CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-282

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-282/N-000 BZ
Medical Division	Division of Pulmonary and Allergic Drug Product (HFD-570)
Brand Name	Mucinex (tentative)
Drug Substance	Guaifenesin
Drug Product(s)	Guaifenesin 600 mg [redacted] mg extended-release tablets
Indication	Expectorant
Sponsor	Adams Laboratories, Inc. (14801 Sovereign Road, Fort Worth, TX 76155)
Type of submission	Amendment to the original NDA
Date of submission	1/11/2002
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2 (HFD-870)

1. Summary

On 1/11/2002, Adams Laboratories submitted a major amendment to NDA 21-282/N-000 for approval of guaifenesin extended release (ER) 600 mg [redacted] tablets. This submission is the sponsor's response to the agency's approvable letter dated on 12/21/2001.

From clinical pharmacology and biopharmacetuic persepective, the follwing comments were sent to the sponsor regarding dissolution specifications:

Strength		The sponsor's proposal	The Agency's recommendation
600 mg	Apparatus Agitation Medium Specification	[redacted]	[redacted]

Upon reviewing the present submission, it is found that the sponsor revised the product specification for 600 ER [redacted] products, as well as the stability protocols in accordance with the agency's recommendations. The new acceptance criteria will apply to both release and stability tests of both formulations.

2. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II is of the opinion that the submission is acceptable from a clinical pharmacology and biopharmaceutical perspective. No more action is indicated.

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC	NDA 21-282	Division File
	HFD 870	Young Moon Choi, Emmanuel Fadiran
	HFD 570	Ladan Jafari

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/s/

Young-Moon Choi
3/5/02 09:44:24 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
3/5/02 10:00:38 AM
BIOPHARMACEUTICS
I concur

Addendum

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-282/N-000 AZ
Medical Division	Division of Pulmonary and Allergic Drug Product (HFD-570)
Brand Name	Mucinex (tentative)
Drug Substance	Guaifenesin
Drug Product(s)	Guaifenesin 600 mg —— extended-release tablets
Indication	Expectorant
Sponsor	Adams Laboratories, Inc. (14801 Sovereign Road, Fort Worth, TX 76155)
Type of submission	Amendment to the original NDA , Category 3S
Date of submission	6/25/2001
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2 (HFD-870)

1. Summary

On 06/26/2001, Adams Laboratories submitted amajor amendment to NDA 21-282/N-000 for approval of guaifenesin extended release (ER) 600 mg/ —— tablets. This submission is the sponsor's response to the agency's approvable letter dated on 4/26/2001.
Upon reviewing the dissolution data, this reviewer recommended the following dissolution method and specification in the review dated on 12/4/2001.

However, from a chemistry perspective, there was some concern regarding the proposed dissolution method and specification with respect to the stability and hardness data:

Based on the low variability (less than 2 %) of dissolution of 12 tablets from same batch and small difference (less than 4%) of average dissolution between the tablets with upper and lower limit of hardness, the proposed as well as recommended dissolution methods and specifications may not appropriately discriminate a good batch from a bad batch.

Therefore, the following dissolution specifications are recommended.

Strength		The sponsor's proposal	The Agency's earlier recommendation	The Agency's current recommendation
600 mg	Apparatus Agitation Medium Specification	hour: NLT hour: NLT	hour: NMT hour: hour: hour: NLT	hour: NMT hour: hour: hour: NLT

2. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II is of the opinion that the submission is acceptable from a clinical pharmacology and biopharmaceutical perspective, provided adequate response to the following comment on dissolution method and specification is given by the sponsor. Please forward the "Comments to the Sponsor" as appropriate.

3. Comments to the sponsor

The following dissolution method and specifications are recommended for 600 mg guaifenesin extended release formulations.

Recommended Dissolution Method and Specification for 600 mg ER

Apparatus:

Medium:

Recommended specification:

Time (Hour)	600 mg ER
	NMT
	NLT

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC NDA 21-282 Division File
HFD 870 Young Moon Choi, Emmanuel Fadiran
HFD 570 Ladan Jafari

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/s/

Young-Moon Choi
12/12/01 10:22:38 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
12/12/01 10:26:30 AM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-282/N-000 AZ
Medical Division	Division of Pulmonary and Allergic Drug Product (HFD-570)
Brand Name	Mucinex (tentative)
Drug Substance	Guaifenesin
Drug Product(s)	Guaifenesin 600 mg ; ——— extended-release tablets
Indication	Expectorant
Sponsor	Adams Laboratories, Inc. (14801 Sovereign Road, Fort Worth, TX 76155)
Type of submission	Amendment to the original NDA , Category 3S
Date of submission	6/25/2001
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2 (HFD-870)

1. Executive Summary

On 06/26/2001, Adams Laboratories submitted amajor amendment to NDA 21-282/N-000 for approval of guaifenesin extended release (ER) 600 mg ——— tablets. This submission is the sponsor's response to the agency's approvable letter dated on 4/26/2001. In that letter, the following three concerns from a clinical pharmacology and biopharmaceutic perspective were forwarded to the sponsor:

(1) ———
(2) the potential difference in dissolution characteristics by scoring of the products, and
(3) the dissolution method/specification

The first concern is related with safety update and needs to be reviewed by the reviewing medical officer. Secondly, the scoring is not an issue ——— there is no scoring on the to-be-marketed oval shape tablet, in which the surface area is not changed. The sponsor provided dissolution profiles of the ——— oval tablet without scoring. The dissolution profiles are similar. The f2 values are 78 for 600 mg tablet ——— (Calculated by the reviewer).

For dissolution method /specification, the sponsor provided dissolution data using both ——— and paddle methods in ———

Upon reviewing the dissolution data, this reviewer is of the opinion that the ——— method is acceptable. However, the proposed dissolution specification by the sponsor is not acceptable. This reviewer recommends the following dissolution method and specification:

Strength		The sponsor's proposal	The Agency's recommendation
600 mg	Apparatus	———	———
	Agitation	———	———
	Medium	———	———
	Specification	— hour: ———	— hour: NMT ———
		— hour: ———	— hour: ———
		— hour: NLT —	— hour: ———
		— hour: NLT —	— hour: NLT —

———

2. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the sponsor's submission and found it is acceptable from a clinical pharmacology and biopharmaceutical perspective, provided adequate response to the following comment on dissolution method and specification is given by the sponsor. Please forward the "Comments to the Sponsor" as appropriate.

3. Comments to the sponsor

The following dissolution method and specification is recommended for 600 mg guaifenesin extended release formulations.

Recommended Dissolution Method and Specification for 600 mg ER

Apparatus:

Medium:

Recommended specification:

Time (Hour)	*600 mg ER*
	NMT
	NLT

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC	NDA 21-282	Division File
	HFD 870	Young Moon Choi, Emmanuel Fadiran
	HFD 570	Ladan Jafari

4. Table of contents

5. Summary of the Clinical Pharmacology and Biopharmaceutics Findings -Question Based Review-

5-1. Background

Guaifenesin is an expectorant that increases the output of respiratory tract fluid. By reducing the viscosity of the secretions, guaifenesin increases the efficiency of the cough reflex and the ciliary action to remove accumulated secretions from trachea and bronchi. It is known to be readily absorbed from the intestinal tract and is rapidly metabolized (Half -life of approximately 1 hour).

Various formulations of guaifenesin are on the market. The Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use monograph provides for immediate release guaifenesin ~~usage~~ as follows:

> Adults and children, 12 years and older: 200 to 400 mg every 4 h, not to exceed 2400 mg in 24 h. Children ≥ 6 < 12 years: 100 to 200 mg every 4 h, not to exceed 1200 mg in 24 h. Children ≥ 2 < 6 years: 50 to 100 mg every 4 h, not to exceed 600 mg in 24 h.

NDA 21-282/N-000 for guaifenesin extended release (ER) 600 mg, ——— mg tablets was submitted by Adams Laboratories (14801 Sovereign Road, Fort Worth, TX 76155) on 06/29/2000. The guaifenesin ER tablet is a bilayer tablet, composed of an immediate release layer and a modified release layer.

By claiming the more convenient dosing regimen (BID compared to QID of immediate release formulation), the sponsor seeks to acquire approval for the use of guaifenesin ER 600 mg ——— ——— as an expectorant, in adults and children, ——— and older:

Proposed dosing regimen:
For adults and children, 12 years and older, one or two 600 mg ——— tablet every 12 h, not to exceed 2400 mg in a 24-h period.
For children ≥ 6 < 12 years, ———

The Human Pharmacokinetics and Bioavailability section of this original NDA submitted on 6/29/2000 has been reviewed and an approvable letter has been issued to the sponsor. (Refer to the Agency's Approvable Letter dated 4/26/2001for full comments). In that letter, the following three comments were forwarded to the sponsor from a clinical pharmacology and biopharmaceutic perspective:

———

———

The ——— of the 600 mg ——— ——— tablets suggest s that these products can be or ought to be ——— prior to oral ingestion. For this reason, the ——— of these tablets should be removed or, alternatively, data on the effect of ——— the tablet on the modified release characteristics of the 600 mg tablets should be provided. Submit comparative data in the strength and the profile dissolution data of each of the ——— whole tablet using your proposed assay and dissolution condition.

