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January 18, 2007

Dr. Heinz Schneider
Vice President, Regulatory & Scientific Affairs
Consumer Healthcare Product Association
900 19th Street, NW, Suite 700
Washington, DC 20006

Dear Dr. Schneider:

Thank you very much for giving me an opportunity to review the report entitled "Efficacy Meta-Analysis of 10 mg Phenylephrine vs. Placebo in Adults with Acute Nasal Congestion Due to Common Cold" prepared by the CHPA Phenylephrine Task Group.

When reviewing the report, I have concentrated on the statistical analyses of each of the individual studies, as well as the Meta Analysis involving seven of the eight studies. I have also had an opportunity to review Appendices 1-5 and the individual study analyses and the Meta analyses.

Statistical analyses on each of the individual studies were performed using Mixed Model analyses, and in my opinion, these analyses were correctly performed and the results have been accurately described in Tables 3 and 4 and nicely illustrated in Figures 1-8, 9, and 13.

Meta analyses were performed using each of the five models 1.a, 1.b, 2.a, 2.b, and 3 with the report emphasizing the results of models 2.b and 3. Of the five models considered, I believe that Model 2.b is the most appropriate and most accurately describes the efficacy of Phenylephrine when compared to placebo. The results are accurately described in Table 5 and effectively illustrated in Figures 1-8, 10-12, and 14-16.

Finally, I agree with the report's basic conclusion that Phenylephrine at a dose of 10 mg is an effective decongestant.

If I can provide you with anything else, please let me know.

Sincerely,

Dallas E. Johnson
Professor Emeritus

CURRICULUM VITAE

NAME: **Dallas E. Johnson** **Year Born:** 1938
TITLE: Professor **Address:** Department of Statistics
Dickens Hall 101
Kansas State University
Manhattan, KS 66506-0802

DEGREES:

B.S., Mathematics Education, Kearney State College, 1960
M.A.T., Mathematics Education, Colorado State University, 1964
M.A., Mathematics, Western Michigan University, 1966
Ph.D., Statistics, Colorado State University, 1971

EXPERIENCE:

Professor of Statistics, Kansas State University, 2001-
Professor of Statistics, and Head, Department of Statistics, Kansas State University, 1995-2001
Professor of Statistics, Kansas State University, and Consultant, KSU Agricultural Experiment Stat
Associate Professor of Statistics, Kansas State University, and Consultant, Agricultural Experiment Station, 1975-81
Assistant Professor of Mathematics and Statistics, University of Missouri-Rolla, 1971-1975
Instructor, Colorado State University, 1966-1968
Math Instructor, Alma High School, Alma, Neb., 1962-1965
Math Instructor, Orleans High School, Orleans, Neb., 1960-1962
Instructor, The Institute of Professional Education, Arlington, Virginia, 1980-2004
Statistical Consultant, Mobay Chemical Corp., Kansas City, KS, 1982
Statistical Consultant, CH2M-Hill, Reston, Virginia, 1983
Statistical Consultant, Schwan's Sales Enterprises, Inc., Marshall, Minnesota,1982-93
Statistical Consultant, Advanced Genetic Sciences, Inc., Manhattan, Kansas, 1983-1984
Statistical Consultant, The Upjohn Company, Kalamazoo, Michigan, 1984-87
Statistical Consultant, Atlantic-Richfield Company (ARCO), Plano, Texas, 1985.
Statistical Consultant, R. J. Reynolds Tobacco Company, Winston Salem, North Carolina, 1988
Statistical Consultant, Syntex, Palo Alto, CA, 1989
Statistical Consultant, HTX International, Inc., Manhattan, KS, 1989-
Statistical Consultant, Advanced Composite Materials Corporation, Greenville,SC, 1991-92
Expert Witness, O'Connor Cavanaugh, et al., Phoenix, AZ, 1990-92
Visiting Scientist, Sri Lanka, Summer 1991

Statistical Consultant, NOVA Corporation, Calgary, 1992-95
Statistical Consultant, Parke-Davis Pharmaceutical Research, 1992-93
Statistical Consultant, DeKalb Plant Genetics, DeKalb, IL, 1994-96
Statistical Consultant, PSM Corporation, Dallas, TX, 1995
Statistical Consultant, GlaxoSmithKline Philadelphia, 1997-2000
Expert Witness, Arnold, White & Durkee, 1997-98.
Statistical Consultant, VISTAKON, Jacksonville, FL, 1999-
Statistical Consultant, Pfizer, Inc., Groton, CT, 2000
Statistical Consultant, Payless ShoeSource, Topeka, KS, 2000-2001
Statistical Consultant, Merial Corporation, 2001-2003
Statistical Consultant, GlaxoSmithKline, Parsippany, NY, 2001-
Statistical Consultant, GlaxoSmithKline, Philadelphia, 2005
Statistical consultant, U.S. Army Research Laboratory – HRED, 2001-

HONORARY AND PROFESSIONAL SOCIETIES:

American Statistical Association, **Fellow**; V-Chm. of Council, 1977; Board of Directors, 1987-89; **Chair** of the Section on Statistical Education, 1988; Task Force on Outreach for ASA Publications, 1990; **Chair** of the Section on Statistical Consulting, 1993; **Chair**, Coordinating Committee of the Institutional Members of ASA, 1978-1980; ASA Nominating Committee, 1993-94, **Chair**, 1994; **Founding Editor**, *Journal of Agricultural, Biological, and Environmental Statistics*, 1994-98, Associate Editor, 2002- 2004; **Chair**, ASA Committee of Statistics Academic Department Heads and Program Representatives, 1998; ASA Founders Award, 2003; Commerce Bank Distinguished Graduate Faculty Award, 2004; International Biometric Society-ENAR
Founding Editor, *Journal of Agricultural, Biological, and Environmental Statistics,* 1994-1998, Associate Editor, 2002- 2003; **Referee,** *The Journal of the American Statistical Assoc., Technometrics, The American Statistician, Biometrics, Communication in Statistics, and the Journal of Statistical Planning and Inference.*

President, Kansas-Western Missouri Chapter of ASA, 1975-1977
Lecturer, COPSS Visiting Lecture Program in Statistics, 1977-1990
Editorial Board, *Communications in Statistics-Statistical Reviews*, 1983-88
Associate Editor, *The American Statistician*, 1985-92
Associate Editor, *Communications in Statistics - Simulations and Computations*, 1986-92

FIELDS OF RESEARCH COMPETENCE:

Messy Data Analysis
Design and Analysis of Crossover Experiments
Experimental Design and Linear Models
Statistical Methods for the Medical Sciences
Statistical Methods for Agriculture
Bayesian Methods in "Failure-on-Demand" and "Failure-Rate" Models
Model Validation Methods
Multiple Regression and Biased Regression Methods
Applications of Multivariate Methods
Repeated Measures and Longitudinal Studies

CONSULTING EXPERTISE:

Statistical Analyses of Messy Data
Model Building and Regression Analyses
Multivariate Data Analysis Methods
Split Plot and Repeated Measures Experiments
Crossover Designs
Analysis of Clinical Trials
Experimental Design
Covariance Models
Statistical Quality Control Methods
Safety Analysis and Risk Assessment
Development of New Statistical Methodology
Logistic Regression
Designs for Product Development and Improvement

BOOKS:

George A. Milliken and Dallas E. Johnson, 1984, 1992. *Analysis of Messy Data, Vol. 1 - Designed Experiments*, Chapman and Hall, New York.

George A. Milliken and Dallas E. Johnson, 1989. *Analysis of Messy Data, Vol. 2 - Nonreplicated Experiments*, Chapman and Hall, New York.

Dallas E. Johnson, 1998. *Applied Multivariate Methods for Data Analysts*, Duxbury, Belmont, CA

George A. Milliken and Dallas E. Johnson, 2002. *Analysis of Messy Data, Vol. 3 - Analysis of Covariance*, Chapman & Hall/CRC, Boca Raton, FL

PROFESSIONAL PUBLICATIONS (Refereed Statistical Journals):

D. E. Johnson, and Graybill, F. A., 1972. The estimation of Φ^2 in a two-way classification model with interaction. *Journal of the American Statistical Association 67*:388-868.

D. E. Johnson, and F. A. Graybill, 1972. An analysis of a two-way model with interaction and no replication. *Journal of the American Statistical Association 67*:862-868.

D. E. Johnson, 1973. A derivation of Schefe's S-method by maximizing a quadratic form. *The American Statistician 27*:27-29.

D. E. Johnson, and John Kubicek, 1973. Is complete really the right name? *The American Statistician 27*:240-241.

D. E. Johnson and Victor Hegemann, 1974. Procedures to generate random matrices with noncentral distributions. *Communications in Statistics* 3:691-699

D. E. Johnson, 1974. On the moments of the characteristic roots of a noncentral (2x2) Wishart matrix. *The Australian Journal of Statistics 16*: 153-155.

Victor Hegemann and D. E. Johnson, 1976. The power of two tests for nonadditivity. *Journal of the American Statistical Association 71*:945-948.

Victor Hegemann and D. E. Johnson, 1976. On analyzing two-way AoV data with interaction. *Technometrics 18*:273-281.

D. E. Johnson, 1976. Some new multiple comparison procedures for the two-way AoV model with interaction. *Biometrics 328*:929-934.

D. E. Johnson, Stephen A. McGuire, and George A. Milliken, 1978. Estimating Φ^2 in the presence of outliers. *Technometrics 20*:441-455.

M. Marasinghe and D. E. Johnson, 1981. Testing subhypotheses in the multiplicative interaction model. *Technometrics 23*:385-393.

M. Marasinghe and D. E. Johnson, 1982. Estimating Φ^2 in the multiplicative interaction model. *Communications in Statistics - Theory and Methods 11*:315-324.

M. Marasinghe and D. E. Johnson, 1982. A test of incomplete additivity in the multiplicative interaction model. *Journal of the American Statistical Assoc. 77*:869-877.

D. E. Johnson, 1982. Comments on quality of statistical education: Should ASA assist or assess? *The American Statistician 36*:95-96.

J. W. Neill and D. E. Johnson, 1984. Testing for lack of fit in regression models without replication - A review. *Communications in Statistics - Theory and Methods 13*:485-511.

J. W. Neill and D. E. Johnson, 1985. Testing linear regression function adequacy without replication. *Annals of Statistics 13*:1482-1489.

D. E. Johnson and George A. Milliken, 1985. Messy Data. *Encyclopedia of Statistical Sciences, Vol 5.* John Wiley and Sons, Inc., New York.

Shultis, J. K., Johnson, D. E. and Milliken, G. A., 1986. Non-conjugate prior distributions and their estimation for **use** in failure models. *Communications in Statistics-Theory & Methods 15*:2835-2865.

D. E. Johnson, 1988. Book Review of Statistical Design: Theory and Practice. Charles E. McCulloch, Steven J. Schwager, George Casella, and Shayle R. Searle (eds.). *Journal of the American Statistical Association 83*:909.

J. W. Neill and D. E. Johnson, 1989. A comparison of some lack of fit tests based on near replicates. *Communications in Statistics 18*:3533-3570.

G. Weerakkody and D. E. Johnson, 1990. Variance Component Estimation in Multiple Regression Models Having a Nested Error Structure. *Communications in Statistics*, 19:2879-2905.

D. E. Johnson, 1991. Messy Experimental Designs. *Proceedings of the 1991 KSU Conference on Applied Statistics in Agriculture,* 85-101.

G. Weerakkody and D. E. Johnson, 1992. Estimation of Within Model Parameters in Regression Models With a Nested Error Structure. *Journal of the American Statistical Association*, 87:708-713.

M. Remmenga and D. E. Johnson, 1992. Options for Analyzing Unbalanced Split-Plot Experirements: A Case Study, *Proceedings of the 1992 KSU Conference on Applied Statistics in Agricultur*, 170-179.

Johnson, Dallas E. and Goad, Carla ,1993. On Multivariate Analyses of Crossover Designs. *Proceedings of the 1993 Kansas State University Conference on Applied Statistics in Agriculture*, 122-145.

Remmenga, Marta D. and Johnson, Dallas E. (1995). A Comparison of Inference Procedures in Unbalanced Split-plot Designs. *Journal of Statistical Computation and Simulation 51*: 353-367.

Harris, T. Robert and Johnson, Dallas E. (1996). A regression Model With Spatially Correlated Errors for Comparing Remote Sensing and In-Situ Measurements of a Grassland Site. *Journal of Agricultural, Biological, and Environmental Statistics, 1:*190-204.

C. L. Goad and D. E. Johnson, 1997. Alternative Analyses of Crossover Designs with More than Two Periods. *Proceedings of the 1997 KSU Conference on Applied Statistics in Agriculture*, 129-158.

L. Ballou and D. E. Johnson, 1997. Some Experiences with Neural Networks. *Proceedings of the 1997 KSU Conference on Applied Statistics in Agriculture*, 179-190.

C.L. Goad and D.E. Johnson, 2000. Crossover Experiments: A Comparison of ANOVA Tests and Alternative Analyses. *Journal of Agricultural, Biological, and Environmental Statistics, 5*:69-87.

T.M. Loughin, D.E. Johnson, S.E. Ives, and T.G. Nagaraja (2001). Methods for selecting Crossover Designs with Application to an Experiment with Two Factors in a Split-Plot. *Journal of Agricultural, Biological, and Environmental Statistics*, 7: 143-156.

Y. Wang, L.J. Young, and D.E. Johnson (2001). A UMPU Test for Comparing the Means of Two Negative Binomial. *Communications in Statistics - Simulations and Computations* 30:1053-1075.

W.N. Wickremasinghe and D.E. Johnson (2002). Testing Subhypotheses and Estimating Φ^2 in the Nonreplicated Three-Way Multiplicative Interaction Model. *Communications in Statistics, Simulation and Computation 31*: 605-618.

Christina D. Smith and D.E. Johnson (2005). Comparing Analyses of Unbalanced Split-Plot Experiments. Accepted for publication in *Journal of Statistical Computation and Simulation.*

PROFESSIONAL PUBLICATIONS (Non-refereed Statistical Publications):

D. E. Johnson, Aug 1971. Interaction in the Two-Way classification model, invited paper presented at the American Statistical Association Annual Meeting, Ft. Collins, CO.

D. E. Johnson, 1976. Estimating Φ^2 in the presence of outliers. Technical Report US Army Research Office.

G. A. Milliken and D. E. Johnson, 1978. A class of generalized ridge estimators that control the loss in R^2 Contribution No. 79-258-J, Kansas Agricultural Experiment Station.

D. E. Johnson, and George Milliken, 1979. Biased estimation of functions of the parameters in a linear regression model. Contribution No. 79-333-J, Kansas Agricultural Experiment Station.

J. K., Shultis, D. E. Johnson, G. A. Milliken, and N. D. Eckhoff, 1980. Non-conjugate prior distributions in compound failure models. Technical Report to Office of Nuclear Regulatory Commission, Washington, D.C. NRC-04-79-182.

J. K. Shultis, N. D. Eckhoff, D. E. Johnson and G. A. Milliken, 1980. Safe-R and Safe-D, computer codes for the analysis of failure data. Technical Report to Office of U.S. Nuclear Regulatory Commission, Washington, D.C. NRC-04-79-182.

J. K. Shultis, D. E. Johnson, G. A. Milliken, and N. D. Eckhoff. 1980. Gamma - A code for the analysis of component failure rates with a compound poisson-gamma model. Office of Nuclear Regulatory Commission, Washington, D.C. NRC 04-79-182.

Johnson, D. E., 1984. Training students for statistical consulting. *Proceedings of the American Statistical Association Section on Education.*

Johnson, D. E., 1986. Considerations for using extended period crossover designs. *ASA Proceedings of the Biopharmaceutical Section* 183-187.

