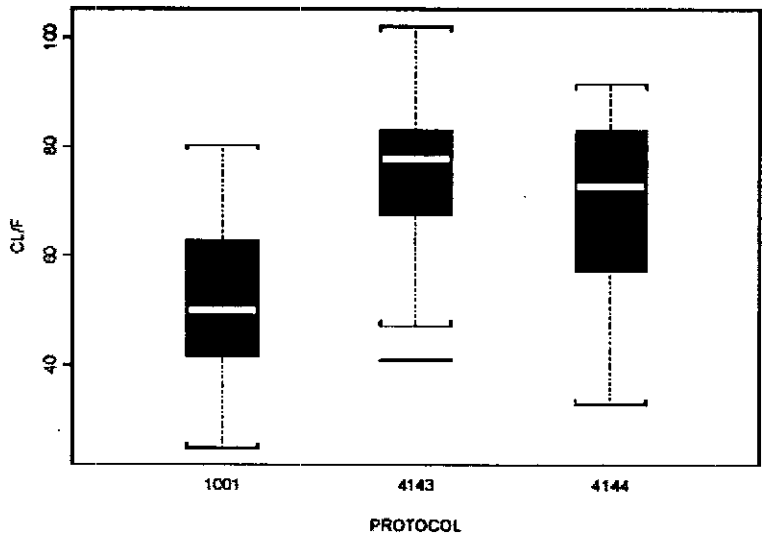


Figure 4.2.5.1.4.2. Mean Apparent Clearance from Individual Studies

Clpo (L/h)	Protocol M016455S/1001 (No juice)	Protocol M016455A/4143 (Grapefruit juice)	Protocol M016455A/4144 (Orange juice)
N	68	23	21
Mean	50.34	75.69	71.55
SD	13.84	15.48	14.74
Min	24.74	41.07	32.96
Median	49.40	77.91	72.74
Max	80.36	102.16	91.68
CV%	27.50	20.50	20.60
95% CI Lower Mean	46.99	68.99	64.84
95% CI Upper Mean	53.69	82.39	78.26

Overall Conclusions and Comments on all Effect of Juices Studies.

- Based on three studies, it appears that grapefruit juice and organ juice reduce the effect of FEX.
- Both grapefruit juice and orange juice appears to have comparable effects.
- Based on Pop PK analysis, the exposure to FEX appears to be reduced by approximately 36% with both grapefruit juice and orange juice.
- The sponsor did not adequately study the effect of grapefruit juice and apple juice on the PK of FEX as originally recommended by the Agency.
- The data from grapefruit juice and orange juice can not be extrapolated to apple juice, unless the sponsor provides adequate supportive information.

- From OCPB and PK perspective, the studies provided by the sponsor on the effect of juices are considered insufficient to conclude adequate effect on FEX exposure.

4.2.5.2. Crossed Referenced Studies

- Study# M106455B/3081: This study was completed as part of the previous NDA 20-872 to support the approval of FEX 180 mg QD. It was a double blind, randomized, placebo controlled, parallel group study comparing the efficacy and safety of FEX 120 mg and 180 mg QD in the treatment of allergic rhinitis.
- The sponsor also included summaries of relevant studies previously submitted under NDAs # 20-625, 20-972, and 20-786.
- Long term safety from the previously submitted clinical study # PJPR0027.

For these studies, please medical Officer's review

4.3 Consult Review (Pharmacometric Consult)

No pharmacometric consult is applicable to this NDA.

4.4

Filing Memo

Clinical Pharmacology and Biopharmaceutics Filing Memo

NDAs: 21-704	**Date of Submission:** December 19, 2003
Generic Name	Fexofenadine HCl (180 mg) and Pesudoephedrine HCl 240
Brand Name:	**Allegra-D 24®**
Formulations:	Extended-Release Tablets
Route of Administration:	Oral
Indication:	Seasonal Allergic Rhinitis and Nasal Congestion
Type of Submission:	NDA
Sponsor:	Aventis Pharmaceuticals
Type of Submission:	New Formulation
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.
Date of Submission:	December 19, 2003
Date Received:	January 12, 2004
Review Date:	January 21, 2004
First Draft	January 22, 2004
Second Draft	January 23, 2004
DFS Draft:	February 4, 2004

Backround:

This NDA is for a new combination product containing immediate release fexofenadine HCl 180 mg and extended release pseudophedrine (PSE) HCl 240 mg for once daily use (Allegra-D 24®).