———

———

———

———

For 600 mg ER tablet, water appeared not an appropriate medium since the dissolution did not reach plateau and is less than [redacted] at [redacted] hour. The sponsor should change the dissolution medium to [redacted] Following are the recommended method and dissolution specification for 600 mg ER:

Recommended Dissolution Method and Specification for 600 mg ER
Apparatus: *USP type II (Paddle) 50 rpm*
Medium: [redacted]
Recommended specification:

Time (Hour)	600 mg ER
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	NLT [redacted]

Labeling Comments

Under the section of [redacted] *please remove the statement,* [redacted]

Under the section of [redacted] *please add the following statement:*
"Do not chew or break." and
"Guaifenesin ER can be administered without regard for the timing of meals."

In response to the above concerns, the sponsor submitted the present amendment on 6/6/25/201.

The first concern is related with safety update and needs to be reviewed by the reviewing medical officer. The scoring is not an issue any more since the sponsor will not use score in to-be-marketed oval shape tablet, in which the surface area is not changed. The sponsor provided dissolution profiles of the [redacted] and the oval tablet without scoring. It appeared that the dissolution profiles are similar. The f2 values are [redacted] for 600 mg tablet [redacted]

The scoring is not an issue [redacted] The labeling [redacted] for OTC and the labeling comments were reflected in the proposed labeling. Therefore, the present review is focused on the dissolution method and specification.

5-2. Dissolution method and specification

Q1. Is the proposed dissolution method and specification appropriate to assure in vivo performance?

The sponsor provided comparative dissolution data of biobatches and stability batches using [redacted] and II (paddle) in [redacted] Also, the dissolution profiles of biobatches are compared in various agitation speeds, i.e., 50. [redacted] rpm (Refer to the Appendix, individual dissolution data in the present review).

It is appropriate to use [redacted] as a dissolution medium, since it has been recommended by the Agency based on the comparative dissolution profile in various media in earlier submission (The original NDA submitted on 6/29/2000).

The apparatus ( ) appeared more appropriate than Apparatus II (Paddle) since the dissolution data of at each time point appeared less variable than paddle method. The large variability using Apparatus 2 (paddle method) seems to be due to the occasional adhering to the dissolution vessel.

An agitation sped of appeared appropriate. It ensures the dissolution of over at hour for both 600 mg tablets. The dissolution profile during the first 6 hours describe smooth rising phase, which may provide more discriminating power and enable to pick up mass dissolution at short time period that may be a cause of dose-dumping in in vivo condition.

Guaifenesin seems to be released faster from 600 mg tablet than in all agitation (i.e., 50, rpm). While the f2 values at 50 rpm are less than the f2 value at rpm indicates that the dissolution profiles of 600 are similar (Refer to the Table1). It was noted that the sponsor provided in vivo dose proportionality data for 600 tablets in the original NDA submitted on 6/29/2000.

Table 1.f2 values at various agitation comparing the 600 mg tablets

	50 rpm	rpm	rpm
F2 values			

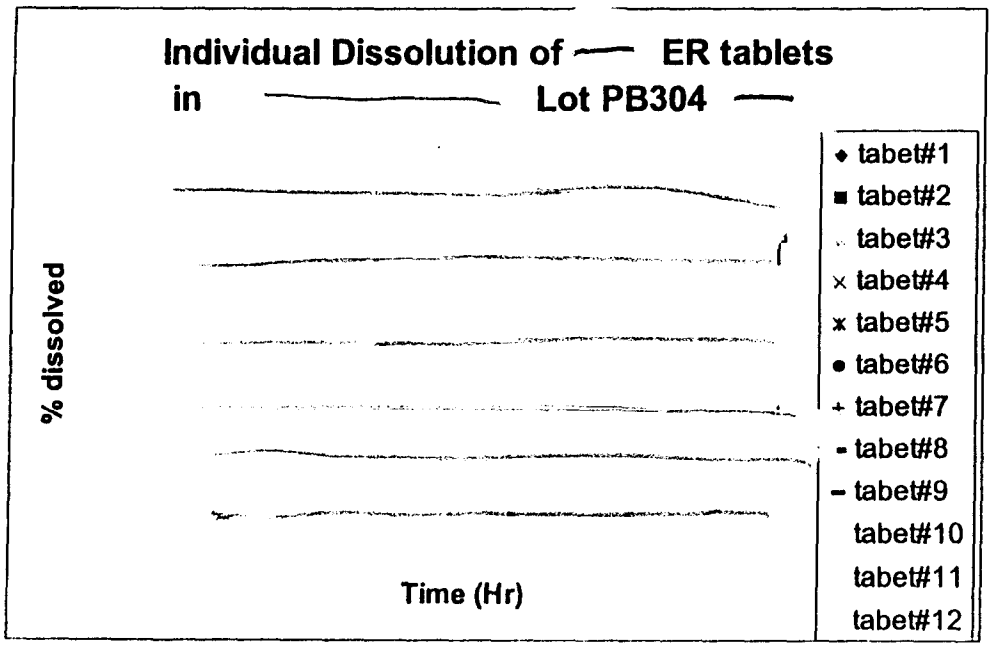
Based on the above data, the following dissolution method and specification are recommended. It should be noted that this recommendation is only based on the biobatches to assure sameness in vivo performance of future products with biobatches.

Strength		The sponsor's proposal	The Agency's recommendation
600 mg	Apparatus		
	Agitation		
	Medium		
	Specification	hour: hour: hour: NLT hour: NLT	hour: NMT hour: hour: hour: NLT

6. Appendix
Individual dissolution data

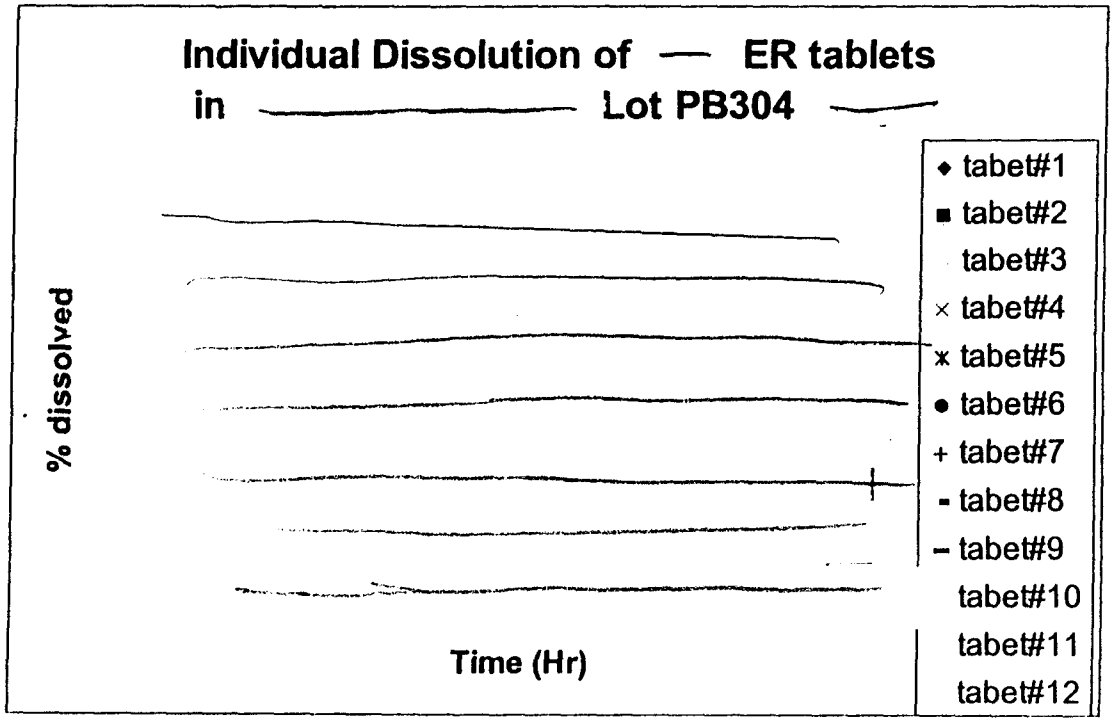
Individual Dissolution of — ER tablets
in — Lot PB 304 biobatch ;

Time (hr)	tabet#1	tabet#2	tabet#3	tabet#4	tabet#5	tabet#6	tabet#7	tabet#8	tabet#9	tabet#10	tabet#11	tabet#12	AVG
													31.8
													42.0
													57.1
													67.4
													75.6
													81.8
													87.1
													91.7
													95.4



