Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Lauren Quinn JD
Director
Regulatory Affairs
973.660.6167
quinnL4@wyeth.com

Wyeth

November 17, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

RE: OTC Monograph for Nasal Decongestant Drug Products
Docket 76N-052N

Dear Sir or Madam:

Reference is made to our November 16, 2006 submission to Docket 76N-052N. This letter is to confirm that all attachments to that submission are releasable.

Sincerely,

Lauren Quinn

WYETH CONSUMER HEALTHCARE
Lauren Quinn, JD
Director, Regulatory Affairs

(5)

STUDY EVALUATION REPORT

STUDY NO. 7032

Willem S. Frederik, M.D., Ph.D.
106 Suffolk Road
Wellesley, Massachusetts
Formerly: Pharmatech Inc.
223 Crescent Street
Waltham, Massachusetts

Reference to raw data
Vol. _____
Pages _____

1. Drug, Dosage Form and Phase

Dimetapp Elixir, each component, every combination, and vehicle, Afrin Nasal spray. Phase II.

2. Protocol Number

No number

3. Dates of Initiation and Completion

Initiated: March 1, 1967
Completed: July 31, 1967

4. Materials Used in Study

Commercial stock bottles of:

1. Dimetapp Elixir	3. Elixir Propadrine	5. Dimetapp vehicle
2. Dimetane Elixir	4. Elixir Neosynephrine	6. Afrin nasal spray

Study Objective

To investigate the use of the Respiron* under controlled conditions, as an instrument to evaluate and compare the nasal decongestant effects of Dimetapp Elixir and related formulations and provide data and other information upon which to base the design of definitive studies in this and related areas in the future.

6. Study Description

a. General Study Design

Single-blind, crossover, randomized study in which each subject received one of 8 treatments on 8 separate days.

b. Description of Subjects

Adults with stable or chronic nasal congestion (etiology not of primary importance). Prior to each treatment nasal resistance as determined by the Respiron was at least 10 mm. H_2O.

* See brochure attached to protocol

AHP4-REG-310-0104290

c. Dosage Schedule

See Randomization Schedule and Drug Code attached to protocol.

d. Observations

1. Nasal resistance as measured by Respiron (in mm. H_2O at a flow rate of 0.5 L/sec.) - 5 readings at each observation time.
2. Pulse
3. Blood pressure
4. Adverse effects

e. Schedule for Observations

Pre-treatment
30 minutes
1 hour
2 hours

Nasal resistance was again measured after Afrin spray at 3 minutes and 5 minutes the objectives in this procedure were two:

1. to obtain a check on the instrument and techniques
2. to obtain an indication of the possible maximum response for a given subject on a particular day.

7. Findings

a. Effect on Nasal Resistance

Please refer to Mr. Preston's memo. Statistical Analysis of Dimetapp Elixir Study No. 7032, dated September 6, 1967, attached to this report.

b. Description of Subjects

Age Group (Years)	Sex: Male	Sex: Female	Total
10-19	1	2	3
20-39	3	1	4
40-60	1		1
Total	5	3	8

All subjects had a diagnosis of perennial allergic rhinitis of 2 to 6 years duration.

c. Blood Pressure and Pulse

There was no clinically significant effect of any treatment on blood pressure or pulse in any subject. Raw tabulations of individual blood pressure readings may be found in the file.

AHP4-REG-310-0104291

d. Adverse Effects

None were reported

8. Conclusions and/or Comments

See Mr. Preston's memo. Statistical Analysis of Dimetapp Elixir Study No. 7032, dated September 6, 1967, attached to this report.

Ellen J. Preston, M.D.

11-22-67
EJP:pcj

AHP4-REG-310-0104292

A·H·ROBINS

date September 6, 1967

memo to Dr. Ellen J. Preston

SUBJECT: Statistical Analysis of Dimetapp Elixir Study No. 7032 (Dr. W. Frederik's Respiron Nasal Resistance Study)

A. Basis for Statistical Analysis

1. The design was a "Randomized Block" one in which each of the 8 subjects received, on a randomized schedule, each of the 8 drug treatments.

2. The 8 drug treatments were selected to form a "2x2x2 Factorial" experiment as follows:

		Phenylpropanolamine (P)			
		0 mg.		10 mg.	
		Phenylephrine (N)		Phenylephrine (N)	
		0 mg.	10 mg.	0 mg.	10 mg.
Dimetane (D)	0 mg.	"Placebo"	"N"	"P"	"N+P"
	8 mg.	"D"	"N+D"	"P+D"	"N+P+D"

(These "treatment codes" are used throughout this memo.)

