PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 17-970 _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III **THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant)

or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # NSABP P-1

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # NSABP P-1

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /X/ Explain: NSABP P-1 trial was conducted by NSABP for Zeneca.
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /X/ Explain _____ Zeneca provided drug to NSABP. & Zeneca provided letter of authorization to NSABP.	NO /___/ Explain _____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

/S/ 9-16-98

Signature of preparer Date

Title: Consumer Safety Officer.

/S/ M.D 9/22/98

Signature of Division Director Date

cc:
Archival NDA 17-970/S-040
HFD-150/Division File
HFD-150/CSO/Chapman
HFD-[redacted]/Mary Ann Holovac
93

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	17970	**Trade Name:**	NOLVADEX (TAMOXIFEN CITRATE)
Supplement Number:	40	**Generic Name:**	TAMOXIFEN CITRATE
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	Nolvadex is indicated for the prevention of breast cancer in women at high risk for developing the disease.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, AMY CHAPMAN

/S/
Signature

10-23-98
Date

cc: Orig. NDA 17-970/S040
HFD-150 /Div. File
HFD-150 / Chapman

NSABP®

NSABP Foundation, Inc.

Patricia Carlson Koehler, Esq.
Executive Director and General Counsel
412/330-4601/4605
412/330-4664 FAX
E-Mail: pkoehler@pgh.auhs.edu

April 24, 1997

TO WHOM IT MAY CONCERN:

Re: NSABP Protocol P-1

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of the NSABP Foundation, Inc. under whose aegis the National Surgical Adjuvant Breast and Bowel Project Protocol P-1 is conducted, (collectively the "NSABP"), that the NSABP did not and will not use in connection with this application, the services of any person in any capacity subject to debarment under sections 306(a) and (b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C.S. §§ 355 (a) and (b).

Patricia Carlson Koehler, Esq.

East Commons Professional Building

Four Allegheny Center - 5th Floor

Pittsburgh, PA 15212-5234

Acting Director Comments on Supplemental New Drug Application

NDA: 17-970/S-040
Drug: Nolvadex (tamoxifen citrate) Tablets
Sponsor: Zeneca Pharmaceuticals
Date: September 22, 1998

The medical review of this supplemental NDA is outstanding and little additional comment is required. The issue of increased thromboembolic events with tamoxifen is a concern that has been addressed in the review and in the labeling. Except for a history of prior thromboembolic events, there is currently no method for identifying women who may be at increased risk of thromboembolism. The draft approvable letter asks for a phase 4 commitment to

A recent publication (N Engl J Med 1998; 339:1793-7, 1840-1841), however, suggests that Factor V Leiden is not the only relatively common mutation that is associated with an increased risk of deep-venous and cerebral thrombosis in homozygous and heterozygous individuals. The G20210A mutation in the prothrombin gene was also found to be associated with an increased risk of cerebral vein thrombosis. Oral contraceptives are also known to be risk factors and the combination of the G20210A mutation and oral contraceptives resulted in a risk of cerbral vein thrombosis that far exceeded the sum of the separate risks. Similar findings have been reported for factor V Leiden and oral contraceptive use. Although the mechanism for this interaction is not yet known, it is reasonable to suspect that the same interaction may occur with tamoxifen. Therefore, the approvable letter should be revised to include the cited results and should recommend that the G20210A prothrombin mutation also be looked for in the phase 4 study. Fortunately, both tests can be performed on blood samples that have already been obtained. If many or most of the thromboembolic events are found to occur in participants with mutations, then screening could be considered. However, it is recognized that screening for these mutations is not yet generally recommended and there are cost-effectiveness concerns. Even so, it is important to determine whether there is a relationship between thromboembolism on tamoxifen and prothrombotic mutations. If there is then individual patients and physicians should be given the option to make that decision for themselves.