Individual Dissolution of — ER tablets
in ——— Lot PB 304 biobatch ; —

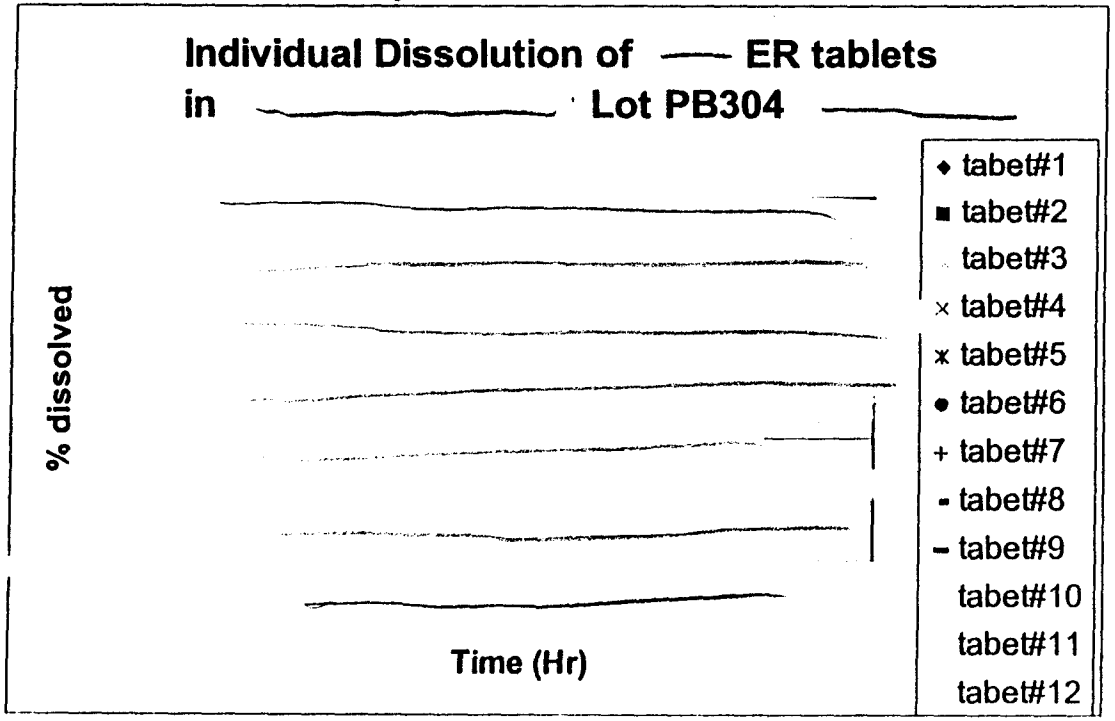
Time (hr)	tabet#1	tabet#2	tabet#3	tabet#4	tabet#5	tabet#6	tabet#7	tabet#8	tabet#9	tabet#10	tabet#11	tabet#12	AVG
													37.2
													47.7
													62.5
													73.1
													80.8
													86.7
													92.2
													96.3
													99.6

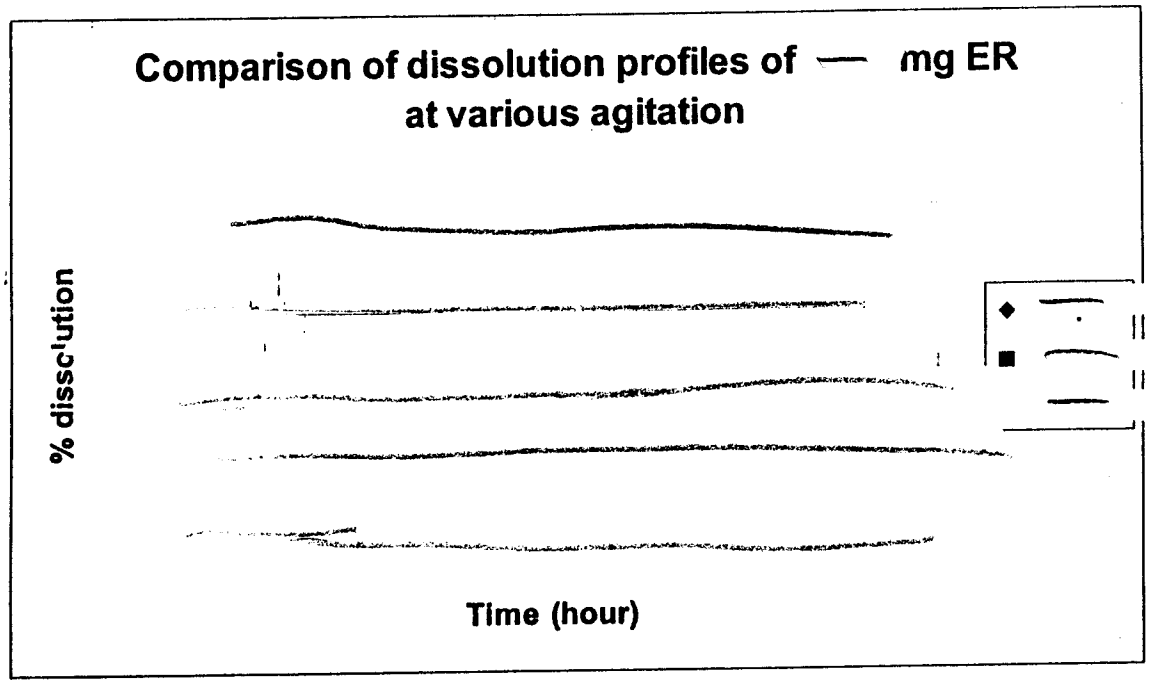


Individual Dissolution of [redacted] ER tablets

in [redacted] Lot PB 304 biobatch ; [redacted]

Time (hr)	tabet#1	tabet#2	tabet#3	tabet#4	tabet#5	tabet#6	tabet#7	tabet#8	tabet#9	tabet#10	tabet#11	tabet#12	AVG
[redacted]													40.3
[redacted]													51.6
[redacted]													66.8
[redacted]													77.4
[redacted]													85.2
[redacted]													90.2
[redacted]													95.3
[redacted]													98.6
[redacted]													100.7

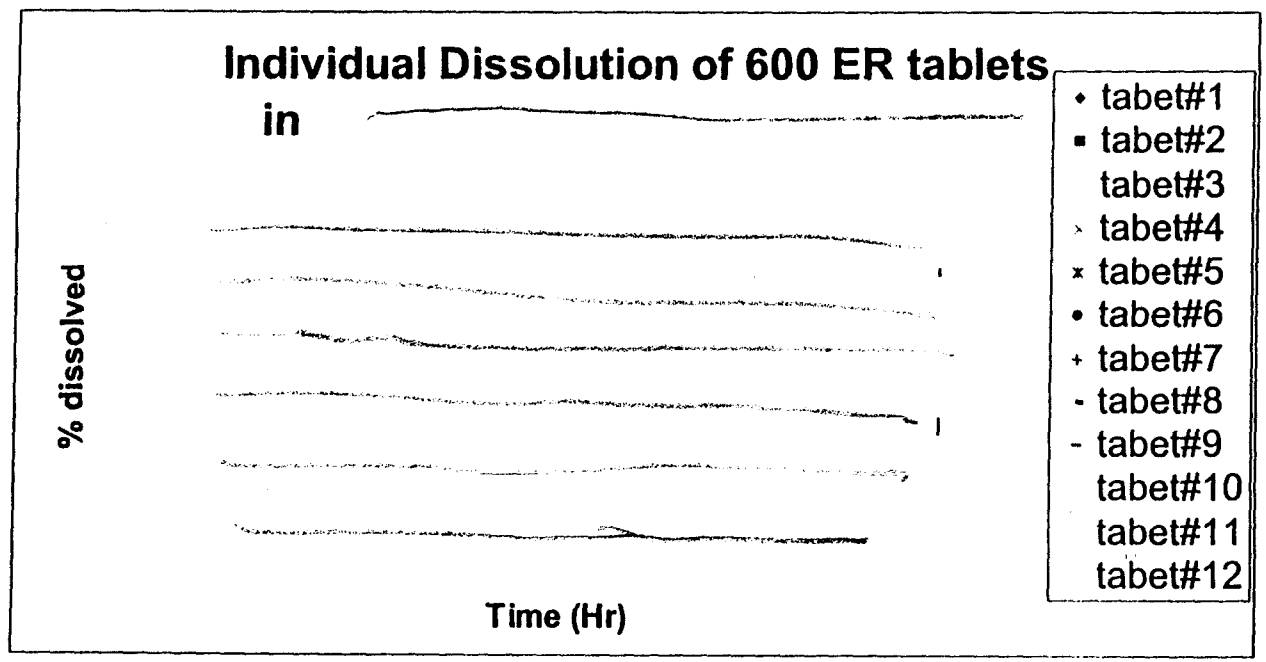



Comparison of dissolution profiles of — mg ER
at various agitation
% dissolution
Time (hour)

Individual Dissolution of 600 ER tablets

in

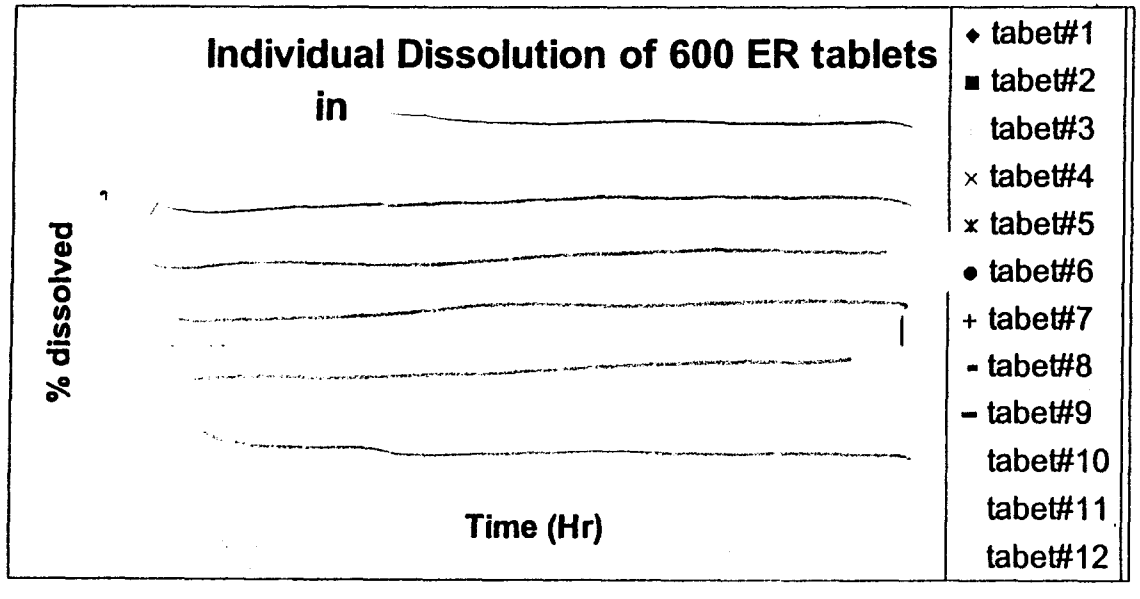
Time (hr)	tabet#1	tabet#2	tabet#3	tabet#4	tabet#5	tabet#6	tabet#7	tabet#8	tabet#9	tabet#10	tabet#11	tabet#12	AVG
													37.3
													49.8
													67.6
													79.8
													88.5
													95.5
													99.9
													102.3
													103.0