Johnson, D. E., 1988. Messy Experimental Designs. *ASA Proceedings of the Section on Statistical Education.*

Johnson, D. E., 1991. Use of Statistical and Biometrical Methods in Sri Lanka. USAID Technical Report, Developmental Alternatives, Inc.

Johnson, Dallas E. and Goad, Carla (1993). A test for Huynh-Feldt Conditions in Crossover Designs and Analyses of Crossover Designs when the Huynh-Feldt Conditions are not Satisfied. An invited paper presented at the 16th Annual Midwest Biopharmaceutical Statistics Workshop, May 19-21, 1993.

Johnson, Dallas E. (1993). Biometry: Challenges in the Agricultural Sciences. An invited paper presented at the 1993 Annual Meeting of the American Statistical Association.

Lee, Eun-Joo and Johnson, Dallas E. (2004). Statistical Analysis Software for Multiplicative Interaction Models. *ASA Proceedings of the Joint Statistical Meetings,* 2488-2495. American Statistical Association (Alexadria, VA).

Smith, Christina D. and Johnson, Dallas E. (2007). Comparing analyses of unbalanced split-plot experiments. *Journal of Statistical Computation and Simulation* 77(2):119-129.

PROFESSIONAL PUBLICATIONS (Refereed Nonstatistical Journals):

Jac F. Morgan, G. E. Wilde, and D. E. Johnson, 1980. Green bug resistance levels in commercial grain sorghum hybrids in the seedling stage. *Jour. of Economic Entomology 73*:510-514.

M. C. Carakostas, W. E. Moore, D. E. Johnson, and J. E. Smith, 1981. Effects of Etiochoanolone and Prednisolone on Intravascular Granulocyte Kinetics in Horses. *Am. J. Vet., Res. 42* 626-628.

D. E. Johnson, U. N. Chaudhuri, and E. T. Kanemasu, 1983. Statistical analysis of line source sprinkler experiments and other non-randomized experiments using multivariate methods. *Soil Science Society of America Journal 47*:309-312.

M. Nuwanyakpa, K Bolsen, G. Posler, D. E. Johnson, and Y. Juico, 1982. Grazing management in the coastal region of Equador: a) Dry matter yield and beef production from four cultivated tropical pastures. *Journal of Agricultural Science, Cambridge.*

G. P. Miller, M. Fuchs, M. J. Hall, G. Asran, E. T. Kanemasu and D. E. Johnson, 1983. Analysis of seasonal multipectral reflectances of small grains. Ag RISTAR Technical Report no. SR-M3-04401.

G. P. Miller, M. Fuchs, M. J. Hall, G. Asrar, E.T. Kanemasu and D. E. Johnson, 1984. Analysis of seasonal multispectral reflectances of small grains. *Remote Sensing of Environment 14*:153-67.

S. L. Nash, M. C. Savides, F.W. Oehme, F. W. and D. E. Johnson, 1984. The effect of acetaminophen on methemoglobin and blood glutathione parameters in the cat. *Toxicology 31*:329-334.

I. E. O. Abdelgadir, J. L. Morrill, J. A. Stutts, M. B. Morrill, M. B., D. E. Johnson, and K. C. Behnke, 1984. Effect of processing temperature on utilization of whole soybeans by calves. *Journal of Dairy Science 67*:2554-2559.

D. M. Andrus, E. Silver, and D. E. Johnson, 1986. Status Brand Management and Clothing Gift Purchases: A Discriminant Analysis. *Journal of Consumer Marketing 3*:5-13.

G. Arsar, R. L. Weiser, D. E. Johnson, E. T. Kanemasu, and J. H. Killeen, 1986. Distinguishing among tallgrass prairie cover types from measurements of multispectral reflectance. *Remote Sensing of Environment 19*:159-169.

K. A. Jacques, D. E. Axe, T. R. Harris, D. L. Harmon, K. K. Bolsen, and D. E. Johnson, 1986. "Effect of Sodium Bicarbonate and Sodium Bentonite on Digestion, Solid and Liquid Flow, and Rumenal Fermentation Characteristics of Forage Sorgum Silage - Based Diets Fed to Steers." *Journal of Animal Science 63*:923-932.

Jerome G. E. Vestweber, F. K. Al-Ani, and D. E. Johnson, 1987. Udder edema in Cattle: Effect of Furosemide, Hydrochlorothiazide Acetazolamide, or 50% Dextrose on Venous Blood Pressure. *American Journal of Veterinary Research 48*:673-675

G. K. Newell, C. L. Hammig, A. P. Jurich, and D. E. Johnson, 1987. "Self-Concept as a Factor in the Quality of Diets of Adolescent Girls." Submitted to *Journal of the American Dietetic Association* Contribution Number 387-296-J, Kansas Agriculture Experiment Station.

K. B. Foehse, R. C. Hoseney, and D. E. Johnson, 1988. "Predicting the Fluidity of Corn Flour/Water Systems." *Cereal Chemistry 65*:501-502. **This paper was presented at the November 87 Annual Meeting of Cereal Chemists and won the Outstanding Paper Award given by the Corn Refiners Association.**

Gunderson, S. L., A. A. Aguilar, D. E. Johnson, and J. D. Olson. 1988. Nutritional value of wet corn gluten feed for sheep and lactating dairy cows. J. Dairy Sci. 71:1204-1210.

Jerome G. E. Vestweber, F. K. Al-Ani, and D. E. Johnson, 1989. Udder Edema in Cattle: Effects of Diuretics (Furosemide, Hydrochlorothiazide, Acetazolamide, or 50% Dextrose) on Serum and Urine Electrolytes. *American Journal of Veterinary Research 50*:1323-1328.

John W. Drake, and Dallas E. Johnson, 1989. Measurements of 747 Cabin Air Quality on Long-Range Flights. *Aviation, Space, and Environmental Medicine.*

David L. Harmon and D. E. Johnson, 1989. Small Intestinal Starch Digestion in Steers: Effect of various levels of abomasal glucose, com starch and corn dextrin infusion on small intestinal disappearance and net glucose absorption. *Journal of Animal Science.*

DelCurto, T.R., R.C. Cochran, L.R. Corah, A.A. Beharka, E.S. Vanzant, and D.E. Johnson, 1990. Supplementation of dormant tallgrass-prairie forage: II. Performance and forage utilization characteristics in grazing beef cattle receiving supplements of different protein concentrations. *Journal of Animal Science 68:*532-542.

D. J. Lawlor, E. T. Kanemasu, W. C. Albrecht, III, and D. E. Johnson, 1990. Seed Production Environment Influence on the Base Temperature for Growth of Sorghum Genotypes. *Agronomy Journal*, 82:643-647.

J. G. Vestweber, R. D. Klemm, H. W. Leipold, D. E. Johnson and W. E. Bailie, 1990. Clinical and Pathologic Studies of Experimentally Induced Pasteurella Haemolytica Pneumonia in Calves. *Am. J. Vet. Res.*, 51:1792-1798.

K. K. Kreikemeier, D. L. Harmon, R. T. Brandt, Jr., T. B. Avery and D. E. Johnson, 1991. Small Intestinal Starch Digestion in Steers: Effect of Various Levels of Abomasal Glucose, Corn Starch and Corn Dextrin Infusion on Small Intestinal Disappearance and Net Glucose Absorption. *J. An. Sci.*, 69:328-338.

E. S. Vanzant, R. C. Cochran and D. E. Johnson, 1991. Pregnancy and Lactation in Beef Heifers Grazing tallgrass Prairie in the Winter: Influence on Intake, Forage, Utilization, and Grazing Behavior. *Journal of Animal Science*, 69:3027-3038.

J. G. Vestweber, D. E. Johnson, G. L. Merrill, and J. J. Staats, 1991. Hematological and Blood Chemistry Profiles of American Bison Grazing on Konza Prairie of Kansas. *Journal of Wildlife Diseases*, *27*:417-420.

R. Oyster, H. W. Leipold, D. Troyer, W. Cash, D. Johnson, and H.D. Stowe, 1991. Laboratory Studies of Bovine Progressive Degenerative Myeloencephalopathy in Brown Swiss Cattle. *Bovine Practice*, 26: 77-83.

R. Oyster, W. Cash, D. Troyer, J. E. Vestweber, H. W. Leipold, D. E. Johnson, 1991. Electrophysiological studies in Bovine Progressive Degenerative Myeloencephalopathy of Brown Swiss Cattle. *Progress in Vet. Neurol. 2*: 243-251.

E. S. Troutt, M. C. Hunt, D. E. Johnson, J. R. Claus, C. L. Kastner and D. H. Kropf, 1992. Characteristics of Low-fat Ground Beef Containing Texture-modifying Ingredients. *J. Food Sci., 57(1):*19-24.

E. S. Troutt, M. C. Hunt, D. E. Johnson, J. R. Claus, C. L. Kastner, D. H. Kropf, and S. Stroda, 1992. Chemical, Physical, and Sensory Characterization of Ground Beef Containing 5 to 30 Percent Fat, 1992. *J. Food Sci., 57(1)*:25-29.

D. A. Mosier, M. L. McFarland, D. E. Johnson, R. G. Elmore, and J. M. Oyler. Career Indecision in Veterinary Medical Students. *Journal of Veterinary Medical Education*, 66-70.

K. E. Warren, M. C. Hunt, C. L. Marksberry, O. Sörheim, D. H. Kropf, D. E. Johnson and M. J. Windisch. 1992. Modified-Atmosphere Packaging of Bone-In Pork Loins. *Journal of Muscle Foods*, 3:283-300.

Reagan, Barbara M., Lattie, Robert K., Crews, Patricia K., Scott, Kurt, Cho, Liling, and Johnson, Dallas E., (1993). Accelerated Lightfastness Testing of Disperse Dyes on Polyester Automotive Fabrics. *Book of Papers, American Association of Textile Colorists and Chemists 25:*25-32. **Paper won first place in AATCC's 1993 Intersectional Technical Paper Competition in Montreal in October.**

Beaty, J.L., Cochran, R.C., Lintzenich, B.A., Vanzant, E.S., Morrill, J.L., Brandt, R.T. Jr., and Johnson, D.E. (1994). Effect of Frequency of Supplementation and Protein Concentration in Supplements on Performance and Digestion Characteristics of Beef Cattle Consuming Low-Quality Forages. *Journal of Animal Science* 72:2475-2486.

Hague, M.A., Warren, K.E., Hunt, M.C., Kropf, D.H., Kastner, C.L., Stroda, S.L., and Johnson, D.E. (1994). Endpoint Temperature, Internal Cooked Color, and Expressible Juice Color Relationships in Ground Beef Patties. *Journal of Food Science* 58(3):465-470.

Hoag, Linda A., Bedrosian, Jan L., Johnson, Dallas E., and Molineux, Barry (1994). Variables Affecting Perceptions of Social Aspects of Communicative Competence of an Adult AAC User. *Augmentative and Alternative Communication* 10:129-137. **This paper won the Prentke Romich AAC Editors Award, December 7, 1995.**

Scheule, Barbara M, Miller, Judy L., McCahon, Cynthia, and Johnson, Dallas E. (1995). Use of the NACUFS Professional Standards Manual as Reported by NACUFS Members. *The Journal of the National Association of College & University Food Services* 19:73-79.

Scheule, Barbara M, Miller, Judy L., McCahon, Cynthia, and Johnson, Dallas E. (1996). Influence of the NACUFS Professional Standards Manual on Customer Perceptions of Quality and Responsiveness. *The Journal of the National Association of College & University Food Services* 20:77-88.

Prasai, R. K., Kastner, C.L., Kenney, P.B., Kropf, D. H., Fung, D.Y.C., Mease, L.E., Vogt, L.R., and Johnson, D. E. (1997). Microbiological Quality of Beef Subprimals as Affected by Lactic Acid Sprays Applied at Various Points during Vacuum Storage. *Journal of Food Protection, 60: 795-798.*

Bedrosian, Jan L., Hoag, Linda A., Johnson, Dallas E., and Calculator, Stephen N. (1998). Perceptions of Communicative Competence in Adults with Cerebral Palsey. Under revision for the *Journal of Speech and Hearing Research* 41, 667-675.

Olson, K.C., Cochran, R.C., Jones, T.J., Vanzant, E.S., Titgemeyer, E.C., and Johnson, D.E. (1999). Effects of Ruminal Administration of Supplemental Degradable Intake Protein and Starch on Utilization of Low-Quality, Warm-Season Grass Hay by Beef Steers. *Journal of Animal Sciences 77:*1016-1025.

Heldt, J.S., Cochran, R.C., Mathis, C.P., Woods, B.C., Olson, K.C., Titgemeyer, E.C., Johnson, D.E., Vanzant, E.S., and Nagaraja, T.G. (1999). Effects of Level and Source Carbohydrate and Level of Degradable Intake Protein on Intake and Digestion of Low-Quality Tallgrass-Prairie Hay by Beef Steers. *Journal of Animal Sciences 77:*2846-2854.

Duncan, Pamela W.;Wallace, Dennis; Lai,Sue Min; Johnson, Dallas; Embretson, Susan, and Laster, Louise Jacobs (1999). The Stroke Impact Scale Version 2.0: Evaluation of Reliability, Validity, and Sensitivity to Change. *Stroke 30:* 2131-2140.

Levis, P., Chambers IV, E., Johnson, D.E. (2000). Consumption and Liking of a Fat-Modified Product During Short Trial Periods. *Nutrition Research 20:*791-804.

Farmer, C.G., Cochran, R.C., Simms, D.D., Klevesahl, E.A., Wickersham, T.A., Johnson, D.E. (2001). The Effects of Several Supplementation Frequencies on Forage Use and the Performance of Beef Cattle Consuming Dormant Tallgrass-Prairie Forage. *Journal of Animal Science, 79:*2276-2285.

Mathis, C.P., R.C. Cochran, E.S. Vanzant, I.E.O. Abdelgardir, J.S. Heldt, K.C. Olson, D.E. Johnson, J. Caton, D. Faulkner, G. Horn, S. Paisley, R. Mass, K. Moore, J. Halgerson (2001). A collaborative study comparing an in situ protocol with single time-point enzyme assays for estimating ruminal protein degradability of different forages. *Animal Feed Science and Technology 93*: 31-42.

Duncan, P. W., Wallace, D., Studenski, S., Lai, S. M., & Johnson, D. (2001). Conceptualization of a new stroke specific outcome measure: The stroke impact scale. *Topics in Stroke Rehabilitation, 8*(2), 19-33.

Sammel, L.M., M.C. Hunt, D.H. Kropf, K.A. Hachmeister, D.E. Johnson (2002). Comparisons of Assays for Metmyoglobin Reducing Ability in Beef Insde and Outside Semimembranosus Muscle. *Journal of Food Science: Food Chemistry and Toxicology 67*: 978-984.

Sammel, L.M., M.C. Hunt, D.H. Kropf, K.A. Hachmeister, C.L. Kastner, D.E. Johnson (2002). Influence of Chemical Characteristics of Beef Inside and Outside Semimembranosus on Color Traits. *Journal of Food Science: Food Chemistry and Toxicology 67*: 1323-1330.

Lai, Sue Min, Pamela Duncan, Dallas E. Johnson (2002). Depressive symptoms and independence in BADL and IADL. Accepted for publication in the *Journal of Rehab Res andDevelopment.*

Lai, S. M., Duncan, P. W., Keighley, J., & Johnson, D. (in press). Depressive symptoms and stroke recovery. Archives of Physical Medicine and Rehabilitation.

Wickersham, T.A., R.C. Cochran, E.C. Titgemeyer, C.G. Farmer, E. A. Klevesahl, J.I. Arroquy, D. E. Johnson, and D.P. Gnad (2003). The Relative Value of Ruminally Degradable and Undegradable Protein on the Utilization of Low-Quality Prairie Hay by Steers. To appear in the 2003 Cattlemen=s Day.