/S/ MD

Robert L. Justice, M.D.
Acting Director
Division of Oncology Drug Products

Orig. NDA 17-970/S-040
HFD-150/Div. File
HFD-150/AChapman
HFD-150/JBeitz
HFD-150/SHonig

D. files.

OCT 15 1998

MEMORANDUM

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

DATE: October 15, 1998

TO: NDA 17-970/S-040
Division of Oncologic Drug Products, HFD 150

THROUGH: Robert Justice, M.D., Acting Director Division of Oncologic Drug Products, HFD 150

Susan Honig, M.D., Medical Reviewer Division of Oncologic Drug Products, HFD 150

SUBJECT: Consultation regarding screening/monitoring for thrombophilic coagulopathy in patients receiving prolonged tamoxifen therapy.

FROM: Lilia Talarico, M.D. Director Division of Gastrintestinal and Coagulation Drug Products, HFD 180 LT 10-15-98

Tamoxifen is a nonsteroidal antiestrogen that competes with estrogen for binding sites or receptors in target tissues such as breast. Tamoxifen is indicated for the treatment of breast cancer in women with negative axillary nodes and in post-menopausal women with positive axillary nodes following total or segmental mastectomy, axillary dissection and breast irradiation.

Adverse events reported with the use of Tamoxifen have included hypercalcemia, increase incidence of endometrial and uterine cancer, elevation of liver enzymes, and increased incidence of TEE (DVT in 0.8% of tamoxifen patients compared to 0.3% of placebo patients and PE in 0.4% of tamoxifen patients compared to 0.1% of placebo patients).

A prospective, multi center, randomized, double-blind, large clinical trial (NSABP P-1) was conducted by the NSABP from January 1992 to September 1997 to assess the efficacy and safety of long-term Tamoxifen therapy (5 years) compared to placebo for prevention of breast carcinoma in women at high risk of developing the disease. A total of 13.388 women participated in the study, 6492 women received tamoxifen and 6484 received placebo. After an average follow-up of 3.6 years, statistically significant reductions in the risk of invasive

breast cancer (RR= 0.45) and non-invasive breast cancer (RR=0.54) were observed in the tamoxifen-treated group. No statistically significant difference in mortality was observed between the two groups.

Adverse events observed in the clinical trial included increased incidence of endometrial carcinoma, cataract formation and thromboembolic events (TEE).
The TEE included DVT, PE and cerebrovascular events (strokes and TIAs).

This consult will address exclusively the TEE reported in the study population.

The TEE events are summarized in the following table generated from data provided in the medical review of the NDA.

TEE in NSABP P-1

Type of Events	Treatment		
	Placebo N (%)	Tamoxifen N (%)	Risk Ratio (95% CI)
Total PE*:	6 (0.25)	18* (0.75)	3.1 (1.15-9.27)
Age ≤ 49	1 (0.11)	2 (0.21)	2.2 (0.18-22.3)
Age ≥ 50	5 (0.34)	16 (1.10)	3.2 (1.12-11.2)
* 2 fatal PE occurred in the tamoxifen group			
Total DVT**:	19 (0.79)	30 (1.26)	1.6 (0.86-2.98)
Age < 49	8 (0.85)	10 (1.08)	1.3 (0.45-3.69)
Age > 50	11 (0.76)	20 (1.38)	1.8 (0.83-4.20)
** 16 placebo patients and 27 tamoxifen patients required hospitalization.			
Total Strokes:	24 (0.1)	34 (0.13)	1.42
Age ≤ 49	4	3	0.76
Age ≥ 50	20	31	1.55
Total TIA:	21	18	0.86
Age ≤ 49	4	3	0.76
Age ≥ 50	17	15	0.88
Total Thrombotic Events	49	82	1.7

When the TEE were analyzed according to time of event in relation to therapy, the association of thrombosis with tamoxifen appeared to be even stronger since 10 of the DVTs in the placebo group occurred months to years after study termination, whereas the 3 DVTs in the tamoxifen group that occurred after study termination actually occurred when the effect of the drug was still present.