Individual Dissolution of 600 ER tablets

In

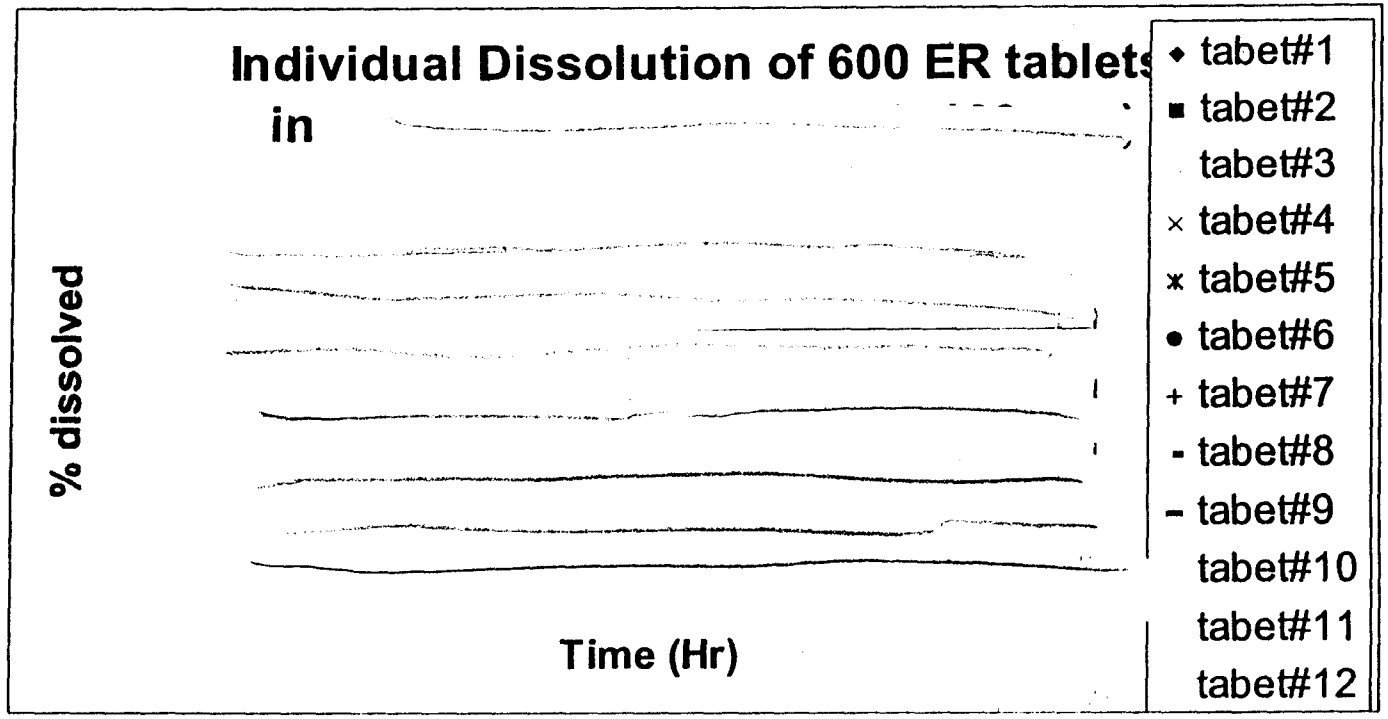
Time (hr)	tabet#1	tabet#2	tabet#3	tabet#4	tabet#5	tabet#6	tabet#7	tabet#8	tabet#9	tabet#10	tabet#11	tabet#12	AVG
													41.8
													54.8
													72.1
													84.5
													92.4
													98.6
													100.3
													102.3
													102.8



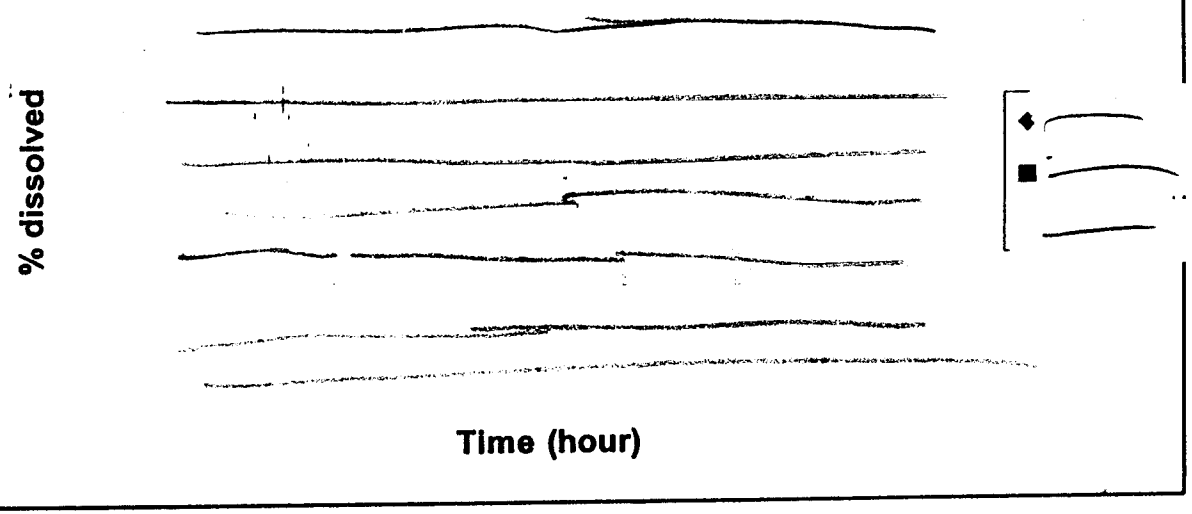
Individual Dissolution of 600 ER tablets

in

Time (hr)	tabet#1	tabet#2	tabet#3	tabet#4	tabet#5	tabet#6	tabet#7	tabet#8	tabet#9	tabet#10	tabet#11	tabet#12	AVG
													44.4
													58.7
													77.0
													90.5
													99.4
													101.5
													105.5
													106.0
													106.4



Comparison of dissolution profiles of 600 mg ER at various aitation



6-Dissolution data for oval tablet (without score)

mg Modified Oval Tablets
Lot # PB01-D01

	hr	hr	hr	hr	hr	hr
Average	39	50	65	75	82	93
SD	1.85	2.30	2.11	1.98	1.90	1.68
Range						
Proposed Limits for						NLT

600 mg Modified Oval Tablets
Lot # PB01-D02

	hr	hr	hr	hr	hr	hr
Average	44	58	76	88	95	102
SD	1.08	1.24	1.00	1.14	1.08	0.94
Range						
Proposed Limits for			NLT		NLT	

2 pages redacted from this section of the approval package consisted of draft labeling

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

/s/

Young-Moon Choi
12/4/01 03:46:38 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
12/4/01 03:58:34 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**N 21-282**	**Brand Name**	-
OCPB Division (I, II, III)	**DPE-II**	**Generic Name**	**Guaifenesin**
Medical Division	**HFD-570 (DPADP)**	**Drug Class**	**Expectorant**
OCPB Reviewer	Young Moon Choi	**Indication(s)**	**Expectorant**
OCPB Team Leader	Emmanuel Fadiran	**Dosage Form**	
	[redacted]	**Dosing Regimen**	
Date of Submission	**6/29/00, 9/14/00, 1/22/01, and 1/29/01**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**4/13/01**	**Sponsor**	**Adams Lab.**
PDUFA Due Date	**4/29/01**	**Priority Classification**	**S**
Division Due Date	**4/19/01**		

Clin. Pharm. and Biopharm. Information

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

Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:	x	3	0	**Used not-to-be-marketed formulation for developmental purpose**
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	x	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1	1	
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	5	2	

Filability and QBR comments

	"X" if yes	*Comments*
Application filable ?	x	
Comments sent to firm ?		See review package

QBR questions (key issues to be considered)	Q1. What is the nature/composition of the extended release formulations? Are there any differences between the formulations used in the pharmacokinetic studies and the marketed or to-be-marketed formulations? Q2. Is the systemic exposure after administration of the extended release formulation comparable to that after the administration of the immediate release tablet in the market (Tussi-Organidin® NR) ? Q3. Are 600 mg ER ——— formulations bioequivalent by standard criteria? Q4. Is there any potential of dose-dumping from the extended release formulation by food? Q5. Are the dissolution conditions and specifications adequately developed to assure in vivo performance and quality of the product?
Other comments or information not included above	
Primary reviewer Signature and Date	Young Moon Choi
Secondary reviewer Signature and Date	Emmanuel Fadiran

CC: NDA 21-282, HFD-850(P. Lee), HFD-570 (Ladan Jafari, Mary Purucker), HFD-870(Young Moon Choi, Emmanuel Fadiran, John Hunt, Hank Malinowski), CDR

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-282/N-000
Drug Substance	Guaifenesin
Drug Product(s)	Guaifenesin 600 mg [redacted] extended-release tablets
Sponsor	Adams Laboratories, Inc.
Type of submission	Original NDA, Category 3S
Date of submission	06/29/2000, 09/14/2000, 01/22/2001 and 01/29/2001
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2

Table of contents

1. Executive Summary

Guaifenesin is only an oral expectorant included in the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use monograph. There are various formulations available in the market.