Originally, fexofenadine was approved for seasonal allergic rhinitis in the US at a dose of 60 mg BID in July 25, 1996 (NDA # 20-625) and subsequently on February 25, 2000 was approved for the same indication at a dose of 180 mg QD, three times the previously approved dose (NDA# 20-872). In addition, the a fixed dose combination of fexofenadine 60 mg and pseudoephedrine 120 mg BID product was approved on December 24, 1997 as Allegra-D extended release tablet for the same indication (NDA #20-786). Therefore, this NDA can be considered as an extension of the currently marketed Allegra-D fixed dose combination tablet. There are three main differences between the two products:

a) Allegra-D approved for twice daily administration, whereas Allegra-D 24 is proposed for once daily administration.

b) The total dose in the new product for each component (180 mg/240 mg) is 2-3 times higher than the currently approved dose for Allegra-D (60 mg/120 mg).

c) The formulation technology is different in each product. For Allegra-D 24 pseudoephedrine component is slowly released from the tablet [ ] while immediate release [ ] technology is used for the release of fexofenadine from the tablet [ ] (see details below). This release technology was not used in the development of the currently approved Allegra-D formulation.

What is the new Formulation?

The formulation consists of [

]

Figure 1. Schematic Illustration of the New Allegra-D 24® Tablet

Appears This Way On Original

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

What is the Mechanism of Drug Release?

The core tablet includes the active ingredient PSE HCl, USP . [

]

What is the Indication?

Allegra-D is an antihistamine/decongestant for the relieve of seasonal allergic rhinitis (SAR) .[ ]in adult and children >12 years of age. The sponsor is seeking approval of Allegra-D 24 — for the same indication as for Allegra-D (BID).

What is the Historical Background of the NDA?

A. End-of-Phase II Meeting:

An End of Phase II meeting was held with the sponsor on January 29, 2002 (IND# 48,486). From the clinical pharmacology perspective, the following main comments were conveyed to the sponsor at that meeting:

- The inclusion of female subjects in the proposed studies (the sponsor proposed exclusion of females).
- The sponsor was advised to use the final to-be-marketed formulation in the proposed studies, otherwise a link would be necessary.
- Collecting blood samples for the determination of C_{min}.
- Monitoring appropriate safety endpoints.
- Optimizing the dissolution method with specifications for each component.
- The sponsor was advised to conduct the BE study following a single and multiple doses and the food effect study after a single dose.
- The 90% CI for Cmax in the effect of food study should be set to 80%-125%.
- It was recommended to the sponsor to study the effect of grapefruit juice and apple juice on the bioavailability of fexofenadine.
- The sponsor was advised to open a new IND for Allegra-D 24. This is because the drug release technology in the new formulation is different from that of the currently approved Allegra-D. Therefore, in early 2003, the sponsor opened a new IND with a pivotal bioequivalence study (#66,289, N000)

B. Pre-NDA Meeting

The Pre-NDA meeting was held with the sponsor on August 27, 2003. From OCPB perspective, here are the main comments:

- In addition to other PK parameters listed in the proposed format, the sponsor was requested to also include Tmax and T ½ for each component following a single dose and at steady state (C_{av}), and degree of fluctuation (C_{max}--C_{min} /C_{av}) for each component.
- IVIVC should be validated before it can be used to set dissolution specifications.

What Studies Are Submitted in the Current NDA:

A. PK Studies:

No new efficacy or safety studies have been conducted with Allegra-D 24 formulation. However, the sponsor submitted three main PK studies and IVIVC analysis. These studies are briefly described below:

1) Study # M106455S/1001:

This is a pivotal, single and multiple dose (steady-state) BE study in healthy subjects. This was two-way crossover study in approximately 70 subjects. Each subject received the following treatments:

Treatment A (Test): The final to-be-marketed formulation of Allegra-D 24 (fexofenadine 180 mg/pseudoephedrine 240 mg ER) tablet as a single dose followed by once daily dosing for 6 days under fasting conditions.

Treatment B (Reference): Fexofenadine 180 mg IR (Allegra) tablet and 240 mg pseudoephedrine (Sudafed® 24 hour, Warner-Lambert) ER tablet coadministered as a single dose followed by once daily for 6 days.

Blood samples were collected over 72 hours and 24 hours following a single dose administration and after the last dose on day 9, respectively. In addition, trough levels were monitored during the multiple dose phase of the study on Days 4-9. The plasma concentration of each component was determined in this study.

