

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020815, S003**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**New Drug Application**  
**Clinical Pharmacology and Biopharmaceutics Review**

**NDA:** 20-815  
**Type of Submission:** SE1 - 003 (Supplement - New Indication)  
**Generic Name:** Raloxifene Hydrochloride  
**Formulation(s);** Tablets  
**Strength(s);** 60 mg  
**Route(s)** PO  
**Brand Name:** EVISTA®  
**Sponsor:** Lilly  
Indianapolis, IN  
**Submission Date(s):** March 30, 1999  
**Reviewer:** Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

**I. SYNOPSIS**

Raloxifene HCl is a selective estrogen receptor modulator (SERM) currently approved for the following indication:

**PREVENTION OF OSTEOPOROSIS IN POST-MENOPAUSAL WOMEN.**

The current supplemental application is for a new indication.

**TREATMENT OF OSTEOPOROSIS IN POST-MENOPAUSAL WOMEN.**

The dosage for both indications is **one 60 mg tablet daily**.

Three clinical pharmacology studies are included in this supplement. These include a traditional interaction study with methylprednisolone and two population pharmacokinetic studies.

In the methylprednisolone interaction study, no effect of raloxifene on methylprednisolone pharmacokinetics was identified.

Factors evaluated in the population pharmacokinetic studies and conclusions reached are summarized in the following table:

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| Factors Evaluated  | Conclusions  |
|--|--|
| Patient specific factors that might alter raloxifene pharmacokinetics        | No new associations were identified that might effect raloxifene dosing.   |
| Pharmacokinetic / pharmacodynamics relationships                             | No clear pharmacokinetic / pharmacodynamic relationships were identified.<br><br>There was a large degree of overlap in plasma concentrations between the 60 and 120 mg doses. However, patients who discontinued treatment due to a lack of efficacy had statistically lower concentrations.  |
| Potential relationships between raloxifene concentrations and adverse events | There were no relationship between serious treatment emergent adverse effects and concentration. However since all serious adverse events were grouped together, the possibility that of a relationships with specific type of event cannot be excluded.<br><br>Patients with deep thrombophlebitis might have higher raloxifene concentrations, however the number of events is too small to definitely establish a relationship. |
| Effects of concomitant medications on raloxifene concentrations              | Information on possible interactions with a few medications were identified. However, there is insufficient data to justify including these potential interactions in the labeling.<br><br>Due to numerous issues, a conclusion of a lack of an interaction cannot be made for any medication.   |

The sponsor wishes to use the population analyses to support labeling for a lack of effect of other drugs on raloxifene concentrations. Issues that preclude making these type of conclusions include but are not limited to the following issues,

- Insufficient Sample Size
- Inappropriate Grouping of Concomitant Medications
- Confounding Due to Multiple Medications
- Metric Evaluated
- Metric Variability and Clinical Significance
- Sampling Time
- Data Exclusion
- Assay Limitations
- Temporal Association
- Lack of Detection of Known Interactions

## II. RECOMMENDATION

The Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE-2) has reviewed NDA # 20-815 SE1 - 003, submitted March 30, 1999. The overall Human Pharmacokinetic Section is acceptable to OCPB. This recommendation, comments, and labeling comments should be sent to the sponsor as appropriate.

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**Table 1 List of Clinical Trials for Supplemental Submission for New Treatment Indications for Raloxifene**

| Study Identifier<br>(Number of<br>Subjects) | Title   | Description  | Page<br>Number |
|---|---|--|----------------|
| H3S-MC-GGGN<br>(N=143)                      | A Comparison of Raloxifene HCl and Placebo in the Treatment of Osteoporosis in Postmenopausal Women by Assessment of Bone Mineral Density                           | Phase II<br><br>Population Pharmacokinetic / Pharmacodynamic Analysis<br>24 months of Data   | 52             |
| H3S-MC-GGGP<br>(N=129)                      | A Comparison of Raloxifene HCl and Placebo in the Treatment of Osteopenia in Postmenopausal Women by Assessment of Bone Mineral Density                             | Phase II<br><br>Population Pharmacokinetic / Pharmacodynamic Analysis<br>24 months of Data   | 52             |
| H3S-MC-GGGK<br>(N=7705)                     | A Comparison of Raloxifene HCl and Placebo in the Treatment of Postmenopausal Women With Osteoporosis   | Phase III<br><br>Population Pharmacokinetic/ Pharmacodynamic Analysis with Multiple Dose levels<br>Includes Evaluation of Drug Interactions<br>36 months of Data | 56             |
| Substudy I<br>(n=5064)                      | Femoral neck or lumbar spine BMD > 2.5 standard deviations below normal peak bone mass  | —  | —              |
| Substudy II<br>(n=2641)                     | At least one prevalent vertebral fracture, determined by a baseline semiquantitative assessment   | —  | —              |
| H3S-MS-GGIP<br>(N=16)                       | A Cross-Over Study to Assess the Pharmacokinetic Interaction of Raloxifene after Multiple Administration, on Methylprednisolone Single Dose in Postmenopausal Women | Phase I  | 61             |