Adams Laboratories (14801 Sovereign Road, Fort Worth, TX 76155) developed guaifenesin extended release (ER) 600 mg/ [redacted] tablets, which are composed of an immediate release layer and a modified release layer, and submitted an original NDA 21-282 for the use of the ER formulations as an expectorant in adult and children, 6 years and older. Proposed dosing regimens are as follows:

For adults and children, 12 years and older, one or two 600 mg [redacted] every 12 h, not to exceed 2400 mg in a 24-h period.

For children ≥ 6 < 12 years, [redacted]

The Human Pharmacokinetics and Bioavailability section of the NDA contained a total of pharmacokinetic studies. Among them [redacted] studies were not reviewed since these studies are [redacted] studies and to-be marketed formulations were not used. Two studies (Study Nos. 99-05 and 99-06) employed the to-be-marketed ER tablet formulations. No safety and efficacy studies were submitted. Therefore, the approval is based upon an examination of the systemic exposure of the to-be-marketed ER formulation compared to those of an immediate release formulation on the market (200 mg immediate release (IR) tablets; Tussi-Organidin ®NR).

The comparative bioavailability and food effect were tested only for higher strength formulation (1200 mg ER). For the lower strength tablet (600 mg ER), the sponsor provided in vivo dose proportionality data for two formulations. Therefore, the approval of the lower strength is dependent on the approval of the higher strength.

AUCs of guaifenesin after single or multiple (i.e., every 12 hours for 6 days) administration of 1200 mg ER is comparable with those after administration of IR product.

The maximum concentration (Cmax) of guaifenesin after single dose of 1200 mg ER is lower than that after single dose of IR product. However, after multiple, it appeared to be comparable.

The minimum concentration (Cmin) appeared highly variable and the 90% confidence interval for the ratio of the geometric mean of Cmin is out of bioequivalence criteria. However, it should be noted that the variability in the Cmin of ER and IR products were similarly high (Refer to the Figures 1 and 2 on pages 5 and 6). The average Cmin of ER at steady state appeared either higher or lower than IR product, and the difference is less than 20 %. Furthermore, a clinical study (1989 Federal Register) showed that a low dose of guaifenesin (190 mg IR formulation every 8 hours) was superior to placebo, in which Cmin was about only 1/15th or 1/27th of the 600 mg ER or 1200 mg ER, respectively (Refer to Figure 3 on page 7).

The systemic exposure (Cmax and AUC) of guaifenesin after administration of 1200 mg ER tablet was not affected by food. However, Tmax was delayed from 0.75 hour to 1.75 hour. There was no sign for dose dumping.

The proposed dissolution specifications are not acceptable for 600 mg ER. The dissolution data appeared inappropriate to set an appropriate specification for 1200 mg ER (Refer to the comments to the sponsor).

It is noted that the biobatch size of 1200 mg ER is [redacted] This would imply a [redacted] Therefore. the additional [redacted] data need to be submitted as a [redacted], when the sponsor produces the [redacted] tablets.

Overall, this reviewer is of the opinion that the present submission is acceptable to support the Bioavailablity and Bioequivalence regulation covered by 21 CFR part 320, provided that the comments to the sponsor regarding the dissolution method and specification are adequately addressed.

Figure 1. Comparison of Cmin0 at steady state, i.e., immediately before the administration of the last dose 1200 mg ER formualtion every 12 hours (Treatment 1) for 6 days or 400 mg IR formulation every 4 hours (Treatment –1) for 6 days.

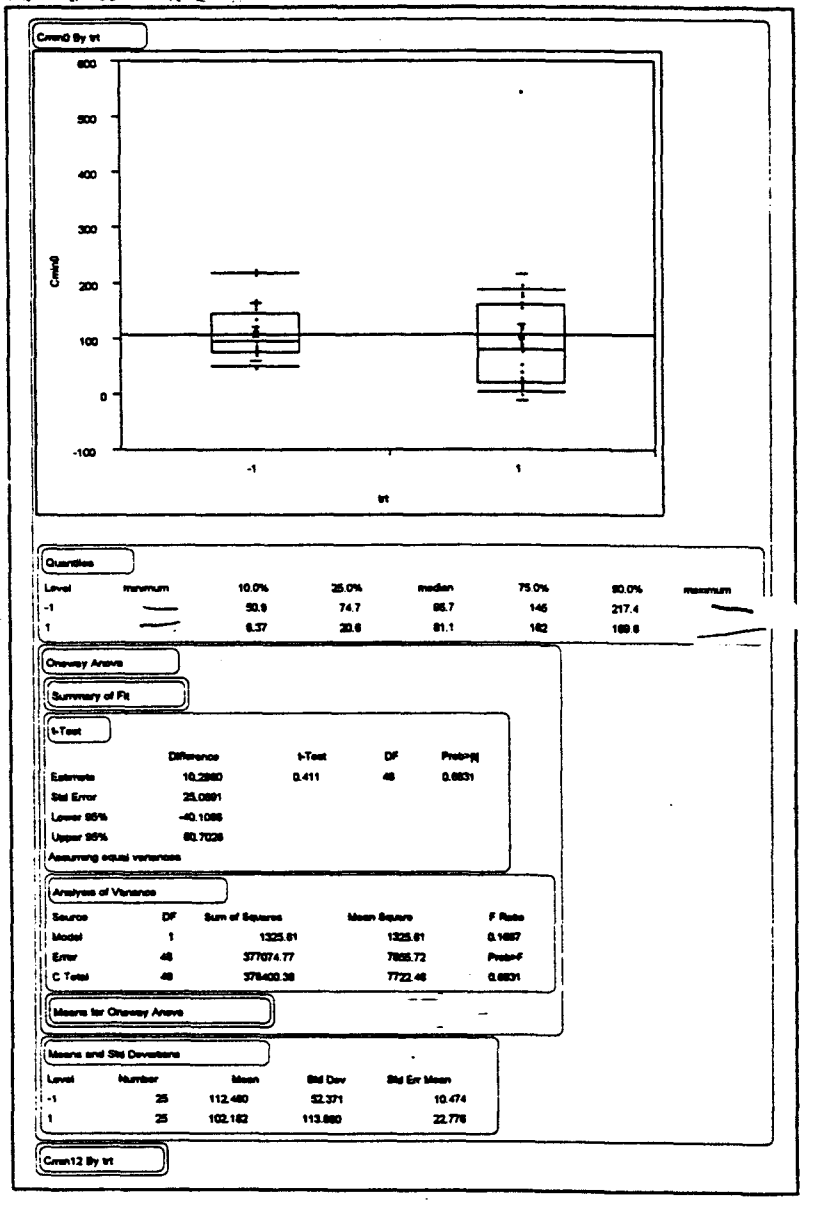


Figure 2. Comparison of Cmin12 at steady state, i.e., at 12 hours after the last dose of 1200 mg ER formualtion every 12 hours (Treatment 1) for 6 days or 400 mg IR formulation every 4 hours (Treatment –1) for 6 days.