2) Study # M106455S/1002:

This is an open label, three-way crossover, three-way treatment, randomized study to assess the effect of food on the PK of Allegra-D 24 in 24 healthy subjects. This was conducted using the final-to-be marketed formulation. All subjects received the following treatments with at least 6 days washout period:

Treatment A: A single dose of Allegra-D 24 under fasting condition.

Treatment B: A single dose of Allegra-D 24 administered under standard conditions for food effect evaluation according to the FDA guidance.

Treatment C: A single dose of Allegra-D 24 administered 1 hour after a high-fat breakfast.

3) Study # KA467:

This is a pilot BE/BA study conducted as a single dose two-way crossover in 12 healthy male subjects. In this study a prototype formulation for Allegra-D 24 was used. Subjects received the following treatments with 7 days washout period:

Treatment A (Test): A single dose of Allegra-D 24.

Treatment B (Reference): Fexofenadine 180 mg IR (Allegra) tablet and 240 mg pseudoephedrine (Sudafed® 24 hour, Warner-Lambert) ER tablet coadministered as a single dose.

This study is similar to the single dose arm of the pivotal BE study described above (#M106455S/1001). Therefore, this study will not be extensively reviewed.

3) IVIVC analysis/report.

The objectives of the IVIVC analysis were:

- To describe the relationship between the *in vitro* dissolution and in vivo absorption profiles of psedudoephedrine from the Allegra-D 24 tablet.
- To assess the internal and external predictability of the *in vivo* behavior of pseudoephedrine from the extended release tablet.
- To determine the control limits of dissolution specifications for pseudoephedrine from the extended release tablet.

Based on OCPB comments at the pre-NDA meeting, the sponsor has validated the IVIVC method. IVIVC will be used by the sponsor as a tool to determine *in-vivo* performance from *in-vitro* dissolution. For IVIVC analysis the sponsor used the *in vivo* absorption data from the above described pivotal BE study (#M016455S/1001).

B. Clinical Reports:

- Study# M106455B/3081: This study was completed as part of the previous NDA 20-872 to support the approval of fexofenadine 180 mg QD. It was a double blind, randomized, placebo controlled, parallel group study comparing the efficacy and safety of fexofenadine 120 mg and 180 mg QD in the treatment of allergic rhinitis.
- The sponsor also included summaries of relevant studies previously submitted under NDAs # 20-625, 20-972, and 20-786.
- Long term safety from the previously submitted clinical study # PJPR0027.

General Comments:

- The sponsor submitted all the information requested at the End-of-Phase II meeting and the Pre-NDA meeting, except the effect of grapefruit juice and apple juice on the BA of both components. Therefore, the sponsor should be contacted as early as possible during the review cycle to check on the status of the effect grapefruit juice and apple juice studies.

RECOMMENDATION:

The NDA is fileable. See also the attached filing form.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaulation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-704	Brand Name	Allegra-D 24
OCPB Division I	HFD-870	Generic Name	Fexofenadine190mg/Pseudoephedrine 240mg
Medical Division	HFD-570	Drug Class	Antihistamine/ decongestant
OCPB Reviewer	Sayed (Sam) Al Habet, R.Ph., Ph.D.	Indication(s)	Allergic rhinitis
OCPB Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.	Dosage Form	Extended release tablet
		Dosing Regimen	Once daily
Date of Submission	December 19, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review	June 30, 2004	Sponsor	Aventis Pharmaceuticals
PDUFA Due Date	October 19, 2004	Priority Classification	S
Division Due Date	September 19, 2004		

Clin. Pharm. and Biopharm. Information

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

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:				
(IVIVC):	X	1		
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
	6			

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**Yes**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included) FDA letter date if applicable.
QBR questions (key issues to be considered)	**This is an extension of the previously approved drug components with different formulation technology and 2-3 times the strength of each component.**	
Other comments or information not included above	**The sponsor may need to be contacted to check on the status of the effect grapefruit juice and apple juice on the BA of each drug component in the proposed formulation.**	
Primary reviewer Signature and Date	**Sayed (Sam) Al Habet, R.Ph., Ph.D.**	
Secondary reviewer Signature and Date	**Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.**	

CC: NDA HFD-570, HFD-870 (Al Habet, Fadiran, Malinowski), CDR (B. Murphy, biopharm file)

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

/s/

Sayed Al-Habet
9/24/04 01:40:30 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
9/24/04 01:49:00 PM
BIOPHARMACEUTICS
I concur