In conclusion, tamoxifen increased the overall risk of TEE compared to placebo. While the difference in incidence of DVTs between the two groups was only numerical, a statistically significant increase in occurrence of PE was observed in the tamoxifen group compared to placebo.
When the two treatment groups were analyzed for presence of predisposing risk factors for DVT, such as surgery, trauma, prolonged immobilization or medical conditions, 16 of the 19 placebo patients who experienced DVT had predisposing risk factors (84%) while 19 of the 30 patients (63%) in the tamoxifen-treated group with DVT had a predisposing factor for thrombosis.

Age was a risk factor for both study groups as both DVTs and PEe were more frequent in patients older than 50 years of age. Notably, other risk factor such as smoking, or precipitating factors as trauma were more frequent in the placebo group.

Venous thrombosis has been calculated to occur in young women with an incidence of about 3.0/10.000 women years. Several factors contribute to the development of TE complication. Patients may be at risk of thrombosis during acquired or environmentally-related circumstances which are usually of limited duration (surgery, prolonged immobilization, pregnancy, chemotherapy, etc.). At the same time, some patients may have life-long predisposition for thrombosis because of underlying genetic abnormalities.

Inherited risk factors for TEE currently known include deficiency of protein C, protein S, Anti-Thrombin III, activated protein C resistance (APCR), increased levels of von Willebrand Factor (vWF). Antihemophilic Factor VIII (Factor VIII:c), genetic mutation of Fact. II, and hyperhomocystenemia. Acquired risk factors for TEE include anticardiolipin antibodies, use of oral contraceptives, underlying conditions such as cancer, cancer chemotherapy, surgery, venous or arterial vascular disease, prolonged immobilization.

The relative risk (RR) for TEE for patients with protein C deficiency is about 3.5 and increases to 6.5 in the presence of a mutation. The relative risk of TEE for patients with protein S-deficiency about 2.1. The relative risk for TEE for patients with AT-III deficiency is about 5.
A RR of about 2 was found for patients with non-O blood group and of 4.5 for patients with Fact.VIII:c greater than 150%. The relative risk for TEE for patients with hyperhomocystenemia was found to be 2.5 and to increase with age and in women. The prevalence of carriers for the AG to A mutation at nucleotide 20210 in the prothrombin gene is 2.3% in the normal population and 6.2% in patients with TEE. This genetic trait is associated with elevated levels of plasma prothrombin and a RR for TEE of 2.8 compared to normal subjects. The relative risk of APC resistance has been calculated at 6.6 and increases with decreasing APC-sensitivity ratio.

Resistance to APC is nearly always caused by a guanine to adenosine substitution at nucleotide 1,691 of Factor V and replacement of arginine at position by glutamine at position 506 (Fact.V Q506 or Fact.V Leiden). The prevalence of APC resistance in the normal population of nearly 7% makes this defect the most prevalent known inherited risk factor for thrombosis.
The risk of TEE in patients with Fact.V Leiden is increased from 3/1000 to 28/10000 women

year. The use of oral contraceptives incases the risk even more.
The risk of thrombosis is greatly enhanced for all patients with a genetic thrombophilic defect when concomitant acquired risk factors are also operative.

The incidence of thrombosis was clearly increased in the tamoxifen-treated patient population. The thrombotic events may have been caused by the treatment or by the combined effect of treatment superimposed to a genetic predisposition. Given the frequency of Factor V Leiden in the general population, this genetic defect should be considered as a likely predisposing factor. The diagnosis of APC resistance can be made with high accuracy by means of easily available and inexpensive laboratory tests such as a modified APTT. The APC-resistance test has a sensitivity in excess of 90% and a specificity of 85%.

The possibility that the increased incidence of thromboses in the tamoxifen-treated patients was the result of the effect of the drug in combination with a genetic predisposing defect can still be evaluated in the available study patients who experienced thrombotic events. A retrospective diagnosis of APC-resistance or other genetic defects could also be made on stored blood samples (if available) for patients lost to follow up.

Screening for APC-resistance should be recommended for all patients receiving prolonged tamoxifen therapy. Screening for other genetic defects may be needed for patients with family history or repeated episodes of thrombosis. The diagnosis of a genetic thrombophilic predisposition is clinically relevant particularly for thromboprophylaxis. Affected patients can be adequately advised of their risk of thrombosis and of additional risk factors that can precipitate a thrombotic event. Informed patients can participate in the prevention and in the early diagnosis of such complications.