Lee, Kyung-Eun, Carol W. Shanklin, Dallas E. Johnson (2003). Development of Service Quality Measurement for Foodservice in Continuing Care Retirement Communities. *Foodservice Research International, 14*, 1-21.

Duncan, Pamela, Stephanie Studenski, Lorie Richards, Steven Gollub, Sue Min Lai, Dean Reker, Subashan Perera, Joni Yates, Victoria Koch, Sally Rigler, and Dallas E. Johnson (2003). A Randomized Clinical Trial of Therapeutic Exercise in Sub-Acute Stroke. Accepted for publication in *Stroke.*

Lawrence, T.E., M.E. Dikeman, M.C. Hunt, C.L. Kastner, and D.E. Johnson (2003). Staged Infection Marianation with Calcium Lactate, Phosphate and Salt May Improve Beef Water-Binding Ability and Palatability Traits. Submitted for publication.

Lawrence, T.E., M.E. Dikeman, J.W. Stephens, E. Obuz, J.R. Davis, M.C. Hunt, C.L. Kastner, and D.E. Johnson (2003). In Situ Investigation of the Calcium-Induced Proteolytic and Salting-in Mechanisms Causing Tenderization in Calcium-Enhanced Muscle. Submitted for Publication.

Klevesahl, E.A., R.C. Cochran, E.C. Titgemeyer, T.A. Wickersham, C.G. Farmer, J.I. Arroquy, D.E. Johnson (2003). Effect of a Wide Range in the Ratio of Supplemental Rumen Degradable Protein to Starch on Utilization of Low-quality, Grass Hay by Beef Steers. *Animal Feed Science Technology, 105*:5-20.

Wickersham,, T.A., R.C. Cochran, E.C. Titgemeyer, C.G. Farmer, E.A. Klevesahl, J.I. Arroquy, D.E. Johnson, and D.P. Gnad (2004) Effect of Postruminal Protein Supply on the Response to Ruminal Protein Supplementation in Beef Steers Fed Low-Quality Grass Hay. *Animal Feed Science and Technology,* 115:19-36.

Arroquy, J.I., R.C. Cochran, T.A. Wickersham, D.A. Llewellyn, E.C. Titgemeyer, T.G. Nagaraja, D. E. Johnson (2004). Effects of Type of Supplemental Carbohydrate and Source of Supplemental Rumen Degradable Protein on Low Quality Forage Utilization by Beef Steers. *Animal Feed Science and Technology 115:*247-263.

Arroquy, J.I., R.C. Cochran, m. Villarreal, T.A. Wickersham, D.A. Llewellyn, E.C. Titgemeyer, T.G. Nagaraja, D. E. Johnson, D. Gnad (2004). Effect of Level of Ruemen Degradable Protein and Type of Supplemental Non-Fiber Carbohydreate on Intake and Digestion of Low-Quality Grass Hay by Beef Cattle. *Animal Feed Science and Technology 115:*83-99.

Lambert, B.D., Titgemeyer, E.C., Loest, C.A., Johnson, D.E. (2004). Effect of Glycine and Vitamin Supplementation on Sulfur Amino Acid Utilization by Growing Cattle. *Journal of Animal Physiology, A. Animal Nutrition* 88:288-300.

Wickersham, E.E., J.E. Shirley, E.C. Titgemeyer, M.J. Brouk, J.M. DeFrain, A.F. Park, D.E. Johnson, and R.T. Ethington. (2004). Response of lactating dairy cows to diets containing wet corn gluten feed or a raw soybean hull-corn steep liquor pellet. *J. Dairy Sci. 87*:3899-3911.

Arroquy, J.I, R.C. Cochran, T.G. Nagaraja, E.C. Titgemeyer, and D.E. Johnson (2005). Effect of types of non-fiber carbohydrate on in vitro forage fiber digestion of low-quality grass hay. *Animal Feed Science and Technology* 120:93-106.

Chambers, Delores H., Edgar Chambers IV, and D. E. Johnson (2005). Flavor description and classification of selected natural cheeses. *Culinary Arts and Sciences, Vol.* 5: 641-654.

Linda A. Hoag, J.L. Bedrosian, K.F. McCoy, and D.E. Johnson (2005). Informativeness and speed of message delivery trade-offs in augmentative and alternative communication. *Journal of Speech, Language, and Hearing Research.* In press.

Villarreal, M., Cochran, R.C., Johnson, D.E., Towne, E.G., Wilson, W.T., Harnett, D.C., and Goodin, D.G. (2006). The use of pasture reflectance characteristics and arbuscular mycorrhizal root colonization to predict pasture characteristics of tallgrass prairie grazed by cattle and bison. *Grass and Forage Science,* 61: 32-41.

Seyfert, Mark, Melvin C. Hunt, Jeannine P. Grobbel, Suzanne M. Ryan, Dallas E. Johnson, and Rene A. Monderen (2006). Potassium Lactate and Fresh-Pork-Sausage Formulation Effects on Shelf Life in Lighted and Unlighted Display. *Journal of Food Science* 71:390-394.

Mancini, R.A., M.C. Hunt, M. Seyfert, D.H. Dropf, K.A. Hachmeister, T.J. Herald, and D.E. Johnson (2007). Comparison of ascorbic acid and sodium erythorbate: Effects on the 24 h display colour of beef lumbar vertebrae and *longissimus lumborum* packaged in high-oxygen modified atmospheres. *Meat Science* 75: 39-43.

Seyfert, Mark, Melvin C. Hunt, M. Lundesjo Ahnstrom, and D.E. Johnson (2007). Efficacy of lactic acid salts and sodium acetate on ground beef colour stability and metmyoglobin-reducing activity. *Meat Science* 75: 134-142.

Ahnstrom, Maria Lundesjo, Mark Seyfert, Melvin C. Hunt, and Dallas E. Johnson (2007). Dry aging of beef in a bag highly permeable to water vapour. *Meat Science* 73:674-679.

Mancini, R.A., M.C. Hunt, K.A. Hachmeister, M.A. Seyfert, D.H. Kropf, D.E. Johnson, S. Cusick, and C. Morrow (2005). The utility of Lactate and Rosemary in Beef Enhancement Solutions: Effects on *Longissimus* Color Changes During Display. *Journal of Muscle Foods* 16: 27-36.

HONORS:

Selected as the outstanding graduate student in Statistics by the faculty at Colorado State University, 1970.

Selected as an Outstanding Teacher for the 1971-72 academic year by the students and faculty of the University of Missouri-Rolla.

Nominated for the Annual Distinguished Graduate Faculty Award at Kansas State University, 1977.

Nominated for an Outstanding Undergraduate Teaching Award at Kansas State University, 1977.

Invited Professor at Universidad Nacional Autonoma De Mexico, Mexico City, January 1979.

Elected a Fellow of the American Statistical Association, 1983.

Lecturer, COPSS Visiting Lecture Program in Statistics, 1977-1990.

Alcoa Foundation Science Support Grant, $7500, 1987.

Alcoa Foundation Science Support Grant, $7500, 1988.

Named the Outstanding Chapter Member of the Kansas-Western Missouri Chapter of the American Statistical Association in conjunction with ASA's 150th Anniversary Meeting, (1990)

Selected as the Founding Editor of Journal of Agricultural, Biological, and Environmental Statistics, a joint publication of the American Statistical Association and the International Biometrics Society, (1994).

Received the Don Owen Award from the San Antonio Chapter of the American Statistical Association and Marcel Dekker, Incorporated. This award is given to a statistician who embodies the accomplishments of Don Owen: Excellence in Research, Contributions to Editorial Activities, and Service to the Statistical Community, May, 1997.

Received the American Statistical Association Founders Award, 2003.

Received the Commerce Bank Distinguished Graduate Faculty Award, 2004.

COURSES TAUGHT:	BOOKS USED:
1. Introduction to Probability and Statistics	Freund, Devore; Walpole and Myers
2. Introduction to Statistical Methods	Snedecor and Cochran; Ott; Huntsberger; Johnson
3. Regression and Correlation	Draper and Smith; Ott; Myers
4. Analysis of Variance and Covariance	Snedecor and Cochran; Ott
5. Experimental Design	Cochran And Cox, Mead
6. Mathematical Statistics I and II	Hogg & Craig; Mood, Graybill, & Boes; Berger &
7. Linear Models I and II	Cassella
8. Experimental Design Theory	Graybill
9. Multivariate Analysis I and II	John
10. Analysis of Messy Data	Giri
11. Design & Anal. of Crossover Designs	Milliken and Johnson
12. The Theory of Mixed Models	Personal Notes
13. Multivariate Methods	Personal Notes & miscellaneous papers & books
	Morrison; Chatfield and Collins; Wichern and Johnson;
	Johnson

GRANTS AND CONTRACTS:

1975-76 U.S. Army Research Office Grant entitled "Variance Estimation in the Presence of Outliers, $16,596.

1977 Proposal submitted to U.S. Army Research Office entitled "Variance Estimation in the Presence of Outliers - II", $25,235. Not Funded

Proposal submitted to NSF entitled "Variance Estimation when the Data is Contaminated with Outliers, $27,328. Not Funded

1977 Proposal submitted to the U.S. Office of Naval Research (with G.A. Milliken) entitled "Interpreting Interaction in Two-way Models," $68,339. Not Funded

1978 NRC Grant entitled "Computer Package for Bayesian Analysis of Attribute Data with Arbitrary Prior Distributions," Principal Investigator was K. Shultis, Nuclear Engineering, $94,002. Funded

Faculty Research Award, $500.

1979 Faculty Research Award, $800.

1980 NRC Grant described above was continued for an additional two years, $120,000, Funded.

1981 NSF Proposal for Departmental Computing Equipment, $20,000, Funded.

1985-87 Goddard Space Flight Center Graduate Student Grant entitled "Statistical Methods and Models for Comparison of Land Surface Observations made on Areal Units of Unequal Size," $54,000 ($18,000/year for three years - funded graduate support for a PhD grad student), Funded.

1986 Grant from Pioneer Hybrids to work on Kriging Methods, $8904.

1987-88 Research Award from the Alcoa Foundation, $15,000.

1988 AMS Grant for Conference on Spatial Statistics and Imaging, $500

1988 Proposal submitted to U.S. Environmental Protection Agency entitled "Spatial Statistics Methodology for Analyzing Space-time Associational Relationships and SAS programs for Analyzing Such Data, $72,572. Not funded

1989 The Menniger Clinic Contract entitled "Statistical Analysis for Normal Development and Life Course in Japan and America," $4000.

NSF Equipment Grant - co-submitter - Not funded

1990 Sterling-Winthrop Research Institute Grant, $5000. Funded

Proposal to NSF for an NSF Faculty Women in Science Award (Nominated Dr. Sallie Keller-McNulty), $50,000. Not funded.

1991 D.A.I. Grant to visit Sri Lanka, $6,000. Funded

1992 NSF Grant Proposal for Graduate Research Traineeships in Statistics, $1,110,000. Not funded.

1993 Proposal submitted to the U.S. Department of Education entitled "Improving the English Intelligibility of Asian-Language GTAs Using Techniques from Speech-Language Pathology," Approximately $200,000. (Principal Investigator is Ann Bosma Smit). Not Funded.

1994 Proposal submitted to the U.S. Department of Education entitled "Improving the English Intelligibility of Asian-Language GTAs Using Techniques from Speech-Language Pathology," $217,625. (Principal Investigator is Ann Bosma Smit). Not Funded.

1996-98 Proposal entitled "Characterizing Measures of Stroke Rehabilitation Outcomes." Principal Investigator: Pamela W. Duncan, Center on Aging, K.U. Medical Center. Investigators: Dennis Wallace, Ph.D.; Sue Min Lai, Ph.D.; Dallas Johnson, Ph.D.; Stephanie Studenski, MD, MPH; Glaxo-Wellcome Pharmaceutical, and the U.S. Veterans Administration, $613,700. Funded.

1997-99 Proposal entitled ADevelopment of a Stroke Specific Health Status Measure,@ Principal Investigator: Pamela W. Duncan, Ph.D., P.T. (Center on Aging, K.U. Medical Center); Investigators: Dennis Wallace, Ph.D.; Sue Min Lai, Ph.D.; Dallas Johnson, Ph.D.; Stephanie Studenski, MD, MPH; Glaxo-Wellcome Pharmaceutical, $319,499. Funded.

1997-02 Proposal entitled A Kansas Claude D. Pepper Older Americans Independence Center. Principal Investigators: Stephanie A. Studenski and Pamela W. Duncan (Center on Aging, K.U. Medical Center); Other investigators include: Dennis Wallace, Ph.D.; Sue Min Lai, Ph.D.; Dallas Johnson, Ph.D.; Subashan Perera, Ph.D.; U.S. Department of Health and Human Services, Public Health Service, $8,028,750. Funded.

2001-02 Proposal entitled AStatistical Services for Scientific Protocol and Manuscript Review.@ Army Research Laboratory - Human Research and Engineering Directorate. $25,000, Funded.

2005-08 Proposal entitled "Communicative Competence and the Use of Prestored Text." Department of Health and Human Services, Public Health Services,

Figure 1
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
15 Minutes Post-Dose

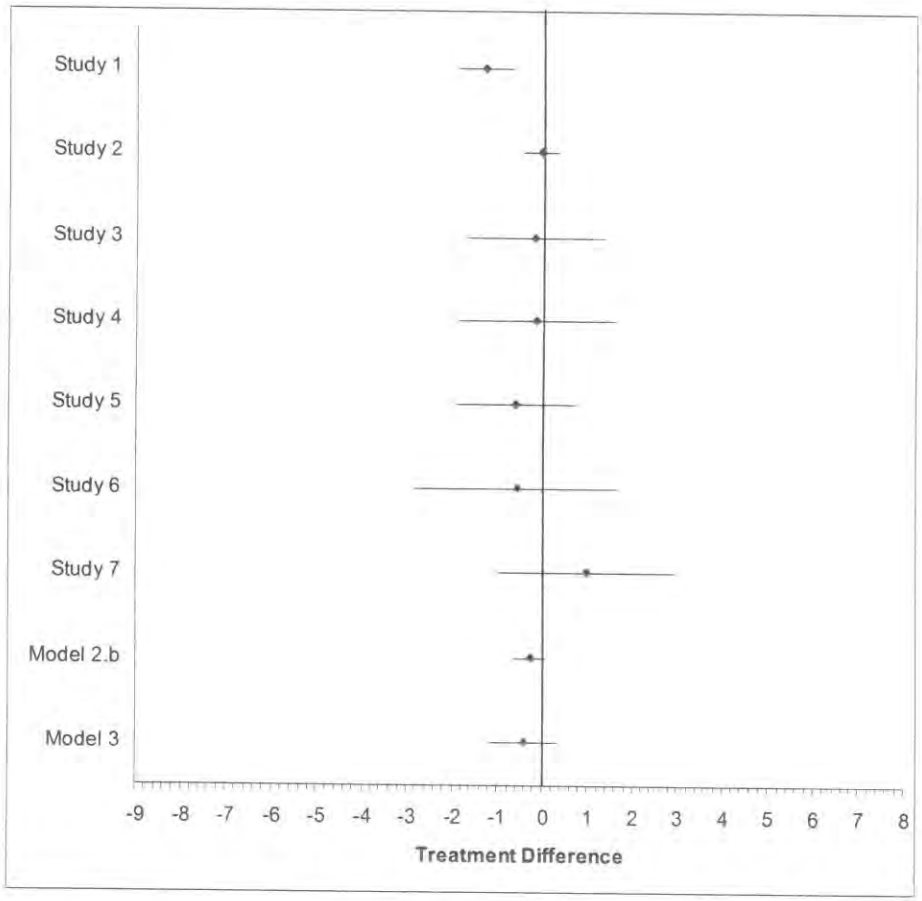

Figure 2
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
30 Minutes Post-Dose