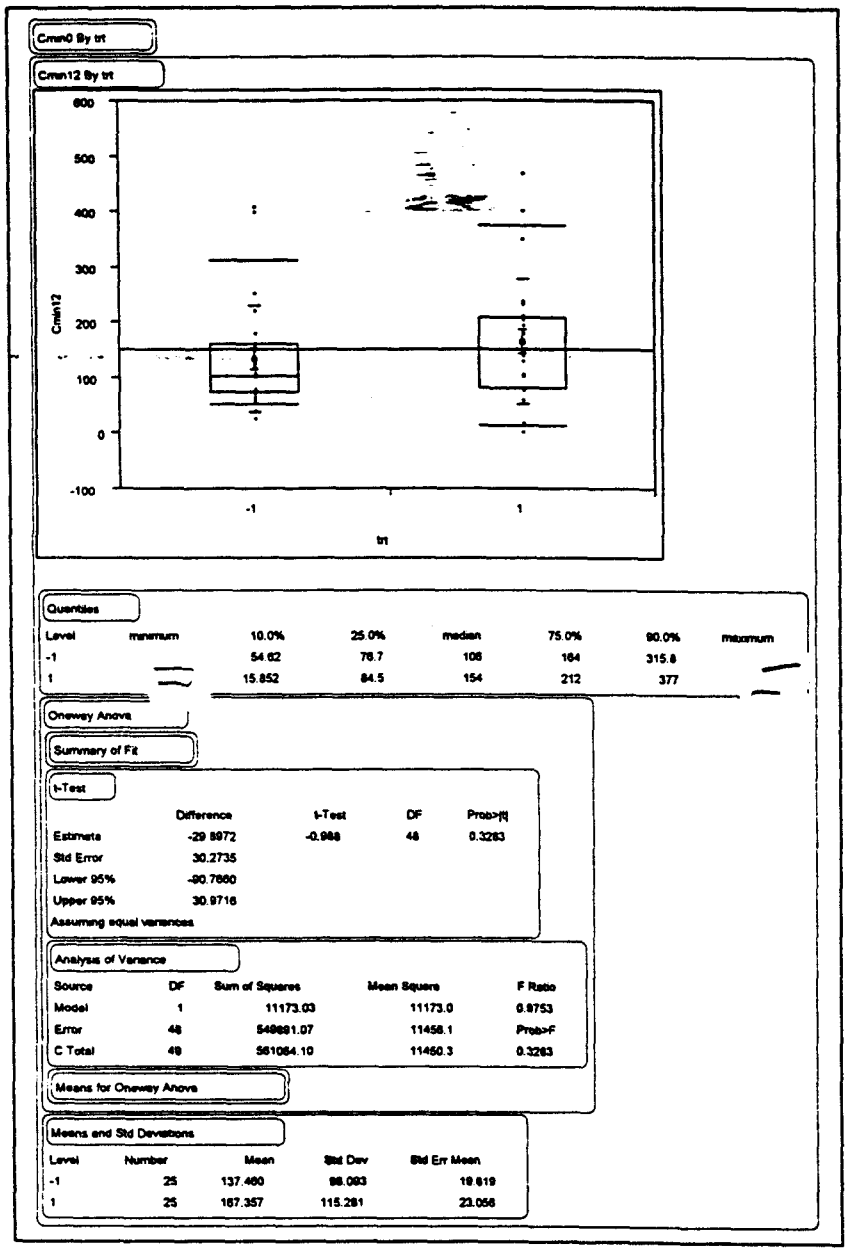
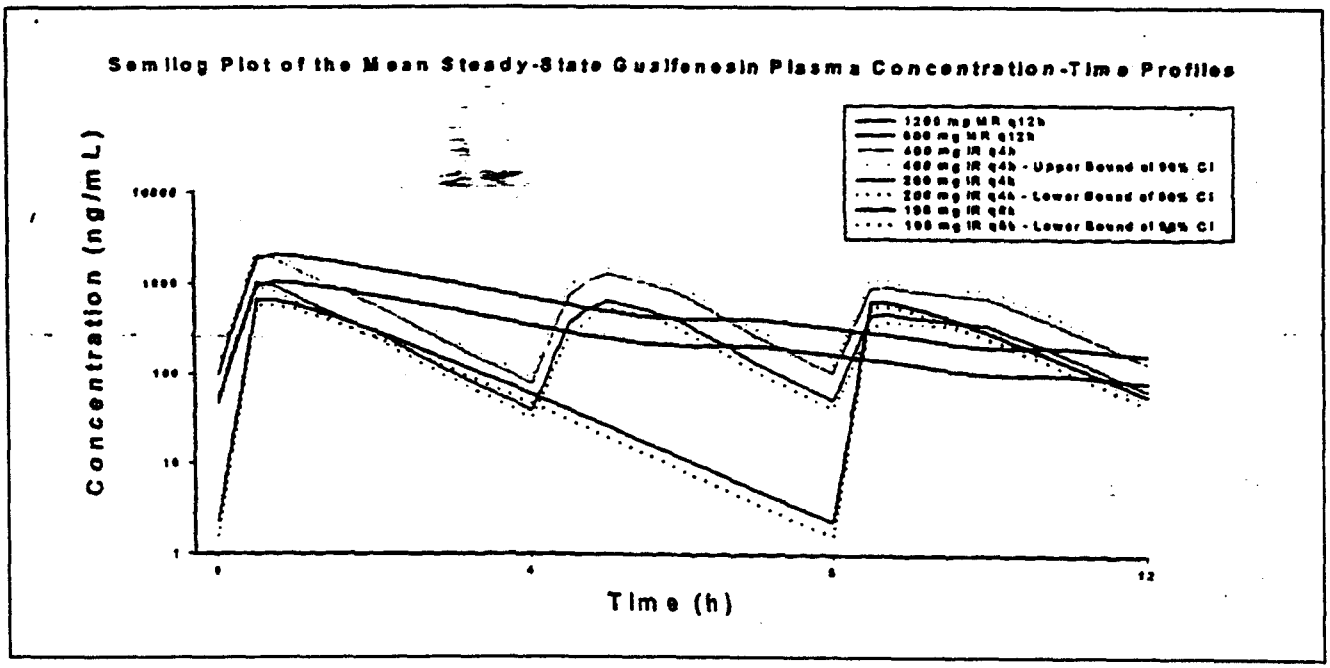


Figure 3. Simulated plasma concentrations of guaifenesin after administration of various formulations. It is shown that the Cmin after administration of 600 ER or 1200 ER formulation is substantially higher than that after 190 mg IR formulation every 8 hours. It should be noted that the 190 mg IR Q8 hours was superior to placebo.



2. Comments to the sponsor

2-1. Dissolution method:

The sponsor is asked to improve the [redacted] for [redacted] mg ER and to submit a proposed specification based on the data in the improved [redacted]
At present, it is not feasible to set up an appropriate [redacted] since only [redacted] of [redacted] mg ER was dissolved up to [redacted] hours and plateau was not reached in all the tested media. It is recommended to investigate the use of [redacted] and/or to [redacted]

If the [redacted] mg ER tablet is [redacted] please submit [redacted] and [redacted] using your proposed [redacted]

For 600 mg ER tablet, water appeared not an appropriate medium since the dissolution did not reach plateau and is less than [redacted] at [redacted]. The sponsor should change the dissolution medium to [redacted] Following are the recommended method and dissolution specification for 600 mg ER :

Recommended Dissolution Method and Specification for 600 mg ER

Apparatus: USP type II (Paddle) 50 rpm
Medium: [redacted]
Recommended specification: [redacted]

Time (Hour)	600 mg ER
[redacted]	NMT [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	NLT [redacted]

2-2. Labeling Comment

Under the section of [redacted] please remove the statement, [redacted]

Under the section of [redacted], please add the following statement:
"Do not chew or break." and
"Guaifenesin ER can be administered without regard for the timing of meals."

3. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the Human Pharmacokinetics and Bioavailability section of NDA 21-282/N-000. It has been found that the submission is acceptable from a clinical pharmacology and biopharmaceutical perspective, provided adequate response to the above comments on dissolution method and specification by the sponsor. Please forward the "Comments to the Sponsor" as appropriate.

YM

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Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

EF

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

cc NDA 21-282/N-000, Division File
HFD-870: Emmanuel Fadiran, John Hunt, Henry Malinowski
HFD-570: Young Moon Choi, Mary Purucker, Juanita Ross, Ladan Jafari

4. Question Based Review

Guaifenesin is an expectorant that increases the output of respiratory tract fluid. By reducing the viscosity of the secretions, guaifenesin increases the efficiency of the cough reflex and the ciliary action to remove accumulated secretions from trachea and bronchi. It is known to be readily absorbed from the intestinal tract and is rapidly metabolized (Half -life of approximately 1 hour).

Various formulations of guaifenesin are on the market. The Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use monograph provides for immediate release guaifenesin usage as follows:

> Adults and children, 12 years and older: 200 to 400 mg every 4 h, not to exceed 2400 mg in 24 h. Children ≥ 6 < 12 years: 100 to 200 mg every 4 h, not to exceed 1200 mg in 24 h. Children ≥ 2 < 6 years: 50 to 100 mg every 4 h, not to exceed 600 mg in 24 h.

The NDA 21-282/N-000 for guaifenesin extended release (ER) 600 mg [redacted] tablets was submitted by Adams Laboratories (14801 Sovereign Road, Fort Worth, TX 76155) on 06/29/2000. By claiming the more convenient dosing regimen [redacted], the sponsor seeks to acquire approval for the use of guaifenesin ER 600 mg [redacted] tablets as an expectorant, in adults and children

The proposed dosing regimen for adults and children, 12 years and older is as follows and the maximum proposed dose is identical as described in the Monograph:

> One or two 600 mg [redacted] every 12 h, not to exceed 2400 mg in a 24-h period.

The Human Pharmacokinetics and Bioavailability section of the present NDA contained a total of [redacted] pharmacokinetic studies ([redacted], 99-05 and 99-06). No safety and efficacy studies were submitted. Only studies 99-05 and 99-06 employed the to-be-marketed ER tablet formulations. Other [redacted] studies ([redacted], are [redacted] studies for formulation development. Studies 99-05 and 99-06 are pivotal comparative bioavailability studies.

Therefore, the present review is focused on these two studies to answer the following questions:

Q1. What is the composition of the extended release formulations? Are there any differences between the formulations used in the pharmacokinetic studies and the to-be-marketed formulations?

Q2. Is the systemic exposure after administration of the extended release formulation comparable to that after the administration of the immediate release tablet in the market (Tussi-Organidin® NR) ?

Q3. Are 600 mg ER and 1200 mg ER formulations bioequivalent by standard criteria?

Q4. Is there any potential of dose-dumping from the extended release formulation by food?

Q5. Are the dissolution conditions and specifications adequately developed to assure in vivo performance and quality of the product?