3. All analyses are based on the arithmetic means of the 5 replicate determinations of nasal resistance that were made at each observation period.

4. Separate analyses have been made for each time period (i.e. ½, 1 and 2 hours) for "inspiration" and, similarly, for "expiration."

5. In order to be more nearly consonant with statistical requirements for the analysis of variance (i.e. homoscedasticity and normality), the data have been transformed as follows:

$$\ln(\text{observation})/\ln(\text{pre-drug})$$

B. Interpretation of the Statistical Analysis

The following points are largely implicit, or should be, in the interpretation of any statistical analysis, but it is most important, I feel, that due consideration and weight be given to them in the interpretation of these findings and any decisions predicated on them.

1. The restrictions necessarily placed on the selection of subjects for the study, the mixtures of drugs used, conditions of tests, etc., may or may not limit unduly the population to which you might wish

CONFIDENTIAL

AHP4-REG-310-0104293

to project the findings.

2. A finding of "statistical significance" says, in effect, that the differences observed in the experiment (i.e. sample) are of such magnitude, as compared with the inherent variability of the data, that you can reasonably ascribe these differences to "real" population differences rather than to chance. Furthermore, it is clearly desirable to be able to demonstrate "signficiant" findings in replicates of the experiment, but economic and other factors must also be considered.

3. "Statistically significant" (i.e. "real") differences of objective data may or may not be of "clinical significance":

   a. The objective parameter may or may not be relevant (or totally relevant) to the basic clinical effect desired.

   b. Even if relevant, the magnitude of the "real" difference may or may not be "clinically significant."

4. A statistical finding of "not significant" implies only that the information available from the data is inadequate to support a finding of a "real" difference. A more sensitive experiment (i.e. more information) might well result in a given "not significant" difference becoming "significant."

   Parenthetically, it should be recalled that this experiment was set up as a "pilot" trial with the understanding that additional trials might well be required for more nearly definitive conclusions.

5. It is altogether necessary and proper to consider simultaneously the six separate analyses (viz. "inspiration" and "expiration" at ½, 1 and 2 hours). Cognizance, however, should be taken of the high degree of correlation among the data. While "trends," "clues," etc., are an essential and appealing ingredient of the art of experimentations, the state of statistical theory and methodology largely dictates that any simultaneous consideration be on an intuitive rather than an analytic level.

C. Results and Statistical Analysis

1. The results for the 8 treatments (i.e. non-factorial) are summarized in Table 1 for which the data have been converted to the "% of the pre-drug observation" for each subject and the geometric means calculated for the 8 subjects involved. In none of the 6 sets of data is there a statistically significant difference among the 8 treatments (analysis of variance was performed). The data appear to be highly consistant and are surely of heuristic value and will be referred to in connection with other analyses. [see page 3 for table.]

2. Table 2 shows the direction, magnitude and level of statistical significance for the "main effects" and "interactions" for "2x2x2 factorial" experiment. [see page 4 for table.]

AHP4-REG-310-0104294

TABLE 1

SUMMARY OF RESULTS

INSPIRATION

Rank	½ hour	1 hour	2 hours	Over-all
1	N+D (54.7)*	N+D (67.4)	D (77.4)	N+D
2	P (82.6)	P (100.8)	N+D (83.5)	P
3	N+P+D (91.5)	P+N (109.6)	P (96.8)	D
4	D (98.9)	D (110.4)	N+P+D (99.1)	N+P+D
5	N (112.6)	N (113.9)	P+N (113.7)	P+N
6	P+N (115.2)	N+P+D (115.1)	P+D (152.7)	N
7	P+D (115.7)	P+D (148.0)	N (172.6)	P+D
8	Placebo (149.4)	Placebo (174.0)	Placebo (184.8)	Placebo

EXPIRATION

Rank	½ hour	1 hour	2 hours	Over-all
1	N+D (63.9)	P+N (76.2)	P (76.0)	N+D
2	P (74.9)	N+D (86.3)	N+D (84.9)	P
3	N+P+D (85.0)	P (87.2)	N+P+D (85.5)	P+N
4	P+N (89.9)	N (95.4)	P+N (97.5)	N+P+D
5	Placebo (100.1)	N+P+D (113.0)	D (104.1)	N
6	N (100.8)	Placebo (115.0)	Placebo (130.3)	Placebo
7	P+D (117.0)	D (126.0)	N (132.0)	D
8	D (123.7)	P+D (155.3)	P+D (145.1)	P+D