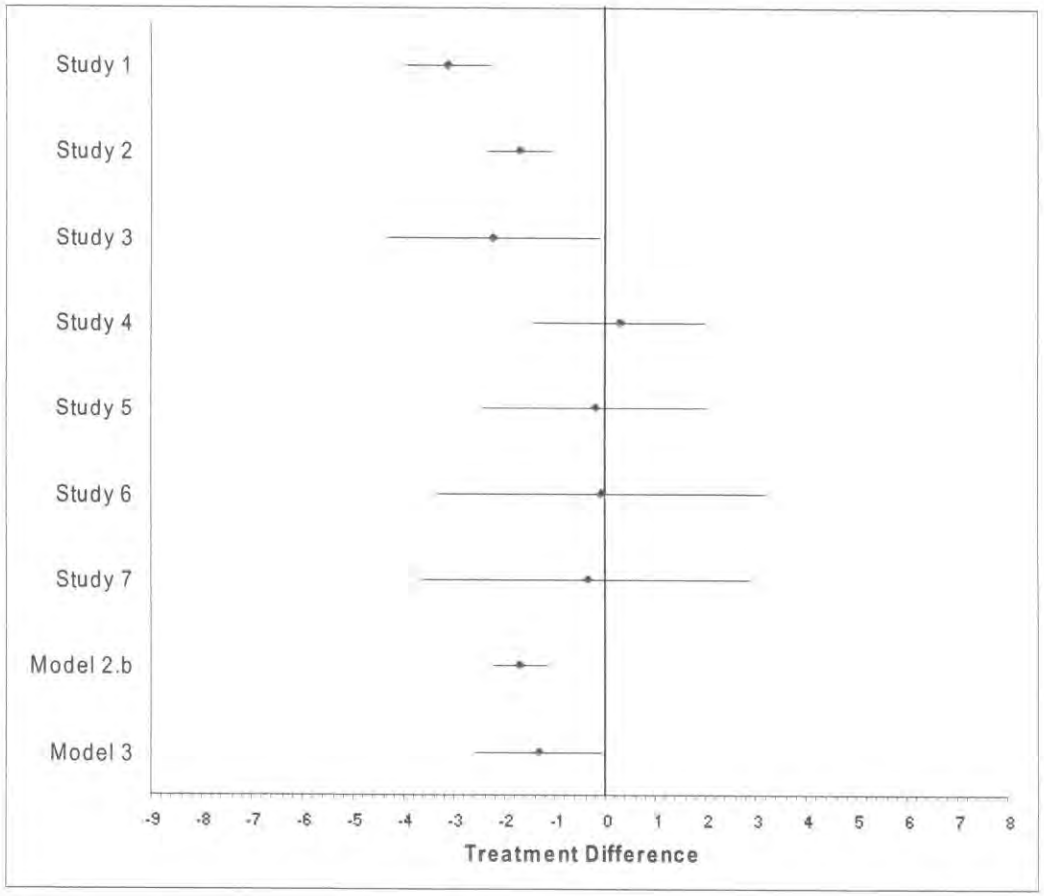

Figure 3
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
45 Minutes Post-Dose

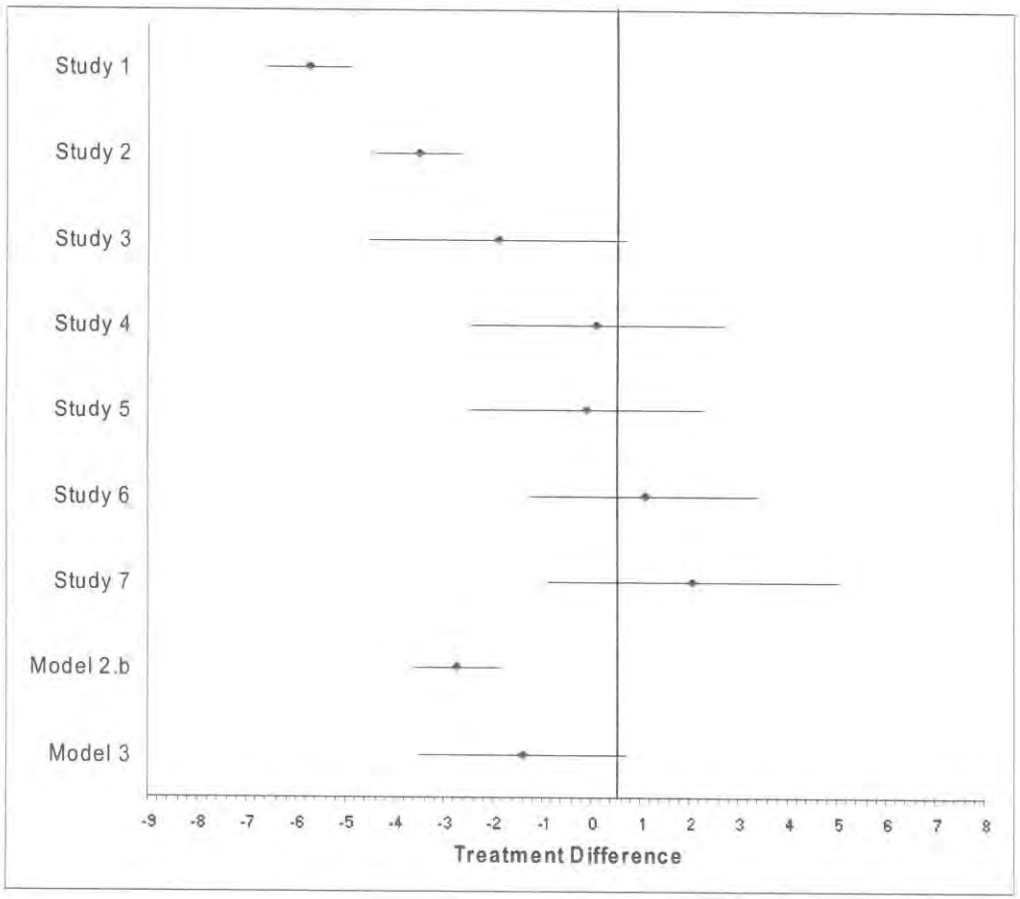

Figure 4
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
60 Minutes Post-Dose

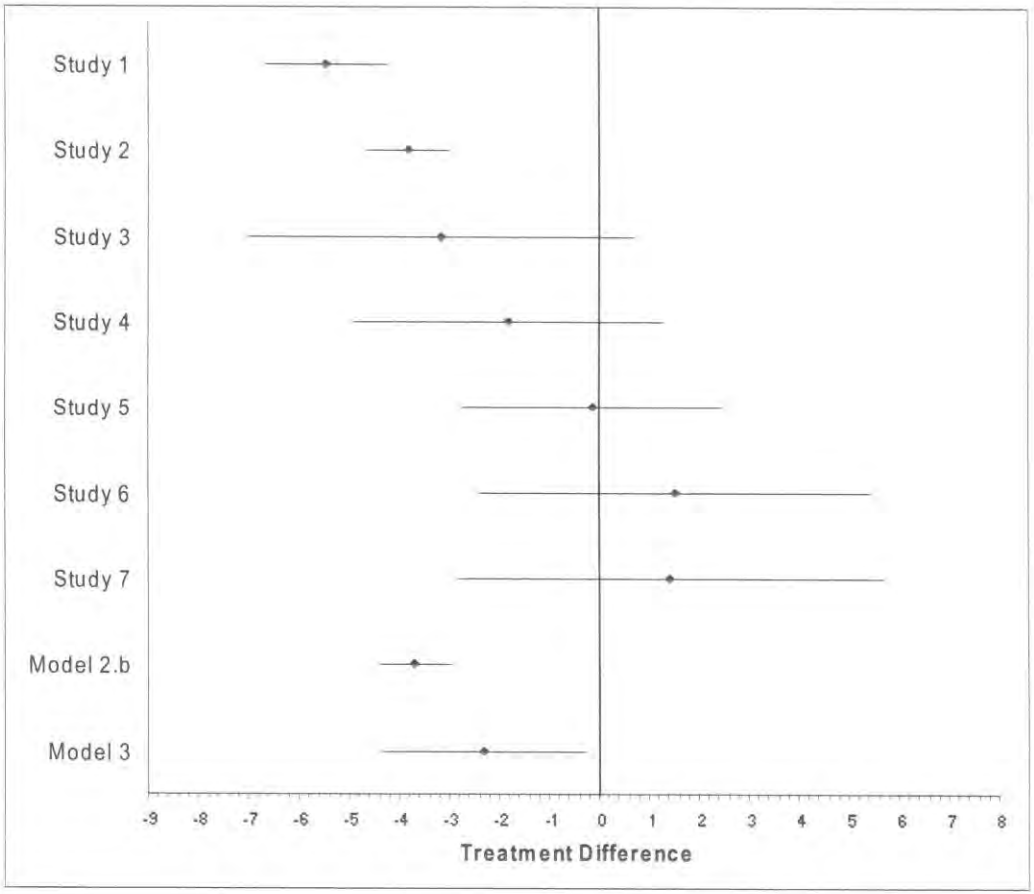

Figure 5
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
90 Minutes Post-Dose

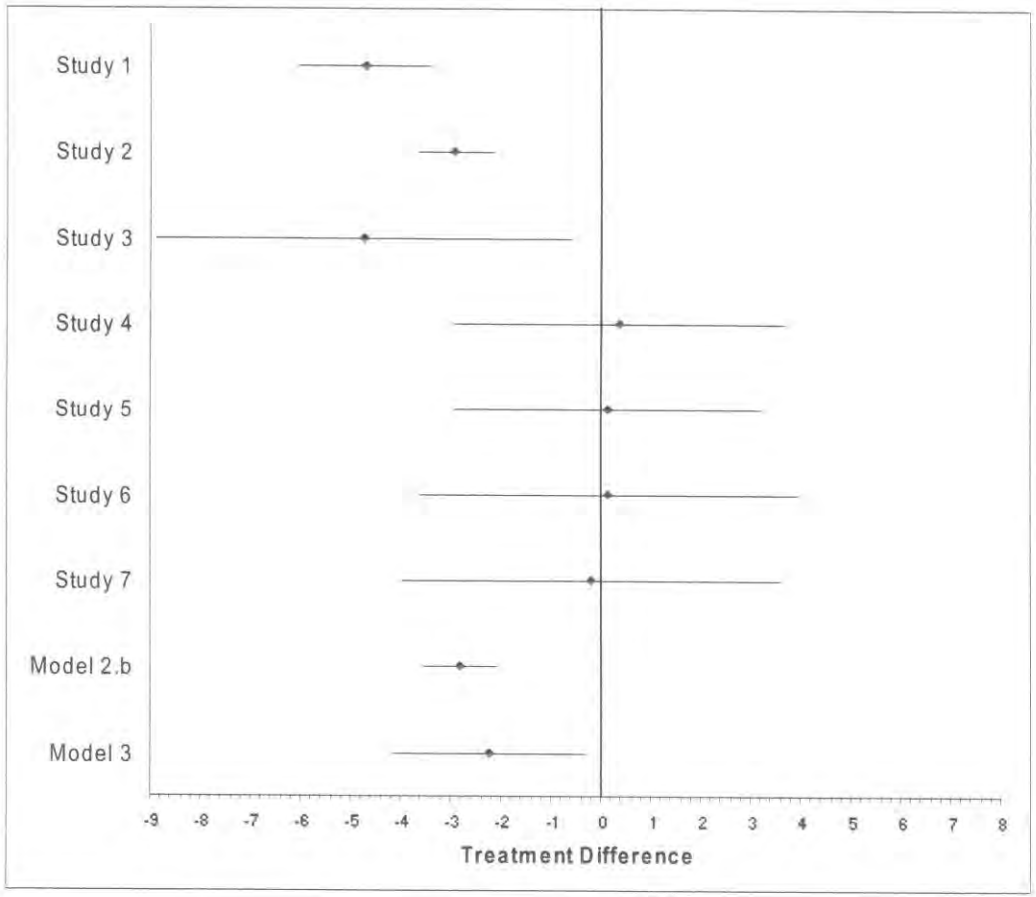

Figure 6
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
120 Minutes Post-Dose

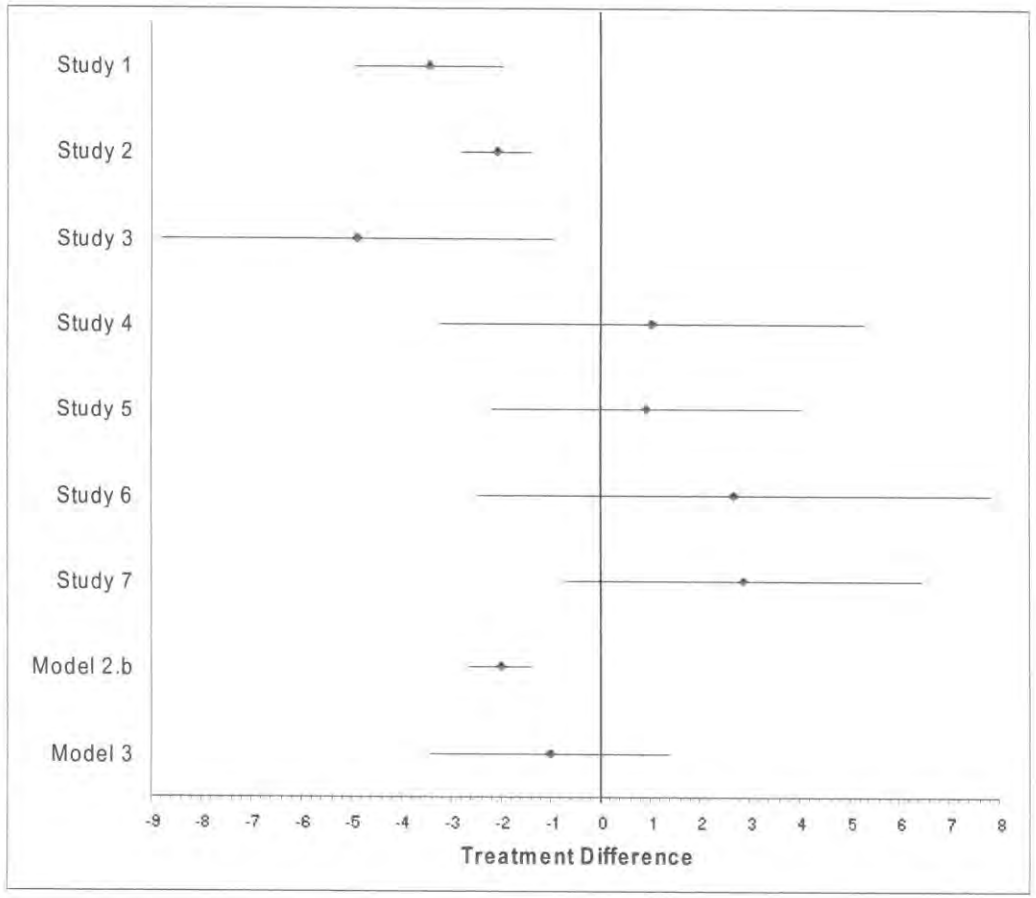

Figure 7
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
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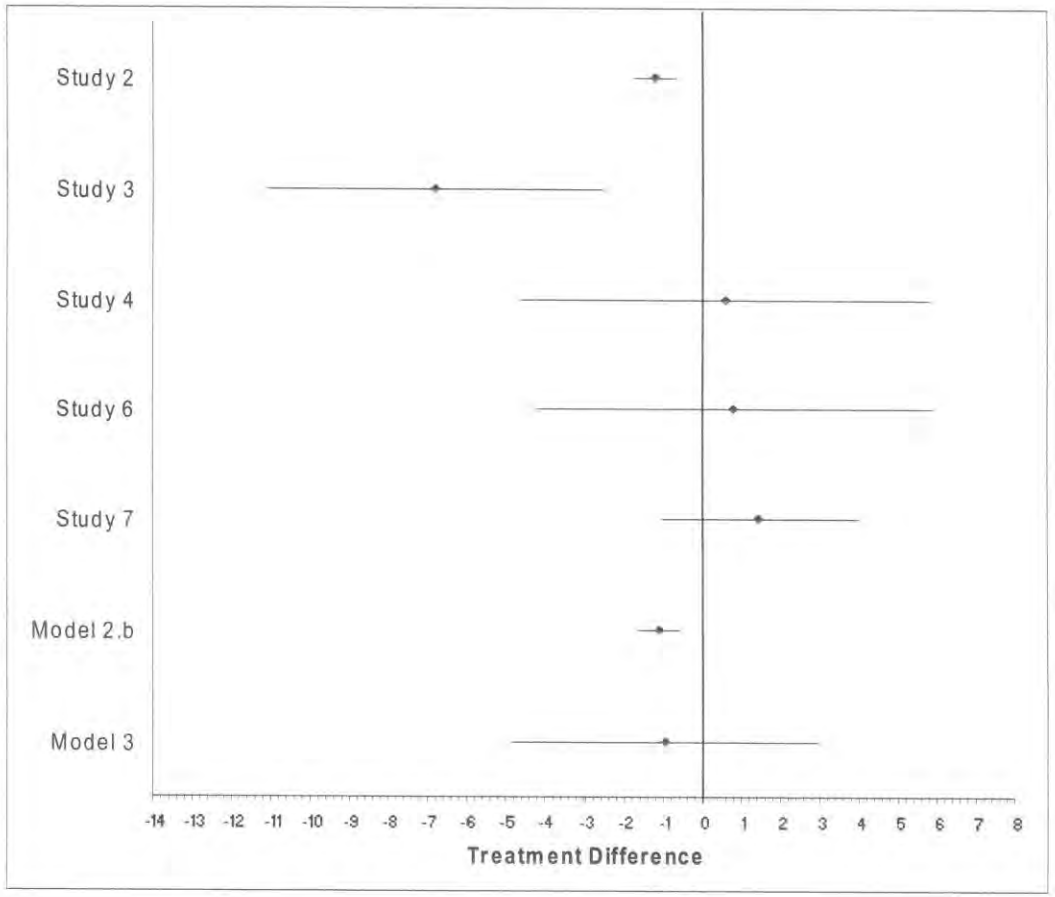