Table I. the pivotal Study Nos. and design.

Study No	Design
Study 99-05	a crossover, comparative single and multiple dose bioavailability study of [redacted] guaifenesin 1200 mg ER tablet given BID vs. administration of guaifenesin immediate release (2x200 mg) tablets (Tussi-Organidin® NR), given every 4 h.
Study 99-06	A combined dose-proportionality and food-interaction study. The study had an open, single-dose, three-way cross-over design, with a 7-day wash-out period between each of the three treatments. The following doses were given: 1) a 600 mg ER dose under fasting conditions 2) a 1200 mg ER dose under fasting conditions 3) a 1200 mg ER dose after intake of a high-fat breakfast.

Q1. What is the nature/composition of the extended release formulations? Are there any differences between the formulations used in the pharmacokinetic studies and to-be-marketed formulations?

The guaifenesin ER tablet is a bilayer tablet, composed of an immediate release layer and a modified release layer.

The immediate release layer is

The composition of the guaifenesin ER tablet is as follows (Table 2):

Table 2. The composition of the extended release formulations

Guaifenesin ER tablet 600 mg

Modified Release Layer	
Carbomer 934 P, NF	
Hydroxypropyl Methylcellulose, USP	
Guaifenesin	
Magnesium Stearate, NF	
Immediate Release Layer	
Microcrystalline Cellulose, NF	
Sodium Starch Glycolate, NF	
Guaifenesin	
Magnesium Stearate, NF	
Total tablet weight	

The manufacturer of guaifenesin, USP is . The guaifenesin is produced by Adams Laboratories Inc., at the Fort Worth, Texas facility (14801 Sovereign Road, Fort Worth, TX 76155) and used to manufacture the 600 mg tablets.

The bilayer tablet formulation used in studies 99-05 and 99-06 is the to-be-marketed formulation. The size of batch PB304 used in study 99-05 is of the for

the [redacted] tablets. The intended commercial batch size for the 600 mg strength is [redacted] tablets (Table 3).

Table 3. The formulation information used in the pivotal pharmacokinetic studies

Study no.	Dosage form	Lot/Batch Number	Lot/Batch Size (tablets)	Formulation
99-05	Guaifenesin ER 1200 mg tablet	Lot PB304	[redacted]	[redacted]
99-06	Guaifenesin ER 1200 mg tablet	Lot PB304	[redacted]	[redacted]
	Guaifenesin ER 600 mg tablet	Lot PB322	[redacted]	To-be-marketed

Reviewer's Comment:

[redacted]

Q2. Is the systemic exposure after administration of the extended release formulation comparable to that after the administration of the immediate release tablet in the market (Tussi-Organidin® NR)?

Study 99-05 was a comparative single and multiple dose bioavailability study of the [redacted] guaifenesin 1200 mg ER tablet given BID vs. administration of guaifenesin immediate release (2x200 mg) tablets (Tussi-Organidin® NR), given every 4 h.

Mean plasma guaifenesin concentrations after multiple dosing following administration of the ER tablet and the IR tablet are shown in Figure on page 14.

The mean pre-dose guaifenesin concentrations for the IR tablet on Days 4 and 5 were (mean ± SD) 116.2 ± 51.4 ng/ml and 109.4 ± 52.7 ng/ml, respectively, as compared to 111.5 ± 52.4 ng/ml pre-dose on Day 6. The mean pre-dose guaifenesin concentrations for the ER tablet on Days 4 and 5 were (mean ± SD) 157.1 ± 304.5 ng/ml and 97.1 ± 110.4 ng/ml, respectively, as compared to 101.2 ± 113.9 ng/ml pre-dose on Day 6. The data indicate that steady-state was obtained.

Estimated pharmacokinetic parameters are displayed in Table 4. Ninety percent confidence intervals for the ratio of the geometric means of the pharmacokinetic parameters for guaifenesin are shown in Table 5.

AUCs after single dose or multiple dose of 1200 mg ER appeared comparable to those after IR product. However, for Cmax after single dose and for Cmin after multiple dose is out of bioequivalence criteria.

When we consider the Cmax as a measure of safety, this reviewer is of the opinion that the lower Cmax after single dose of ER product than that after administration of IR (reference) is not a significant concern.

The minimum concentration (Cmin) appeared highly variable and the 90% confidence interval for the ratio of the geometric mean of Cmin is out of bioequivalence criteria. However, it should be noted that the variability in the Cmin of ER and IR products were similarly high (Refer to the Figures 1 and 2 on Pages 6 and 7). The average Cmin of ER at steady state appeared either higher or lower than IR product, and the difference is less than 20 % (Table 4 at page 14). Furthermore, a clinical study (Federal Register/ Vol54, No.38, Feb. 28/1989) showed that a low dose of guaifenesin (190 mg IR formulation every 8 hours) was superior to placebo, in which Cmin was expected only $1/15^{th}$ or $1/27^{th}$ of the 600 mg ER or 1200 mg ER, respectively (Figure 3).

Therefore, this reviewer is of the opinion that the present submission for comparative bioavailability study is acceptable, even though Cmin is out of the bioequivalence criteria.

Plasma Guaifenesin Concentrations Following the Administration of Either 3 Doses of a 400 mg Immediate Release Formulation Given 4 Hours Apart or a Single Dose of a 1200 mg Modified Release Formulation (Mean, Standard Error)

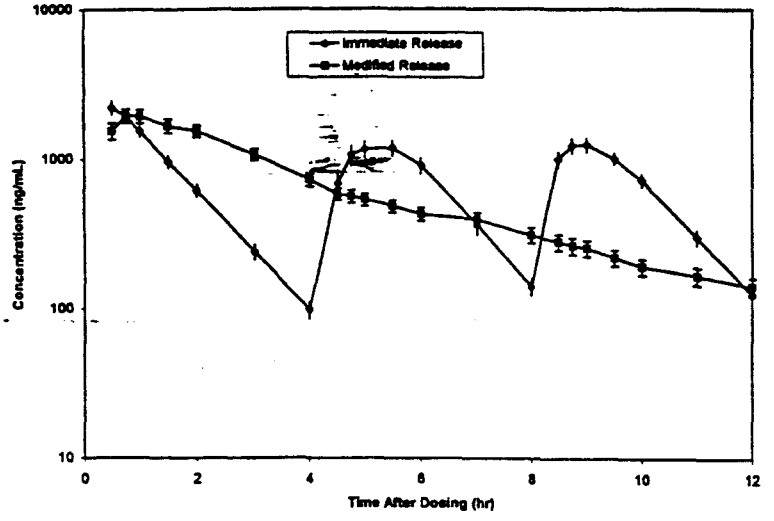

Table 4. Pharmacokinetic parameters of guaifenesin after single and multiple dosing of the ER tablet (1200 mg BID) and the IR tablet (2x200 mg every 4 h).

Single-dose		
	Guaifenesin 1200 mg ER tablet Mean ±SD (n=26)	**Guaifenesin 400 mg IR tablet Mean ±SD (n=25)**
C_{max} (ng/ml)	2111 ± 978	2463 ± 1033
T_{max} (h)*	0.75 (	0.5 (
$AUC_{(0-12h)}$ (h·ng/ml)	7876 ± 3346	8382 ± 3282
$AUC_{(0-\infty)}$ (h·ng/ml)	8686 ± 3855	8529 ± 3362
$t_{½}$ (h)	3.31 ± 1.73	0.78 ± 0.09

Multiple-dose		
	Guaifenesin 1200 mg ER tablet Mean ±SD (n=25)	**Guaifenesin 400 mg IR tablet Mean ±SD (n=25)**
C_{max} (ng/ml)	2350 ± 886	2278 ± 791
T_{max} (h)*	0.75 ,	0.5
$AUC_{(0-12h)}$ (h·ng/ml)	8202 ± 2875	7751 ± 2697
Cmin 0 (ng/ml)	102 ± 114	112± 52
C_{min} 12 (ng/ml)	167 ± 115	137 ± 98

* Median and range.

Table 5. 90% confidence intervals for the ratio of the geometric means of the pharmacokinetic parameters for guaifenesin, after single and multiple dosing of the bilayer tablet and the administration of guaifenesin immediate release.

	Single-dose	**Multiple-dose**
C_{max}	72.9% – 96.3%	90.7% – 114%
$AUC_{(0-12h)}$	83.5% – 101%	96.0% – 115%
$AUC_{(0-\infty)}$	89.8% – 108%	-
Cmin 0		28.1% - 81.9%
C_{min} 12	-	67.1% – 160%

Q3. Are 600 mg ER and 1200 mg ER formulations bioequivalent by standard criteria?

Q4. Is there any potential of dose-dumping from the extended release formulation by food?

Above questions were answered by reviewing Study 99-06, that was a combined dose proportionality and food interaction study of the guaifenesin ER tablet.

Mean (SD) pharmacokinetic parameters and 90% confidence intervals for the geometric mean ratios of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ for guaifenesin are presented in the following Tables 6 and 7.

Table 6. Pharmacokinetic parameters of guaifenesin after single dosing of the 600 mg ER tablet under fasting conditions and of the 1200 mg ER tablet under fasting and fed conditions, respectively.