* ( ) = Geometric Mean (% of pre-drug observation)
8 subjects pe. mean
Codes (see above)

CONFIDENTIAL

AHP4-REG-310-0104295
AHP4-REG-310-0104295

TABLE 2

TABLE OF EFFECTS

(2x2x2 Factorial)

[Data: ln (observation)/ln (pre-drug)]

INSPIRATION

Main Effects	½ hour	1 hour	2 hours
Dimetane (D)	-0.12074✓	-0.07529	-0.15764*
Phenylephrine (N)	-0.09041	-0.12204✓	-0.03764
Phenylpropanolamine (P)	-0.00515	-0.00078	-0.03858
Interactions: NxD	-0.04967	-0.00846	-0.03534
PxD	+0.12142*	+0.14652*	+0.17041**
NxP	+0.10404	+0.08641	+0.00461
NxPxD	-0.03732	-0.04815	-0.09330

EXPIRATION

Main Effects	½ hour	1 hour	2 hours
Dimetane (D)	+0.00458	+0.08020	-0.01748
Phenylephrine (N)	-0.07239	-0.09593✓	-0.05458
Phenylpropanolamine (P)	-0.00823	-0.00678	-0.05475
Interactions: NxD	-0.09160✓	-0.02888	-0.07227
PxD	+0.04763	+0.08459✓	+0.10161*
NxP	+0.04388	+0.01238	-0.00945
NxPxD	+0.02033	-0.00479	-0.04093

** Indicates $p \leq .01$
* Indicates $p \leq .05$
✓ Indicates $p \leq .10$

Negative (-) = decreased nasal resistance
Positive (+) = increased nasal resistance

AHP4-REG-310-0104296

3. Table 3 shows the direction, magnitude and level of statistical significance for the "main effects" and the "interaction" for the "2x2 factorial" experiment in which only those treatments in which phenylpropanolamine was at the "zero" level were considered in the analysis.

TABLE 3

TABLE OF EFFECTS

(2x2 Factorial - Phenylpropanolamine at "zero" level)
[Data: ln (observation)/ln (pre-drug)]

	Main Effects	½ hour	1 hour	2 hours
INSPIRATION	Dimetane (D)	-0.2422*	-0.2219✓	-0.3280**
	Phenylephrine (N)	-0.1945✓	-0.2085✓	-0.0422
	Interaction			
	NxD	-0.0124	+0.0397	-0.0580

	Main Effects	½ hour	1 hour	2 hours
EXPIRATION	Dimetane (D)	-0.0431	-0.0044	-0.1191
	Phenylephrine (N)	-0.1163✓	-0.1083	-0.0451
	Interaction			
	NxD	-0.1119✓	-0.0241	-0.0313

** indicates $p \leq 0.01$
* indicates $p \leq 0.05$
✓ indicates $p \leq 0.10$

Negative (-) = decreased nasal resistance
Positive (+) = increased nasal resistance

D. Conclusions and/or Comments

1. The replicated determinations, the consistancy of the mean results and the magnitude and uniformity of the "error mean squares" in the analysis of variance are indicative of the relatively high degree of precision of the data and lend considerable support to their credibility.

2. Perhaps the most definitive (and intriguing) finding is the statistically significant adverse interaction between Dimetane and phenylpropanolamine (Table 2). In 5 of the 6 sets of data, the "PxD" interaction is significant and in all cases the direction is toward increased nasal resistance.

   As an illustration of the "meaning" of a "PxD" interaction, consider Table 4.

AHP4-REG-310-0104297

TABLE 4

ILLUSTRATION OF THE "DxP" INTERACTION

(Inspiration: ½ hour)

	Phenylpropanolamine 0 mg.	Phenylpropanolamine 10 mg.	Difference
Dimetane at 0 mg.	6.57	6.51	0.06 (Decrease)
Dimetane at 8 mg.	6.45	6.51 (.39)	0.06 (Increase)
Difference (effect)	0.12 (Decrease)	0.00 (none)	

"PxD" Interaction = 0.12

Note that when phenylpropanolamine (P) is not present (i.e. at its zero level), 8 mg. of Dimetane (D) has the effect of reducing nasal resistance by 0.12 units. However, when phenylpropanolamine is present at its 10 mg. level, 8 mg. of Dimetane has no effect on the nasal resistance. The interaction is 0.12 units (i.e. 0.12 + 0.00).