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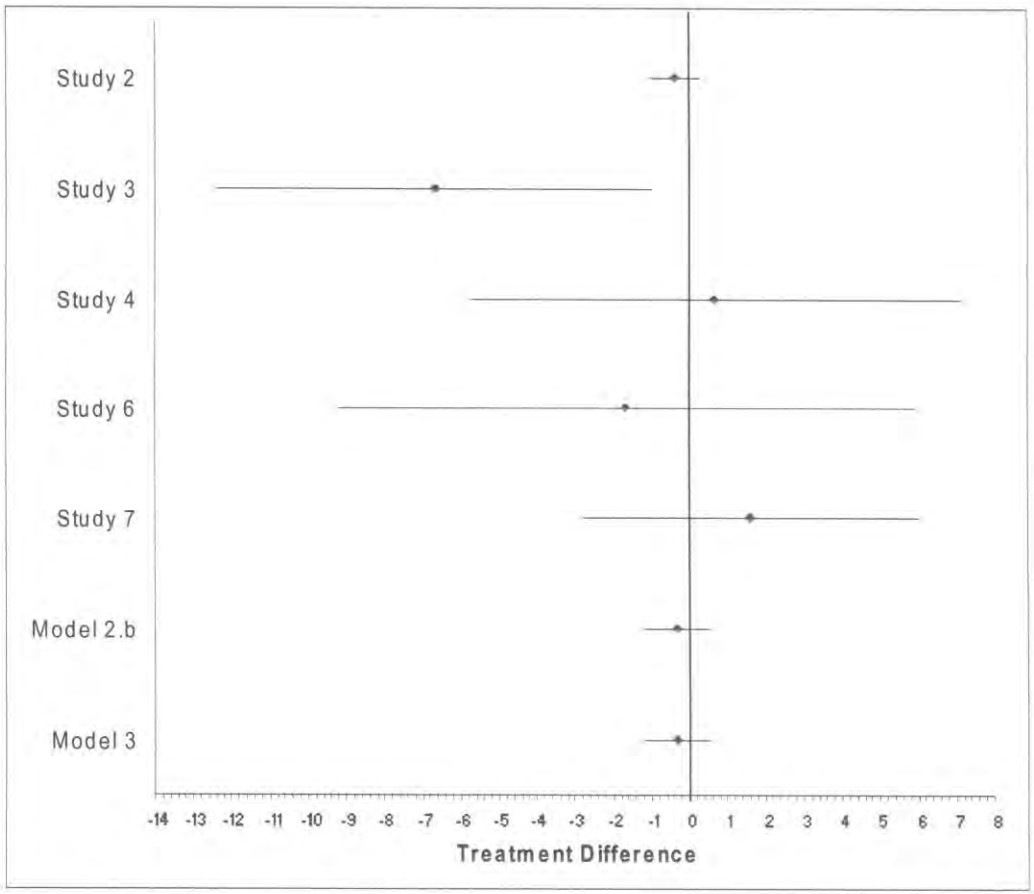

Figure 9
% Change from Baseline by Study and Time (minutes) with 95% Confidence Limits for Each Treatment
Patient is Random

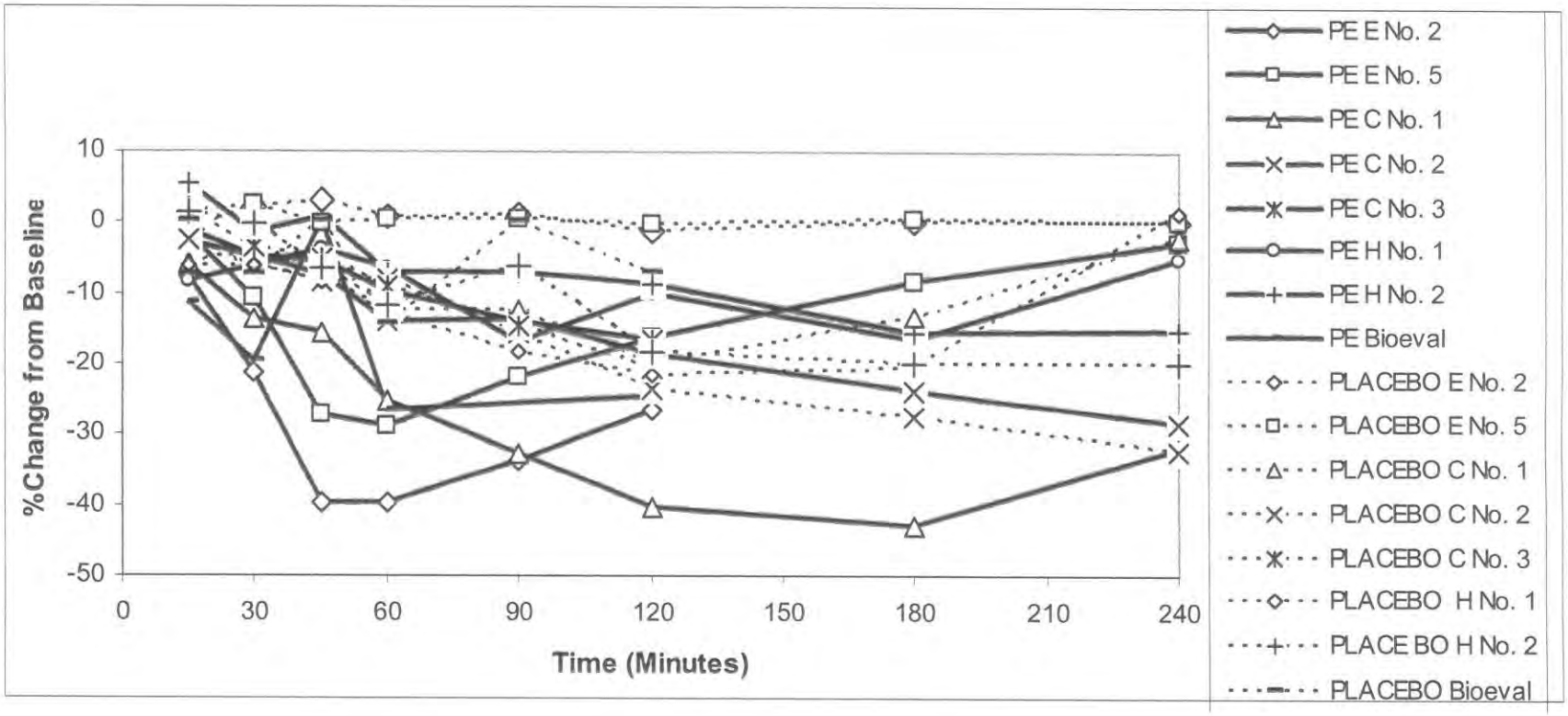

Figure 10
% Change from Baseline by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 2.a – Patient is Fixed

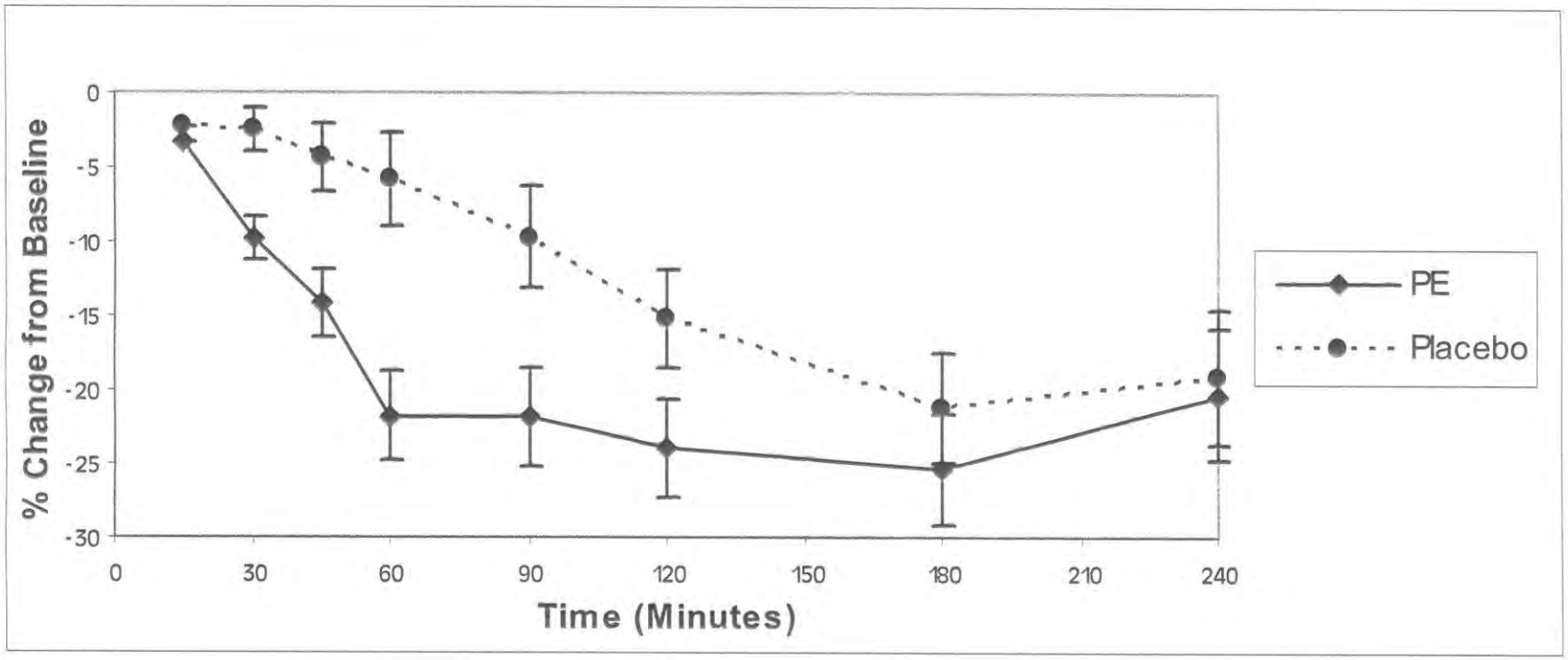

Figure 11
% Change from Baseline by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 2.b – Patient is Random

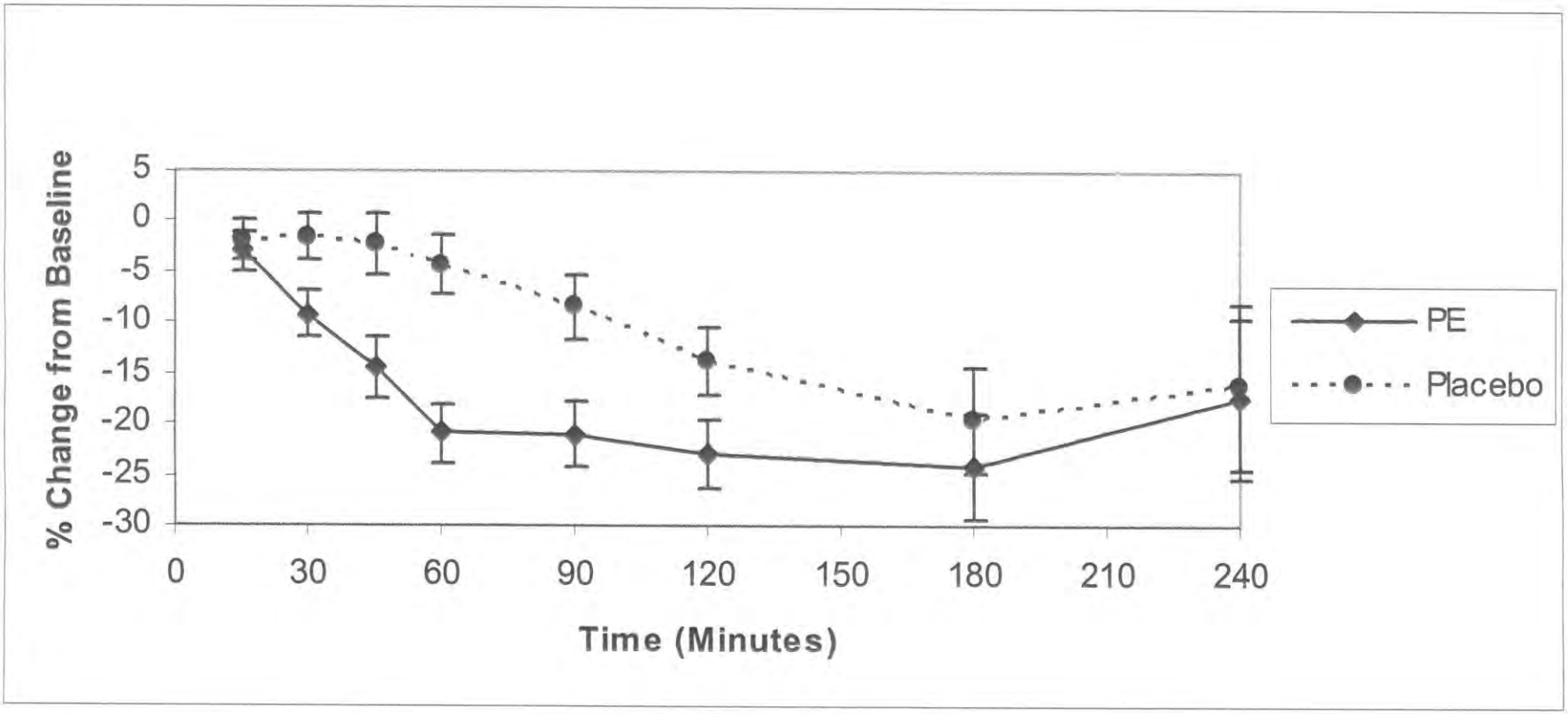

Figure 12
% Change from Baseline by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 3 – Patient, Study, and Treatment-by-study Interaction are Random