Parameter	600 mg ER tablet, fasting (mean±SD)	1200 mg ER tablet, fasting (mean±SD)	1200 ER tablet, food (mean±SD)
C_{max} (ng/ml)	1074.3 ± 451.3	1994 ± 707.1	1988.1 ± 1170.4
$AUC_{(0-t)}$ (ng·h/ml)	3621.1 ± 1225.4	7643.3 ± 2387.8	7528.4 ± 2658.5
$AUC_{(0-\infty)}$ (ng·h/ml)	3671.0 ± 1225.6	8104.8 ± 2573.1	7544.5 ± 2655.8
T_{max} (h)*	0.75	0.75	1.75
$t_{½}$ (h)	2.04 ± 0.90	3.30 ± 1.87	0.93 ± 0.19

* median and range.

Table 7. Bioequivalence test results

	90% Confidence Intervals * Guaifenesin 1200 mg ER tablets Food vs. Fasting	90% Confidence Intervals ** Guaifenesin 600 mg vs. 1200 mg ER tablets
C_{max} (ng/ml)	82.0% – 105%	92.5% – 119%
$AUC_{(0-t)}$ (h·ng/ml)	90.8% – 105%	86.8% – 100%
$AUC_{(0-\infty)}$ (h·ng/ml)	85.8% – 99.9%	82.9% – 96.4%

* 90% confidence intervals for the ratio of the geometric means of the pharmacokinetic parameters for guaifenesin, after single dosing of the 1200 mg ER tablet under fasting conditions and after intake of a high-fat breakfast.

** 90% confidence intervals for the ratio of the geometric means of dose-normalized pharmacokinetic parameters for guaifenesin, to demonstrate dose proportionality between single-dose administration of a 600 mg ER tablet and a 1200 mg ER tablet.

5. ASSAY METHODOLOGY AND VALIDATION

Guaifenesin levels in plasma were determined by —— using ———— . and using ———— ' as the internal standard. The method was validated prior to initiating analysis of the study samples.

PRE-STUDY METHOD VALIDATION

Description of method: ————

a) Specificity

No major interference peaks were found for guaifenesin or the internal standard. No interference was observed with co-administered ————

b) Calibration Curve

A power regression equation: $y = Ax^B$ was used to describe the standard curve. The lower and upper limits of quantitation were ————

c) Precision, Accuracy and Recovery

The inter-assay precision of the quality controls at nominal concentrations of 15 ng/ml, 90 ng/ml and 720 ng/ml was 6.2%, 2.1% and 3.6%, respectively. The inter-assay accuracy (as % difference from nominal value) was –4.0%, –2.3% and 3.5%, respectively. The mean recovery of the samples at nominal concentrations of 15 ng/ml, 90 ng/ml and 720 ng/ml was 81.2%, 81.4% and 78.8%, respectively, with low coefficients of variation.

e) Stability

Acceptable stability of guaifenesin was observed after 2 freeze/thaw cycles. Guaifenesin in plasma was stable at room temperature for at least ——— Extracted samples stored under injection conditions (bench top) were stable for at least ———

Study 99-05:
The total number of samples analyzed in study 99-05 was 2472. All samples were analyzed in singlet, and a total of 127 samples (5.1%) were re-analyzed. Seventy-four samples were re-analyzed at the request of the sponsor, but in almost all of these cases the original results were reported as final. Quality controls were analyzed in triplicate and calibrators in duplicate. Inter-assay accuracy for guaifenesin quality controls with nominal concentrations of 15 ng/ml, 90 ng/ml and 720 ng/ml (as % difference from nominal value) was –2.8%, 0.5% and 3.6%, respectively. Inter-assay precision was 3.4%, 2.9% and 4.2%, respectively. The intra-assay accuracy and precision was acceptable.
In conclusion, the assay performance in this study was acceptable.

Study 99-06:
The total number of samples analyzed in study 99-06 was 1185. All samples were analyzed in singlet, and a total of 96 samples (8.1%) were re-analyzed. Almost all of these re-assays were caused by the fact that the original result exceeded the upper limit of quantitation. Quality controls were analyzed in triplicate and calibrators in duplicate. Inter-assay accuracy for guaifenesin quality controls with nominal concentrations of 15 ng/ml, 90 ng/ml and 720 ng/ml (as % difference from nominal value) was 0.4%, 3.8% and 3.9%, respectively. Inter-assay precision was 6.5%, 6.2% and 8.2%, respectively. The intra-assay accuracy and precision was acceptable.
In conclusion, the assay performance in this study was acceptable.

6. DISSOLUTION

Dissolution Profiles of 600 ER and 1200 ER tablets

In vitro dissolution tests were performed with the batches of the products that were used in the pivotal comparative studies.

Mean dissolution data in five different media for 1200 mg ER and 600 mg ER products are attached.

For 600 mg ER, seems to be an appropriate medium rather than water. However, 1200 mg ER, all the tested media appeared to be not appropriate, because at 12 hours only % of the tablet was dissolved, and plateau was not reached in all the tested media. Furthermore, the dissolution profile of each strength appeared different.

f2 similarity factors are listed in the following table.

	Deionized water
f2 **	

** f2 larger than 50 ensures sameness or equivalence of the two curves.

Therefore, the following dissolution method and specification is recommended only for 600 mg ER, and the sponsor is asked to improve the dissolution condition of 1200 mg ER.

Recommended Dissolution Method and Specification for 600 mg ER

Apparatus:

Medium:

Recommended specification:

Time (Hour)	600 mg ER
	NMT
	NLT

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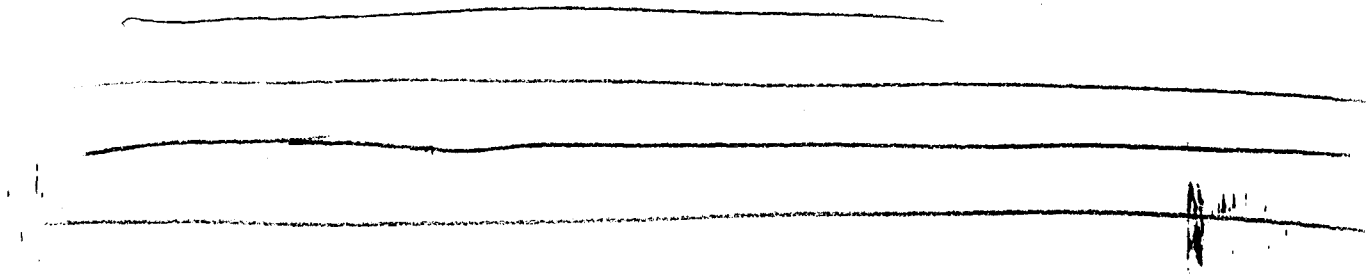
Summary of Guaifenesin ER ——— 600mg Dissolutions in Different Media



Guaifenesin ER 600mg: (Averages from Tables 6-10)

Hours:														
Diss 1:	24	32	44	54	63	72	81	88	94	97	98	100	101	101
Diss 2:	33	43	54	62	70	77	83	89	93	95	99	99	101	101
Diss 3:	36	46	61	72	80	87	94	97	100	100	100	102	103	104
Diss 4:	36	45	59	67	76	83	88	92	95	98	99	101	101	102
Diss 5:	25	32	43	53	65	77	87	97	100	102	103	104	103	104

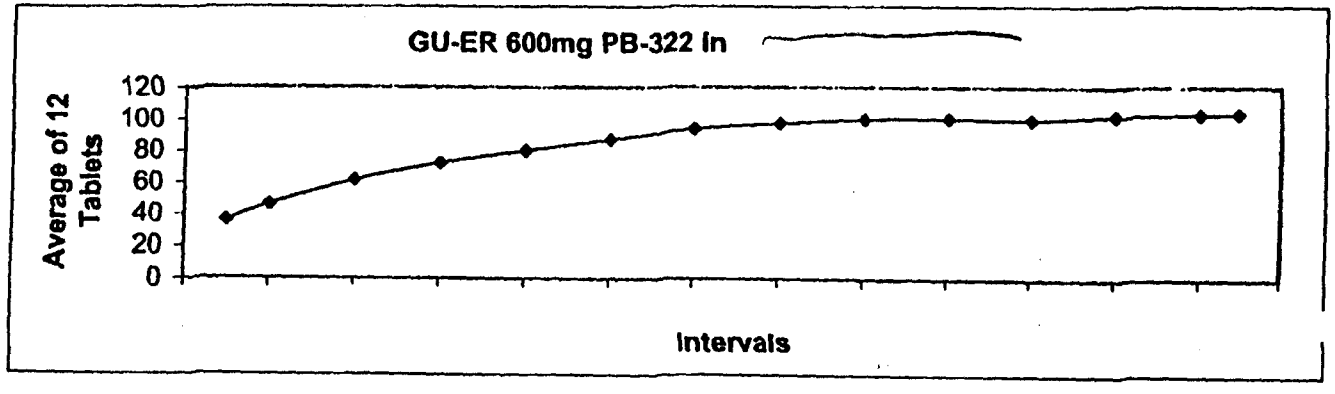
Note: Dissolution 1: ——— H_2O
Dissolution 2:
Dissolution 3:
Dissolution 4: ———
Dissolution 5: ———

Gualfenesin ER 600mg - Lot # PB-322 Dissolution Data for NDA

Dissolution 3: **Medium:** [redacted]
Intervals [redacted]

Baths: J and K for total of 12 tablets

Hours:													
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
Avg	36	46	61	72	80	87	94	97	100	100	100	102	103	104



8 pages redacted from this section of the approval package consisted of draft labeling