/S/

Lilia Talarico, M.D.

OCT 1 - 1998

Pregnancy Testing for Premenopausal Women Taking Tamoxifen

Consultation

It is interesting to note that of 13,388 women randomized to tamoxifen versus placebo for 5 years in the clinical trial, only five women became pregnant – four receiving placebo and one receiving tamoxifen. Tamoxifen has been marketed since 1971 for use in both early and late stage breast cancer. In premenopausal women with metastatic breast cancer, it is an alternative to oophorectomy or ovarian irradiation.

A proposed revision of the labeling would include a contraindication stating, "Breast Cancer Prevention: Women who are pregnant or who may become pregnant should not take NOLVADEX to prevent breast cancer. Effective nonhormonal contraception must be used by all premenopausal women taking NOLVADEX if they are sexually active. Animal studies suggest that the use of NOLVADEX during pregnancy may harm the fetus. (See WARNINGS – Pregnancy Category D).

With the inclusion of the above proposed contraindication. I see no reason to require baseline pregnancy tests or routine pregnancy tests for women while taking tamoxifen. Obviously, any woman who for any reason thought she might be pregnant should be evaluated accordingly.

/S/

Ridgely C. Bennett, M.D., M.P.H.
Medical Officer, HFD – 580
September 30, 1998

I concur /S/ ND, Ph.D. 9/30/98

I concur /S/ M.D. 10-1-98

cc: Orig. NDA 17-970/S-040
HFD-150/Div. File
HFD-150/Honig

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
Wilmington, DE 19850-5437

NOLVADEX® (tamoxifen citrate) Tablets

ITEM 13: Pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG.

1. Active ingredients(s):

   (Z)2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

2. Strength(s):

   10 mg and 20 mg

3. Trade Name:

   NOLVADEX® (tamoxifen citrate) Tablets

4. Dosage Form, Route of Administration:

   Tablet, Oral

5. Applicant Firm Name/Holder of the New Drug Application:

   Zeneca Pharmaceuticals
   A Business Unit of Zeneca Inc.
   1800 Concord Pike
   Wilmington, DE 19850-5437

6. NDA Number:

   17-970

7. Approval Date (Original):

   December 30, 1977

8. Applicable Patent(s):

(i) US Patent No. 4,536,516

(a) Expiration Date:

August 20, 2002

(b) Type of Patent:

US Patent No. 4,536,516 contains claims to the drug substance and method of use claims for the treatment of hormone dependent tumors.

(c) Name of Patent Owner:

Zeneca Limited
Macclesfield, Cheshire, England

(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

Cushman Darby and Cushman
Intellectual Property Group of
Pillsbury Madison and Sutro, LLP
1100 New York Avenue
Washington, DC 20005-3918

(e) Original Declaration:

The undersigned declares that US Patent No. 4,536,516 covers the formulation, composition, and/or method of use of NOLVADEX® (tamoxifen citrate) Tablets. This product is currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

Richard A. Elder

RICHARD A. ELDER
CHIEF IP COUNSEL
PHARMACEUTICALS

ZENECA
Pharmaceuticals Group
ZENECA Pharmaceuticals / Stuart Pharmaceuticals
Business Units of ZENECA Inc.

1800 Concord Pike
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Delaware 19897 USA

Telephone (302) 886–2132
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William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

JAN 27 1998

Re: NOLVADEX® (tamoxifen citrate) Tablets
NDA 17-970

The requirements of the Generic Drug Enforcement Act of 1992 regarding verification of the use of debarred individuals under section 306 (a) or (b) have been deferred as per agreement with FDA and in accordance with a draft guidance entitled "FDA Approval of New Cancer Treatment Uses in Marketed Drug and Biological Products" dated March 13, 1997.

Sincerely,

William J. Kennedy, Ph.D.

WJK/jr