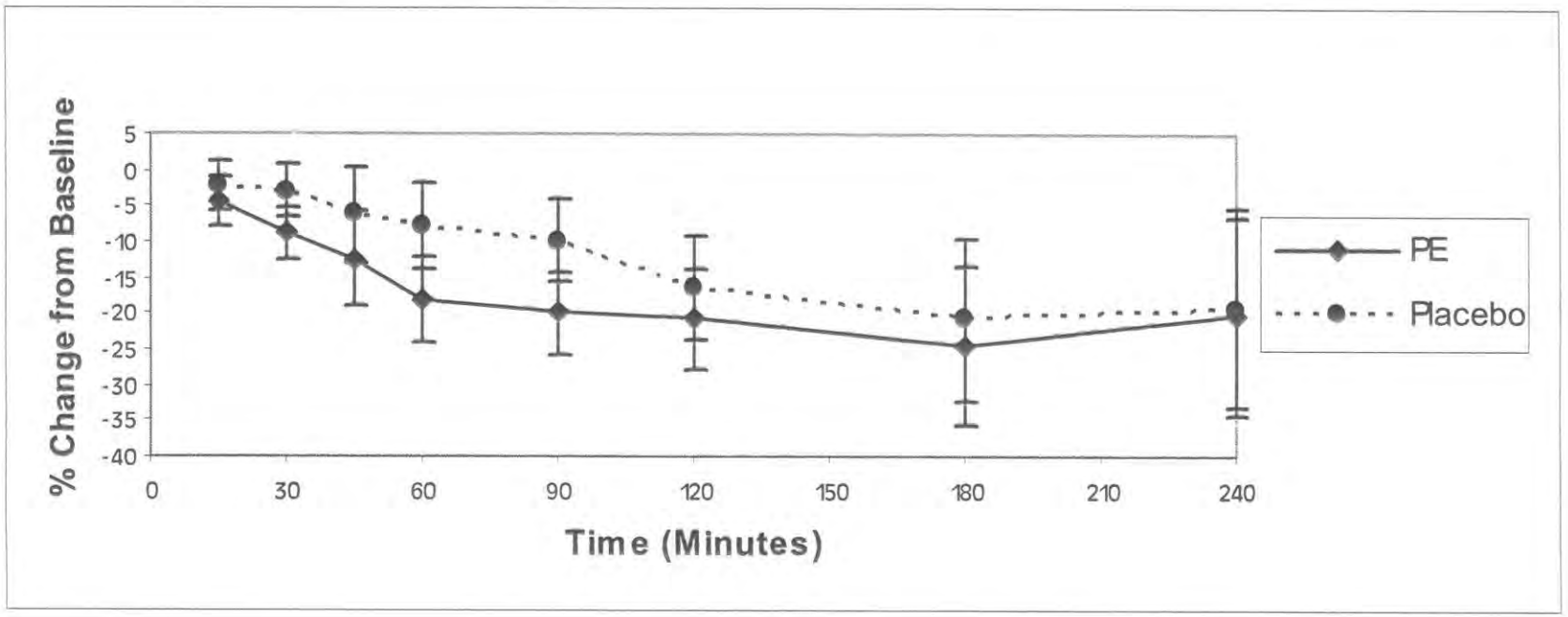

Figure 13
LN-Ratio By Study and Time (minutes) with 95% Confidence Limits for Each Treatment
Patient is Random
LN-Ratio Has Been Back-transformed from the ln Scale to Base10 Scale

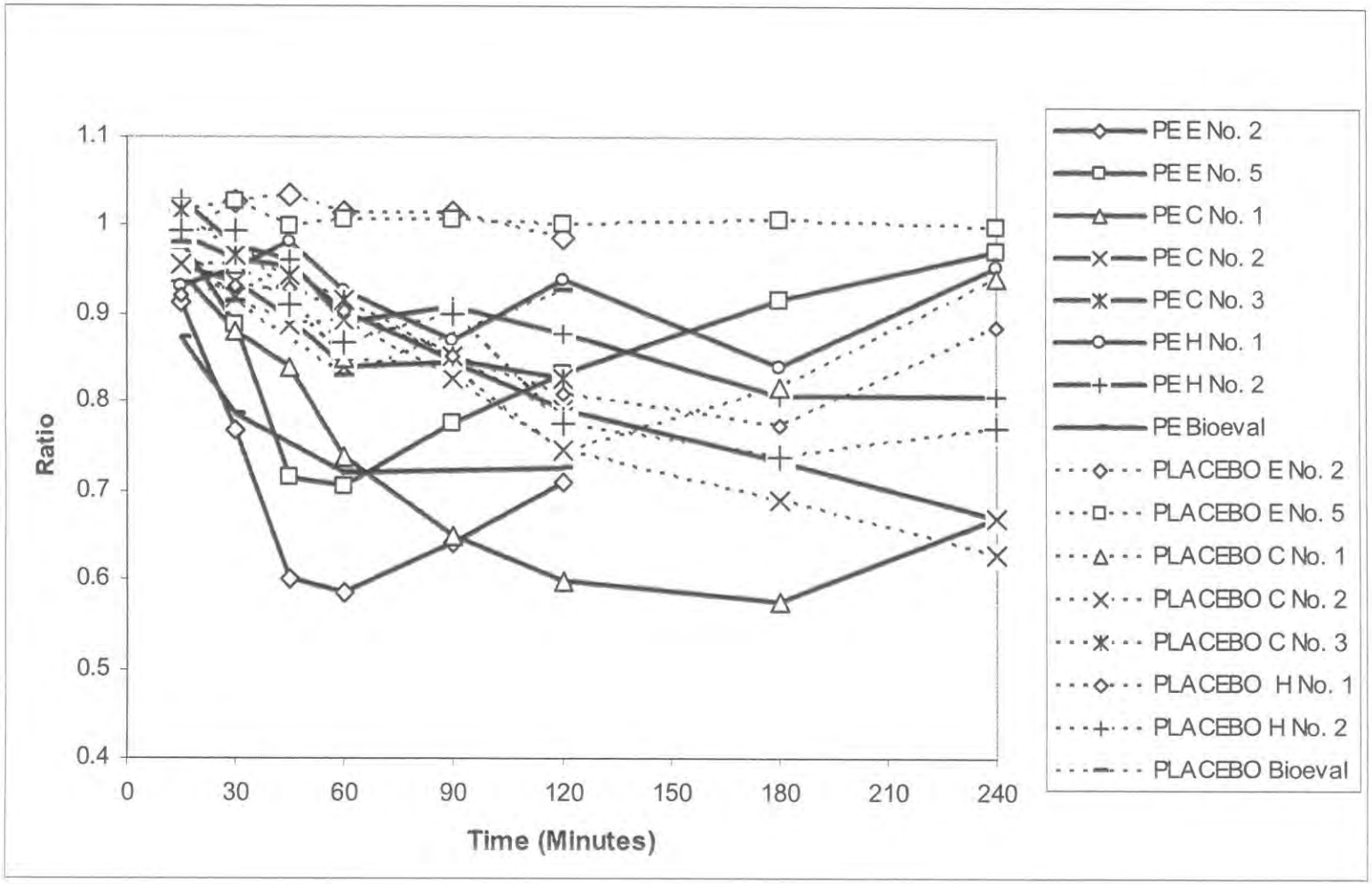

Figure 14
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LN-Ratio Has Been Back-transformed from the ln Scale to the Base10 Scale

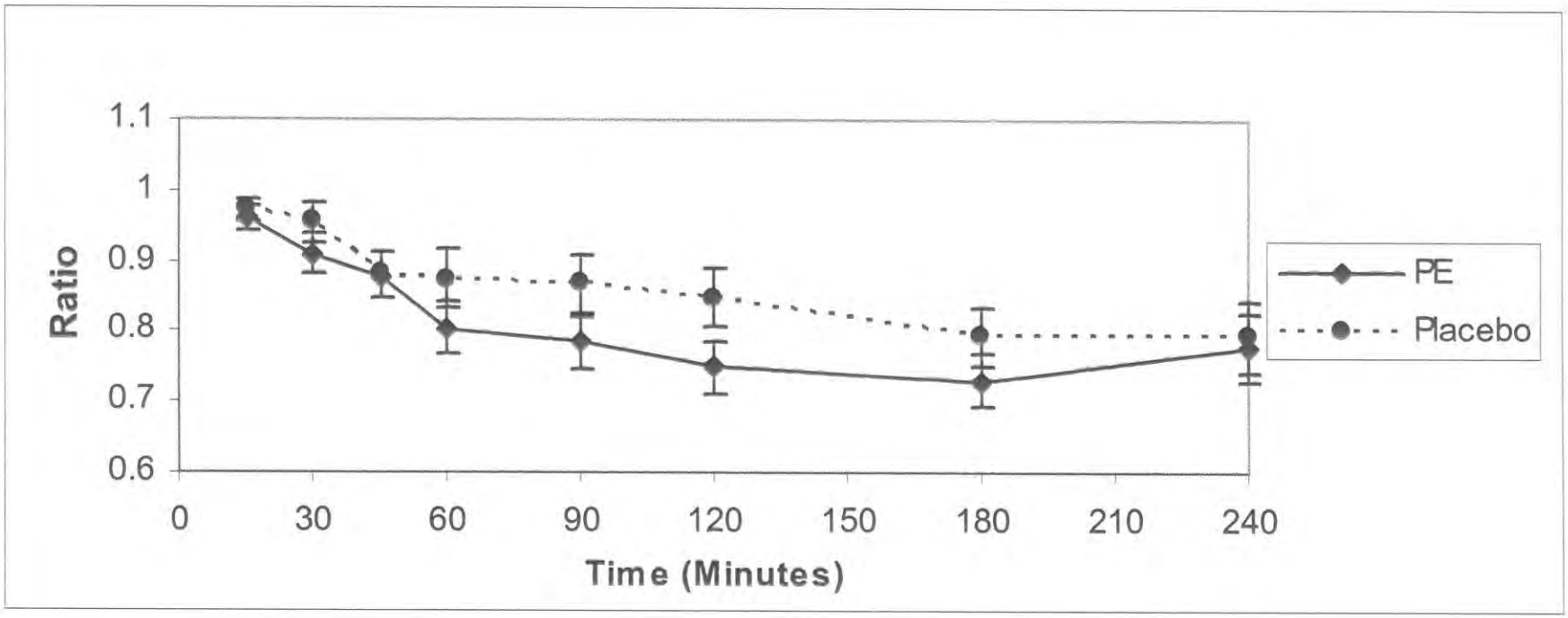

Figure 15
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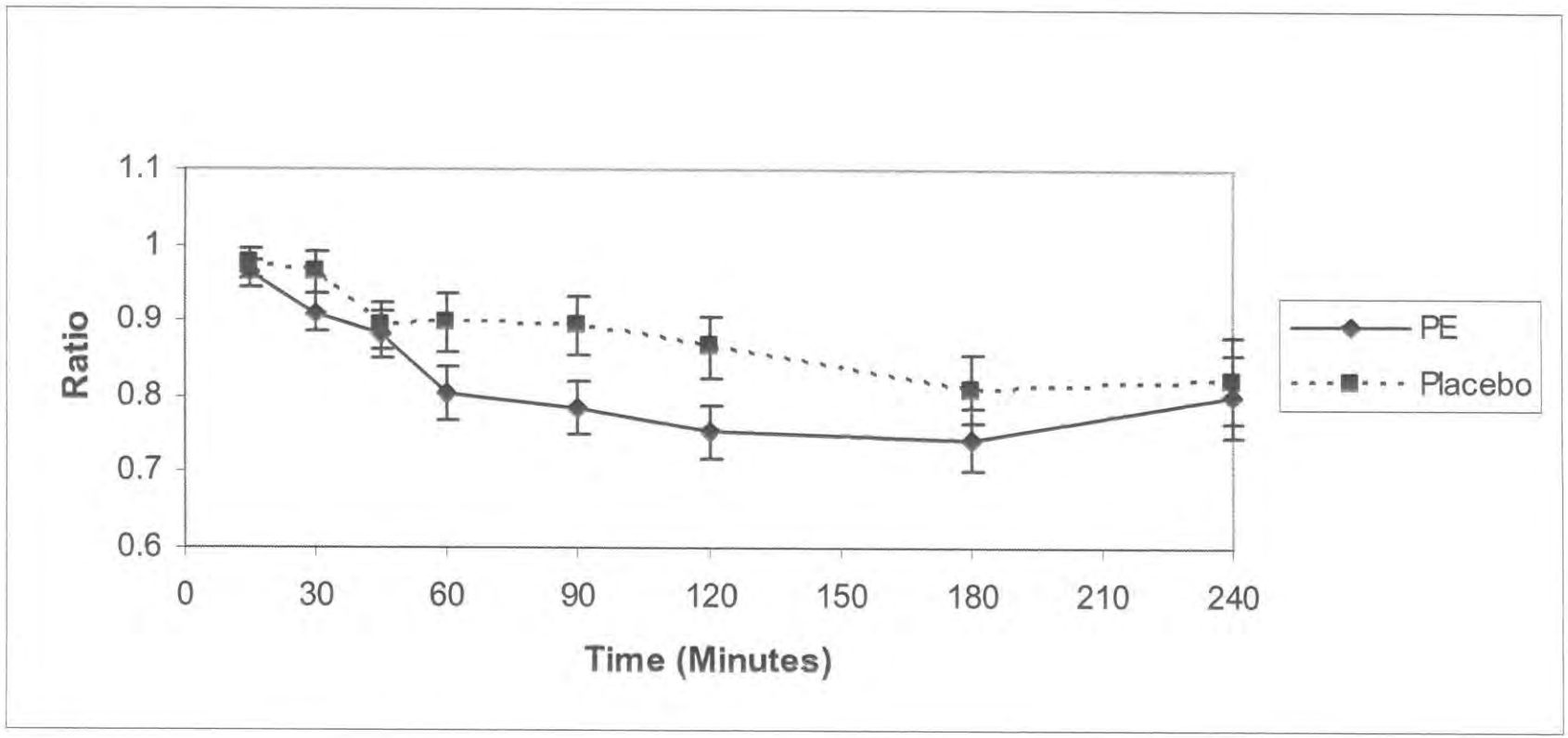