Of course, the interaction is symmetric. When Dimetane is absent, 10 mg. of phenylpropanolamine has the effect of decreasing nasal resistance by 0.06 units. With 8 mg. of Dimetane present, 10 mg. of phenylpropanolamine has the effect of increasing nasal resistance by 0.06 units. Again the interaction is 0.12 units (i.e. 0.06 + 0.06).

Perhaps a more cogent way to look at these data is in terms of the "interaction" as a failure of the two treatment effects to be "additive." When given separately the drugs decrease nasal resistance by 0.06 units and 0.12 units for phenylpropanolamine and Dimetane, respectively. The combined effect of the drugs is only 0.06 units (0.57 - 0.51) instead of 0.18 units (0.12 + 0.06). In the absence of interaction, the "anticipated" results for the combination would have been 0.39 units instead of 0.51 units.

This adverse "PxD" interaction is reflected in Table 1 in which the "P+D" combination ranks seventh in "Inspiration" and eighth in "Expiration."

5. Because of the "PxD" interaction, conclusions about the effects of Dimetane are based on the supplementary 2x2 analysis summarized in Table 3. It can be seen that Dimetane is effective in decreasing nasal resistance during inspiration. The effect is not significant during expiration, but "tends" to be in the "right" direction.

It "appears" also that the Dimetane effect persists, if not increases, during the first 2 treatment hours.

AHP4-REG-310-0104298

6. Phenylephrine has the statistically significant effect of reducing nasal resistance for both inspiration and expiration.

   There is some evidence, however, that the effect of phenylephrine does not persist for two hours.

7. There is one statistically significant ($p \leq 0.10$) "NxD" interaction, but all of these interactions "tend" to be "favorable." A "favorable" interaction can be interpreted conversely to the "adverse" "PxD" interaction as discussed above [i.e. not only are the "favorable" separate effects of Dimetane and of phenylephrine additive, but there could be a supplementary favorable effect from the combination (potentiation?)(synergism?)]. Simple additive effects (i.e. no interaction) appear to me to be adequate justification primae faciae for the formulation of a drug combination.

8. No definitive statement can be made about the statistical significance of phenylpropanolamine because of the significant "PxD" interaction. The effect, however, appears to be "favorable."

9. Rather surprisingly, as I understand it, there appears to be a tendency toward an "adverse" interaction between phenylephrine and phenylpropanolamine (i.e. "NxP" interaction). None of these interactions, however, is significant. In this connection, note both Tables 1 and 2.

10. It should be pointed out that there is no detrimental data with respect to the Dimetapp ("N+P+D") formulation per se. The third order "NxPxD" interaction "tends" toward being "favorable" (Table 2) and this formulation appears to be "superior" to the placebo in all of the sets of data (Table 1). On the other hand, the Dimetapp formulation appears to be "inferior" to the Dimetane-phenylephrine (N+D) combination (Table 1).

Please let me know if you have any comments or questions about these analyses or if you desire any additional analyses.

Lester W. Preston, Jr.

cc: Mr. Bell

LWP/bl

CONFIDENTIAL

AHP4-REG-310-0104299

A·H·ROBINS

date September 20, 1967

memo to Dr. Ellen J. Preston

SUBJECT: Statistical Analysis of Dimetapp Elixir Study No. 7032 - 11
(Dr. W. Frederik's Respiron Nasal Resistance Study)

Per our recent discussions of the previous analysis and in consideration of the manifold imponderables, I recommend the following points be accepted as working hypotheses for the present:

1) "N+D" better than "N+P+D" better than "Placebo"

2) a) "N+P+D" equivalent to "P+N"; therefore, "D" = ?

b) "N+P+D" better than "P+D"; therefore, "N" = F*

c) "N+P+D" worse than "N+D"; therefore, "P" = A*

3)

	A Priori	Main Effect	Added	Interaction
"D"	F	F	?	? = F
"N"	F	F	F	? = F
"P"	F	?	A	A

4)

	A Priori	Main Effect	Added	Interaction
"D"	F	F	F	? = F
"N"	F	F	F	? = F

(F = Favorable
*(A = Adverse

Lester W. Preston, Jr.

LWP/bl

CONFIDENTIAL

AHP4-REG-310-0104300

AHP4-REG-310-0104300