Figure 16
LN-Ratio by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 3 – Patient, Study, and Treatment-by-Study Interaction are Random
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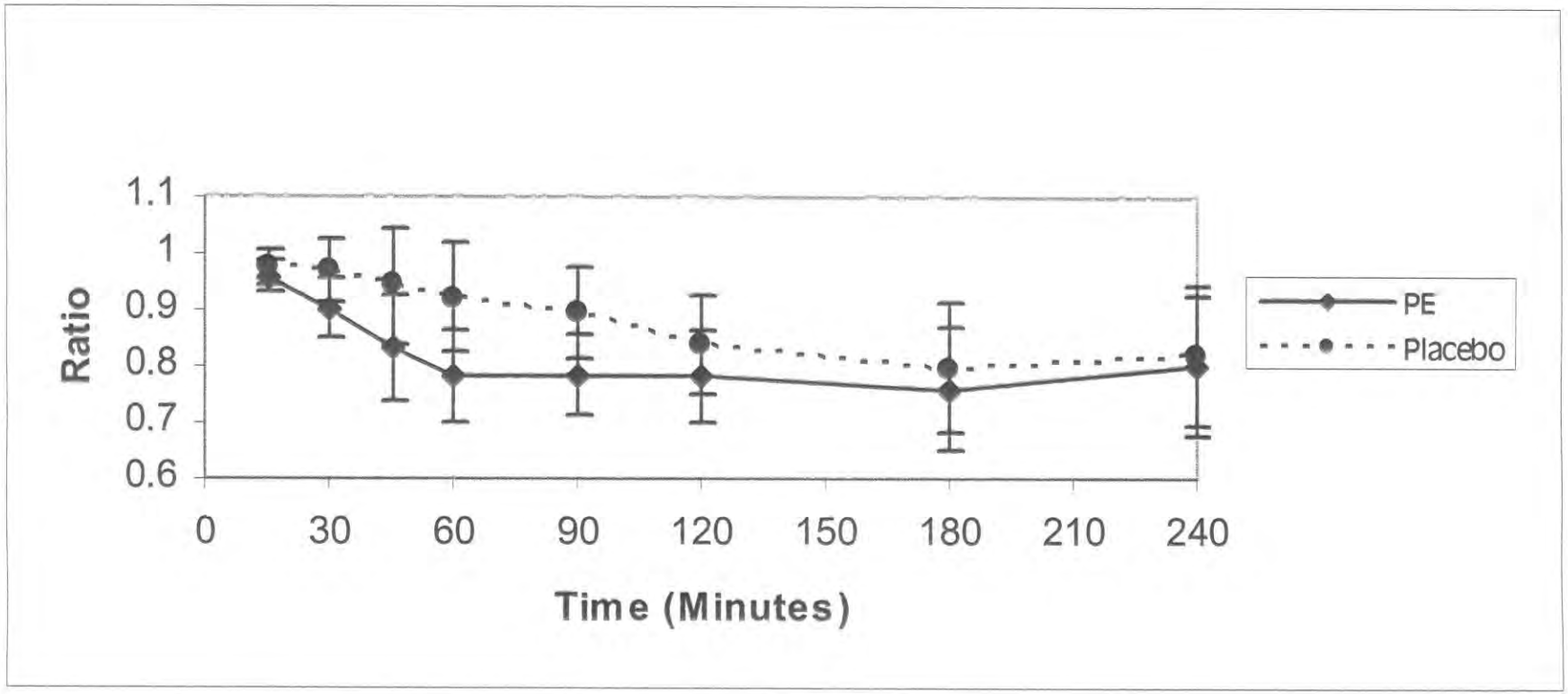

Consumer Healthcare Products Association (CHPA) PHENYLEPHRINE TASK GROUP

Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults With Acute Nasal Congestion Due to Common Cold

Final Report (January 30, 2007)

CHPA Phenylephrine Task Group

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Report Date: January 30, 2007

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REPORT

Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults With Acute Nasal Congestion Due to Common Cold

1. BACKGROUND AND OBJECTIVES

Phenylephrine is a sympathomimetic drug which has been used as a nasal decongestant in the United States and globally since the 1940s. At that time, to be marketed in the US a drug had to be proven to be safe whereas proof of effectiveness was not required. Beginning in 1972, as a result of amendments to the US drug law, the FDA initiated the OTC Drug Review and determined on the basis of all available data which medicines could be deemed "generally recognized as safe and effective". To accomplish this task, OTC companies and others submitted thousands of volumes of safety and efficacy information and the FDA assembled outside expert advisory panels which reviewed all available data and established OTC drug monographs for specific OTC drug categories. Similar to other active ingredients used in cough and cold medicines, phenylephrine was evaluated by the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. This panel conducted a review of the information available and deemed phenylephrine as generally recognized as safe and effective as a nasal decongestant at oral doses of 10 mg. The panel's conclusions were published by the FDA in 1976 *(Ref. 1)*. In 1994, the FDA issued the Final Monograph for OTC Nasal Decongestant Drug Products recognizing 10 mg phenylephrine as a safe and effective nasal decongestant *(Ref. 2)*.

The issues associated with the illicit conversion of pseudoephedrine to methamphetamine caused OTC companies to replace pseudoephedrine with phenylephrine in many of their products, which in turn drew new attention to phenylephrine's efficacy. In a recent publication, the authors questioned whether the FDA panel reached a correct conclusion on the basis of the available data at the time of the review in the 1970s *(Ref. 3)*.

These developments prompted a task group of the Consumer Healthcare Products Association (CHPA) to obtain copies of all studies that were cited in the bibliography of the phenylephrine section of the 1976 OTC Review panel report on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. In

addition, a literature search for additional studies investigating phenylephrine's efficacy was conducted. A review of the data led to the conclusion that a meta-analysis would be both feasible for a set of studies and a meaningful contribution to the discussion regarding the efficacy of phenylephrine.

The objectives of the analyses of the CHPA Phenylephrine Task Group were:

- to compare single-dose 10 mg phenylephrine and placebo separately for each crossover and parallel group study of adult patients with acute nasal congestion due to head cold/common cold.
- to perform a pooled (individual-level) meta-analysis comparing 10 mg phenylephrine and placebo using all available raw data from placebo-controlled, single-dose crossover studies in adult patients with acute nasal congestion due to a common cold.

2. STUDIES AVAILABLE FOR THE ANALYSES

Three sources were used for identification and collection of placebo-controlled efficacy studies with orally administered phenylephrine used as single active ingredient.

A. The bibliography of the phenylephrine section of the 1976 OTC Review on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products *(Ref. 1).*

Within this set of data, 14 reports were identified as efficacy trials with single-active phenylephrine:

1) *Memo to Hulme, N.A from H. Stander, "Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2", 1968 (included in FDA OTC Volume 040298)*

2) *Memo to Blackmore from N.A. Hulme, "Neo-Synephrine – Elizabeth Biochemical Laboratoriy Study No. 5", 1970 (included in FDA OTC Volume 040298)*

3) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 1", 1969 (included in FDA OTC Volume 040298)*

4) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 2", 1970 (included in FDA OTC Volume 040298)*

5) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 3", 1970 (included in FDA OTC Volume 040298)*

6) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 1", 1969 (included in FDA OTC Volume 040298)*

7) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 2", 1969 (included in FDA OTC Volume 040298)*

8) *Cohen, B.M., Kuebler W.F., "Conduct of a 200 patient doubleblind placebo controlled study to evaluate the effectiveness of phenylephrine hydrochloride (5 mg) tablets in relieving upper respiratory congestion and symptoms associated with the common cold", Whitehall Laboratories / Bio-Evaluation Inc., 1975 (included in FDA OTC Volume 040288B)*

9) *Memo to Lands from F.P. Luduena, "Comparative Study of the Effects of Neo-Synephrine HCl and Propadrine HCl on Nasal Air Resistance (NAR), Blood Pressure and Pulse Rate of Volunteers", 1959 (included in FDA OTC Volume 040298)*

10) *Memo to Suter from N.A. Hulme, "Nasal Decongestant Study by Elizabeth Biochemicals Laboratories No. 1", 1967 (included in FDA OTC Volume 040298)*

11) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No. 3", 1969 (included in FDA OTC Volume 040298)*

12) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No.4", 1969 (included in FDA OTC Volume 040298)*

13) *McLaurin, J.W., Shipman, W.F,. Rosedale, R.. "Oral Decongestants. A Double-Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective." Laryngoscope, 71: 54-67, 1961*

14) *Rodgers, J.M., Reilly, E.B., and Bickerman, H.A., "Physiologic and Pharmacologic Studies on Nasal Airway Resistance," Clinical Pharmacology and Therapeutics, 14:146, 1973. Data presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association, Washington DC, December 8, 1971*

B. A recently published review on nasal decongestants for the common cold conducted by the Cochrane Collaboration *(Ref. 4)*.
In performing this comprehensive review, the Cochrane Collaboration searched for randomized, placebo-controlled trials with nasal decongestants (including phenylephrine) in adults and children suffering from the common cold. Databases that were searched for this review included MEDLINE, EMBASE, CENTRAL (the Cochrane Central Register of Controlled Trials), and Current Contents.

Only one placebo-controlled trial with oral single-active phenylephrine was identified. This was the publication of *McLaurin et al.* cited under 13 in Section A above.

C. A literature search conducted by CHPA via PubMed (a free service provided by the U.S. National Library of Medicine which provides access to MEDLINE and to articles in selected journals not included in MEDLINE).

In addition to studies already cited under Sections A and B above, this search yielded one placebo-controlled trial with oral phenylephrine:

15) Cohen, B.M., "Clinical and Physiological 'Significance' in Drug-Induced Changes in Nasal Flow/Resistance". European Journal of Clinical Pharmacology, 5:81-86, 1972

In total, 15 studies were identified as placebo-controlled trials of oral phenylephrine used as single-active nasal decongestant.

3. STUDIES INCLUDED IN THE ANALYSES

For inclusion in the analyses, a study had to meet the following criteria:

1. Randomized single-dose, placebo-controlled trial
2. Orally administered, single-active phenylephrine at a dose of 10 mg
3. Adult patients with acute nasal congestion due to a common cold
4. Nasal airway resistance (NAR) was an efficacy endpoint
6. Study report contains sufficient individual subject data to allow reanalysis and/or meta-analysis for the comparison of the 10 mg dose level of phenylephrine and placebo

On the basis of these criteria, 8 studies were considered for the analyses.

1) *Memo to Hulme, N.A from H. Stander, "Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2", 1968 (included in FDA OTC Volume 040298)*

2) *Memo to Blackmore from N.A. Hulme, "Neo-Synephrine – Elizabeth Biochemical Laboratoriy Study No. 5", 1970 (included in FDA OTC Volume 040298)*

3) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 1", 1969 (included in FDA OTC Volume 040298)*

4) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 2", 1970 (included in FDA OTC Volume 040298)*

5) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 3", 1970 (included in FDA OTC Volume 040298)*

6) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 1", 1969 (included in FDA OTC Volume 040298)*

7) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 2", 1969 (included in FDA OTC Volume 040298)*

8) *Cohen, B.M., Kuebler W.F., "Conduct of a 200 patient doubleblind placebo controlled study to evaluate the effectiveness of phenylephrine hydrochloride (5 mg) tablets in relieving upper respiratory congestion and symptoms associated with the common cold", Whitehall Laboratories / Bio-Evaluation Inc., 1975 (included in FDA OTC Volume 040288B)*

The studies are identified in Table 1 (Studies 1 – 8). Of these 8 studies, 7 were of a similar design (i.e., randomized, double-blind, two-treatment, two-period, two-sequence crossover trials, NAR as efficacy endpoint) and were combined for meta-analysis (Studies 1 - 7). The eighth study was a double-blind, parallel group study and was not included in the meta-analysis of the crossover trials. This study (Study 8) was reanalyzed separately as were each of the 7 studies included in the meta-analysis.

There were a total of 163 patients available for analysis as follows:

TABLE 1: STUDIES INCLUDED IN THE ANALYSES

Study No. (design)	Study ID	Baseline Nasal Airway Resistance (NAR) (Phenylephrine/Placebo)	Number of Subjects with Data
1 (crossover)	Elizabeth No. 2	13.43 / 13.08*	16
2 (crossover)	Elizabeth No. 5	12.98 / 12.72*	10
3 (crossover)	Cintest No. 1	22.3 / 20.61*	16
4 (crossover)	Cintest No. 2	28.05 / 26.73*	15
5 (crossover)	Cintest No. 3	21.15 / 21.39*	15
6 (crossover)	Huntingdon No. 1	24.61 / 23.85*	16
7 (crossover)	Huntingdon No. 2	25.11 / 28.36*	25
8 (parallel group)	Bio-evaluation	5.29 / 4.99**	50 (25 per treatment)

* units

**cm H_2O/l/min @ 0.5 l/sec flow

There were 113 subjects included in the crossover trials comprising the meta-analysis. All subjects had data and were included in the analysis.

4. STUDIES EXCLUDED FROM THE ANALYSES

The following 7 studies were excluded from the analyses. Table 2 below provides characteristics of these studies and reasons for their exclusion.

9) *Memo to Lands from F.P. Luduena, "Comparative Study of the Effects of Neo-Synephrine HCl and Propadrine HCl on Nasal Air Resistance (NAR), Blood Pressure and Pulse Rate of Volunteers", 1959 (included in FDA OTC Volume 040298)*

10) *Memo to Suter from N.A. Hulme, "Nasal Decongestant Study by Elizabeth Biochemicals Laboratories No. 1", 1967 (included in FDA OTC Volume 040298)*

11) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No. 3", 1969 (included in FDA OTC Volume 040298)*

12) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No.4", 1969 (included in FDA OTC Volume 040298)*

13) *McLaurin, J.W., Shipman, W.F., Rosedale, R.. "Oral Decongestants. A Double-Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective." Laryngoscope, 71: 54-67, 1961*

14) *Rodgers, J.M., Reilly, E.B., and Bickerman, H.A., "Physiologic and Pharmacologic Studies on Nasal Airway Resistance," Clinical Pharmacology and Therapeutics, 14:146, 1973. Data presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association, Washington DC, December 8, 1971*

15) *Cohen, B.M., "Clinical and Physiological 'Significance' in Drug-Induced Changes in Nasal Flow/Resistance". European Journal of Clinical Pharmacology, 5:81-86, 1972*

TABLE 2: STUDIES EXCLUDED FROM THE ANALYSES

Study No.	Study ID	Reason for Exclusion
9	Lands from Luduena	Subjects were healthy volunteers
10	Elizabeth No. 1	Study investigated phenylephrine at dose levels other than 10 mg
11	Elizabeth No. 3	Study investigated phenylephrine at dose levels other than 10 mg

12	Elizabeth No. 4	Study investigated phenylephrine at dose levels other than 10 mg
13	McLaurin et al.	Participants enrolled were patients with nasal obstruction from a variety of disorders, including coryza, acute and chronic sinusitis, allergic or vasomotor rhinitis and hypothyroidism. No analysis of subgroups was performed.
14	Rodgers et al.	Participants had chronic rhinitis
15	Cohen	Lack of individual–level data (only mean treatment estimates by time point available)

5. METHODS

Efficacy Parameters:

In all studies included in the meta-analysis, NAR was the efficacy endpoint. NAR was determined by an identical procedure (using a modified Butler-Ivy airflow device). According to the original study reports, five NAR measurements were taken at pre-dose and at all post-baseline time points for each study subject. However, these five measurements were not provided in these reports. The average of the five measurements was provided. These average values may have been rounded for listing in these reports.

Subjective impressions of changes in nasal congestion were scored in the studies, but there were insufficient data for analysis.

Two parameters were analyzed for the meta-analysis and for the analysis of each study:

1. Change from baseline (pre-dose) NAR at each post-baseline time point (15, 30, 45, 60, 90, 120, 180, and 240 minutes post-dose), defined as post-baseline NAR - baseline NAR.

2. LN-ratio NAR [defined as LN (NAR at a post-baseline time point) – LN (baseline NAR)] at each post-baseline time point (15, 30, 45, 60, 90, 120,

180, and 240 minutes post-dose). At each time point, this is mathematically identical to the natural logarithm of the ratio of the post-baseline to baseline values, LN (post-baseline NAR at a time point / baseline NAR).

Note that the 45, 90, 180, and 240 minute post-baseline time points were not included in the design of Study 8; the 180 and 240 minute time points were also not included in the designs of Studies 1 and 5.

Criteria for Evaluation:

On the basis of medical considerations and consumer expectations the following criteria were chosen:

- Statistical significance at the 30 minute and 60 minute post-dosing time points (primary time points).
- 20% reduction from baseline NAR for phenylephrine. A 20% reduction from baseline is a reduction noticeable by patients (*Ref. 5*).

Statistical Methods:

Analyses by Study:

In the original study reports, the investigators used analysis of variance (without a covariate adjustment for baseline) to analyze the NAR measurements. However, for this report, the individual data values for each crossover study were analyzed using analysis of covariance (adjusting for pre-dose baseline average measurement, a covariate). For these crossover studies, the statistical model included 'patient' as a random factor. Information on which treatment sequence a patient was randomized to was not available in the original study reports; therefore, treatment sequence and period could not be included in the statistical model and a test for first-order carryover could not be done. Patient was a random factor for the analysis of Study 8 also, but was not included in the statistical model as this was a parallel group study.

Pooled Meta-Analyses:

Since Study 8 was a parallel group study and not a crossover study, it was not included in the meta-analysis.

For all meta-analyses performed for each efficacy parameter, the individual data values for each crossover study were included. Analysis of covariance

(ANCOVA), adjusting for pre-dose baseline average measurement (a covariate) was performed for all analyses.

First, prior to the use of statistical models to compare treatments, an analysis was performed to test "heterogeneity" at each post-dose time point, that is, to determine if the treatment difference between phenylephrine and placebo varied in direction or magnitude from study to study at a post-dose time point. This would further determine if phenylephrine differed from placebo in some studies and not others or if the treatment difference between phenylephrine or placebo was larger for some studies than for others at a post-dose time point. This test for "heterogeneity" is a test of the "treatment-by-study interaction" term from the following statistical models:

- **Model 1:** a fixed effects meta-analysis model using parametric ANCOVA, adjusting for baseline (a covariate), with terms for patient, study (a fixed factor), treatment (a fixed factor), and the treatment-by-study interaction. This model was used twice:
  - Model 1.a: assuming patient as a fixed factor with unequal within-subject variance components across studies
  - Model 1.b: assuming patient as a random factor with unequal within-subject and between-subject variance components across studies.

For the meta-analyses, two statistical models were used to perform analysis of covariance comparing the efficacy of phenylephrine and placebo at each post-dose time point:

- **Model 2:** a fixed effects meta-analysis model which is Model 1 above, but without the treatment-by-study interaction term. Study is again assumed to be fixed. This model was used twice:
  - Model 2.a: assuming patient as a fixed factor with unequal within-subject variance components across studies
  - Model 2.b: assuming patient as a random factor with unequal within-subject and between subject variance components across studies.

- **Model 3:** a random effects meta-analysis model, with baseline, patient, treatment, study, and treatment-by-study interaction in the model, but with patient, study, and treatment-by-study interaction considered random.

The SAS System Version 8.2 PROC MIXED code to generate results from all models analyzed is given in Appendix 1.

The assumptions of the parametric statistical models noted above, normality and equality of variance, were checked by inspection of plots of residuals vs. predicted values and boxplots of residuals for each treatment group (seen in Appendix 2 for by-study analyses and in Appendix 3 for the meta-analysis). Although variances of the two treatments appear to be equal, there appears to be a departure from normality for some analyses, although sometimes the distributions of residuals appear symmetrical. There appears to be comparability between the two efficacy parameters with regard to how well the normality and equality of variance assumptions fit the data for the treatment factor in the model. Differences between studies in term of patient variability were noted in the original reporting of these studies; therefore, within and between-subject variances components were allowed to vary for analyses using Models 1, 2, and 3 (as described above).

All p-values for treatment effect terms in Models 2 and 3 were considered statistically significant if $p \leq 0.05$.

The results of Model 2.a were generally comparable to those for Model 2.b. Determinations concerning the efficacy of phenylephrine are primarily based on the results from Model 2.b and Model 3 for the change from baseline parameter, a more commonly used parameter. A sensitivity analysis was performed using the LN-ratio parameter. Results of analyses of the change from baseline parameter and the LN-ratio parameter were generally comparable. **Therefore, the results of the Model 2.b and 3 change from baseline analyses are presented in the Results section of this report.** A summary table of results of the analyses of the change from baseline and LN-ratio parameters is provided in Appendix 4 (Appendix 4.1 for by-study analyses and Appendix 4.2 for meta-analyses).

Appendix 5 contains a listing of the standard errors of treatments for Models 2.a, 2.b, and 3 for both efficacy parameters for all analyses performed. The 95% confidence intervals on the difference between treatments (generated from PROC MIXED) are also provided; the difference between treatments provided is based on adjusted (least squares) treatment means. Forest plots are provided in Figures 1 to 8 to show the confidence intervals on the treatment difference by post-dose time point for each study (assuming patient is random) and for the meta-analyses (based on Models 2.b and 3).

Treatments means are plotted by post-dose time point for each parameter by study (assuming patient is a random factor) and for the meta-analyses (using all models) in Figures 9 to 16. For figures representing the results of analyses of the change from baseline parameter, percent change from baseline for a treatment is plotted against time. Percent change for a treatment is calculated as: (least squares adjusted treatment mean x 100) / (baseline mean for a treatment). The lower and upper 95% confidence interval limits plotted for a treatment in these figures are the lower and upper confidence limits for the adjusted treatment mean converted to percent change from baseline.

6. RESULTS

RESULTS BY STUDY:

Figures 1 to 8 show an estimate of the treatment difference between phenylephrine and placebo with corresponding 95% confidence interval for each post-dose time point. Estimates and confidence intervals are provided for each study (assuming patient is random) and for the meta-analyses (based on Models 2.b and 3). Confidence intervals that do not contain 0 are statistically significantly in favor of phenylephrine over placebo.

Statistically significant differences in favor of phenylephrine over placebo were found in Studies 1, 2, 3 and 8. The results are indicated in Table 3.

Statistically significance differences were not found between phenylephrine and placebo for Studies 4, 5, 6, and 7, but directional differences were found as shown in Table 4. The maximum percent changes from baseline achieved for phenylephrine in these studies were 29%, 17%, 17%, and 16%, for Studies 4, 5, 6, and 7, respectively. However, for placebo, the maximum percent changes from baseline were 32%, 21%, 22%, and 20%, respectively.

TABLE 3: RESULTS OF STUDIES WITH STATISTICALLY SIGNIFICANT DIFFERENCES

Study No. (design)	Study ID	Statistic	Post-dose time points statistically significant ($p \leq 0.05$) in favor of phenylephrine over placebo							
			15 mins	30 mins	45 mins	60 mins	90 mins	120 mins	180 mins	240 mins
1 (crossover)	Elizabeth No. 2	Significant?	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	#	#
		Treatment Difference (Confidence Interval)	-1.26 (-1.87, -0.65)	-3.11 (-3.97, -2.26)	-5.74 (-6.60, -4.87)	-5.44 (-6.64, -4.25)	-4.70 (-6.03, -3.38)	-3.44 (-4.91, -1.96)		
2 (crossover)	Elizabeth No. 5	Significant?	NS	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	NS
		Treatment Difference (Confidence Interval)	-0.05 (-0.44, 0.35)	-1.68 (-2.33, -1.03)	-3.51 (-4.38, -2.65)	-3.82 (-4.64, -3.01)	-2.90 (-3.65, -2.15)	-2.09 (-2.80, -1.38)	-1.17 (-1.71, -0.63)	-0.38 (-1.05, 0.30)
3 (crossover)	Cintest No. 1	Significant?	NS	$p \leq 0.05$	NS	NS	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$
		Treatment Difference (Confidence Interval)	-0.17 (-1.70, 1.36)	-2.24 (-4.36, -0.12)	-1.90 (-4.53, 0.73)	-3.14 (-7.01, 0.74)	-4.75 (-8.90, -0.59)	-4.88 (-8.80, -0.95)	-6.81 (-11.09, -2.52)	-6.66 (-12.38, -0.94)
8 (parallel group)	Bio-evaluation	Significant?	$p \leq 0.05$	$p \leq 0.05$	##	$p \leq 0.05$	##	$p \leq 0.05$	##	##
		Treatment Difference (Confidence Interval)	-0.60 (-1.14, -0.07)	-0.67 (-1.23, -0.11)		-0.68 (-1.28, -0.09)		-0.96 (-1.48, -0.44)		

Source: Appendix 4.1 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

The design of Study 1 did not include the 180 and 240 min. time points

The design of Study 8 did not include the 45, 90, 180, and 240 min. time points

NS = not statistically significant

TABLE 4: DIRECTIONAL DIFFERENCES IN STUDIES 4, 5, 6, AND 7

Study No. (design)	Study ID	Statistic	Post-dose time points with directional differences (D) in favor of phenylephrine over placebo							
			15 mins	30 mins	45 mins	60 mins	90 mins	120 mins	180 mins	240 mins
4 (crossover)	Cintest No. 2	Directional?	D	-	-	D	-	-	-	-
		Treatment Difference (Confidence Interval)	-0.13 (-1.85, 1.60)	0.31 (-1.40, 2.02)	0.13 (-2.47, 2.74)	-1.81 (-4.90, 1.29)	0.39 (-2.92, 3.70)	1.05 (-3.22, 5.31)	0.63 (-4.62, 5.87)	0.68 (-5.75, 7.12)
5 (crossover)	Cintest No. 3	Directional?	D	D	D	D	-	-	#	#
		Treatment Difference (Confidence Interval)	-0.58 (-1.93, 0.77)	-0.21 (-2.44, 2.03)	-0.07 (-2.46, 2.31)	-0.13 (-2.75, 2.48)	0.15 (-2.93, 3.23)	0.93 (-2.19, 4.05)		
6 (crossover)	Huntingdon No. 1	Directional?	D	D	-	-	-	-	-	D
		Treatment Difference (Confidence Interval)	-0.57 (-2.82, 1.68)	-0.06 (-3.29, 3.17)	1.11 (-1.22, 3.43)	1.53 (-2.37, 5.43)	0.17 (-3.62, 3.96)	2.70 (-2.45, 7.84)	0.83 (-4.25, 5.91)	-1.65 (-9.22, 5.92)
7 (crossover)	Huntingdon No. 2	Directional?	-	D	-	-	D	-	-	-
		Treatment Difference (Confidence Interval)	0.99 (-0.98, 2.95)	-0.36 (-3.61, 2.89)	2.09 (-0.88, 5.05)	1.44 (-2.81, 5.70)	-0.18 (-4.00, 3.63)	2.89 (-0.69, 6.48)	1.49 (-1.05, 4.02)	1.61 (-2.82, 6.03)

Source: Appendix 4.1 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

The design of Study 5 did not include the 180 and 240 min. time points.

RESULTS OF META-ANALYSES:

Using Model 1 results, statistically significant treatment-by-study interactions (all p-values $\leq$0.217) occurred for all time points (15 through 240 minutes) as expected given results of by-study analyses shown above (interaction p-values not provided in any table, but available in Appendix 3). Directional differences in favor of phenylephrine over placebo were seen in all studies, but not at all time points post-dose (Table 4 and Appendix 4.1). Directional treatment differences in favor of phenylephrine over placebo were seen for at least 2 and up to 6 time points in the 8 studies available for analysis.

For meta-analyses, statistical significance in favor of phenylephrine over placebo was achieved at the primary time points (30 and 60 minutes post-dose) and also for the 90 minute post-dose time point for both Models 2.b and 3. Statistical significance in favor of phenylephrine over placebo was also seen for the 45, 120, and 180 minute post-dose time points using Model 2.b (Table 5).

Note that there was a reduced sample size for the 180 and 240 minute time points as compared to earlier time points since only five studies were available for analysis at the 180 and 240 minute time points. Lack of statistical significance seen at the 120 and 180 minute post-dose time points (for Model 3) and at the 240 minute post-dose time point (for Models 2.b and 3) may be due to reduced power given increased variance and/or reduced sample size seen at these time points (Appendix 5).

Using estimates taken from both Models 2.b and 3, the percent changes from baseline for phenylephrine were at most 4%, 9%, 15%, 21%, 21%, 23%, 25%, and 20% for the 15, 30, 45, 60, 90, 120, 180, and 240 minute time points, respectively. Percent changes from baseline were at least 6 percentage points higher and at most 16.6 percentage points higher for phenylephrine as compared to placebo between 30 and 90 minutes post-dose (6 percentage points at 30 and 45 minutes and as high as 16.6 percentage points at 60 minutes).

The average change from baseline NAR for phenylephrine was approximately two-thirds to 2 times greater than that for placebo between 15 and 90 minutes post-dose.

TABLE 5: RESULTS OF META-ANALYSIS

Model	Statistic	Post-dose time points statistically significant ($p \leq 0.05$) in favor of phenylephrine over placebo							
		15 mins	30 mins	45 mins	60 mins	90 mins	120 mins	180 mins	240 mins
2.b	Significant?	NS	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	NS
	Treatment Difference (Confidence Interval)	-0.27 (-0.61, 0.08)	-1.68 (-2.23, -1.14)	-2.71 (-3.57, -1.85)	-3.68 (-4.39, -2.97)	-2.80 (-3.54, -2.06)	-2.02 (-2.67, -1.37)	-1.09 (-1.61, -0.58	-0.33 (-1.21, 0.55)
3	Significant?	NS	$p \leq 0.05$	NS	$p \leq 0.05$	$p \leq 0.05$	NS	NS	NS
	Treatment Difference (Confidence Interval)	-0.41 (-1.18, 0.36)	-1.32 (-2.56, -0.09)	-1.38 (-3.51, 0.74)	-2.30 (-4.34, -0.26)	-2.24 (-4.17, -0.31)	-1.01 (-3.42, 1.40)	-0.95 (-4.85, 2.96)	-0.32 (-1.21, 0.57)

Source: Appendix 4.2 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

NS = not statistically significant

7. SUMMARY AND CONCLUSIONS

Eligible studies:

- Eight out of 14 reviewed studies fulfilled the criteria for inclusion in the analyses (Studies No.1 – 8). One other trial, the study conducted by Cohen (Study No. 15), met all selection criteria except for providing individual patient data. It is important to note that this study demonstrated that 10 mg phenylephrine significantly improved NAR compared to placebo. So it is justifiable to assume that the results of the meta-analysis would still be positive had Study No.15 been included.

Analyses of individual studies:

- Statistically significant differences in favor of 10 mg phenylephrine over placebo were seen in 4 of 8 individual studies analyzed.
- Although the direction and the size of the treatment difference was not consistent for all studies at all post-dose time points (Model 1), directional treatment differences in favor of 10 mg phenylephrine over placebo were seen for at least 2 and up to 6 time points in the 8 studies available for analysis.

Meta-analysis:

- For the meta-analysis including 7 crossover studies (Studies No.1 – 7), phenylephrine was statistically significantly superior to placebo at the primary time points, 30 and 60 minutes post-dose, and at 90 minutes post-dose (using the results of both Models 2.b and 3). Also, phenylephrine was statistically significantly favored over placebo at the 45, 120, and 180 minute post-dose time points (Model 2.b).
- Reductions from baseline were on the order of 20%, a reduction considered to be noticeable by the patient. In one model (Model 2.b), reductions from baseline for phenylephrine were at least 21% from 60 to 180 minutes post-dose. In the second model (Model 3), reductions were 18% at 60 minutes post-dose, and at least 20% from 90 to 180 minutes post-dose.
- Study No. 8 was a parallel group study and was not included in the meta-analysis. In this study, phenylephrine was shown to be statistically significantly superior to placebo at the four time points assessed (15, 30, 60, and 120 minutes post-dose). Therefore, it can be assumed that the results of the meta-analysis would have remained positive had Study No.8 been included.

In conclusion, both the meta-analysis of seven crossover studies and the results of a parallel group study demonstrated that phenylephrine at a dose of 10 mg is an effective decongestant.

References:

Ref.1 FDA, Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. Federal Register, Vol. 41, No.176, p.38399-38400, 1976

Ref.2 FDA, Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products. Federal Register, Vol. 59, No.162, p.43386-43412, 1994

Ref.3 Hendeles, L., Hatton, R.C., "Oral phenylephrine: An ineffective replacement for pseudoephedrine?". Journal of Allergy and Clinical Immunology, 118: 279-280, 2006

Ref.4 Taverner, D., Latte, J., Draper, M., "Nasal decongestants for the common cold (Review)." Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD001953. DOI: 10.1002/14651858.CD001953.pub2.; published in the Cochrane Library 2006, Issue 4

Ref.5 Cohen, B.M., "Clinical and Physiological "Significance" in Drug-Induced Changes in Nasal Flow/Resistance. European Journal of Clinical Pharmacology, 5:81-86, 1972