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### III. ABBREVIATIONS

|                   |  |
|-------------------|--|
| AE                | Adverse Effect or Adverse Event  |
| ACE               | Angiotensin Converting Enzyme  |
| ANOVA             | Analysis of Variance   |
| APCI/LC/MS/MS     | Atmospheric Pressure Chemical Ionization / Liquid Chromatography / Mass Spectrometry / Mass Spectrometry |
| AUCa-b            | area under the plasma-concentration-time curve from time a to time b                                     |
| BMD               | Bone mineral density   |
| CGLF              | Modified Cockcroft-Gault Equation  |
| Cl/F              | Clearance determined after oral drug administration and uncorrected for absorption                       |
| CM                | Concomitant medications  |
| C <sub>max</sub>  | maximum measured concentration   |
| C <sub>min</sub>  | minimum measured concentration   |
| CV                | Coefficient of variation   |
| DMOF              | Decrease in mean of objective function   |
| DVT               | Deep Vein Thrombophlebitis   |
| DPEII             | Division of Pharmaceutical Evaluation II   |
| Fabs              | Fraction absorbed  |
| FBS               | fasting blood sugars   |
| GI                | Gastrointestinal   |
| GITS              | Gastrointestinal Intestinal Therapeutic System   |
| H <sub>1</sub>    | Histamine 1  |
| H <sub>2</sub>    | Histamine 2  |
| HbA <sub>1c</sub> | Hemoglobin A <sub>1c</sub>   |
| k <sub>a</sub>    | absorption rate constant   |
| L/Hr              | Liters per hour  |
| LLOQ              | lower limit of quantitation  |
| M                 | Methylprednisolone   |
| MPE               | Mean prediction error  |
| MSPE              | Mean squared prediction error  |
| MRE               | Mean residual error  |
| n                 | Number of subjects/observations  |
| NDA               | New Drug Application   |
| NSAID's           | Nonsteroidal Anti-inflammatory Drugs   |
| OCPB              | Office of Clinical Pharmacology and Biopharmaceutics   |
| p/a               | posterior / anterior   |
| PE                | Pulmonary Embolus  |
| PK                | Pharmacokinetic  |
| PO                | per os (by mouth)  |
| POP               | Population   |
| qd                | quinque diem (once daily)  |
| RE                | Relative error   |
| RP - HPLC - UV    | Reverse Phase High Pressure Liquid Chromatography with Ultraviolet Detection                             |
| RVT               | Retinal Vein Thrombosis  |
| SD                | Standard Deviation   |
| SEE               | Standard Error of the Estimate   |
| t <sub>1/2</sub>  | half-life  |
| TESS              | Treatment Emergent Serious Adverse Event   |
| T <sub>max</sub>  | time to maximum concentration  |
| TRHP              | Total Raloxifene in Hydrolyzed Plasma  |
| UV                | Ultraviolet  |
| VTE               | Venous Thromboembolism   |

2 pages

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## V. BIOEQUIVALENCE BRIDGING STUDIES

In the study report for Study H3S-MC-GGGK, the pivotal efficacy study for treatment of PMOP, the sNDA mentions that clinical trial batch(s) were used initially and commercial batches were used during the latter part of the trial. It was claimed that the bioequivalence of the pilot scale with commercial batches were determined in study H3S-LC-GGHK.<sup>2</sup>

This study was reviewed with the original NDA submission (20-815: June 8, 1997). At that time, the two formulations were determined by OCPB to be 'bioequivalent with no sequence or carryover effects'.

## VI. POPULATION PHARMACOKINETICS / PHARMACODYNAMICS IN POSTMENOPAUSAL WOMEN

### A. Introduction

According to the sponsor,

*'Population pharmacokinetics were studied in 1300 postmenopausal women. These subjects were studied in three phase II and three phase III studies.'*

These numbers are inconsistent with information reported elsewhere in the sNDA. For example, only two phase II studies and one phase III population pharmacokinetic study are reported. Albeit, 1774 subjects were studied in the phase III study (Study H3S-MC-GGGK) and it is composed of two sub-studies.

### B. Model Development and Validation

#### 1. Model Development - Phase II Studies

To develop a population pharmacokinetic model the sponsor used the first 12 months of data (3 samples) from the following 24 month phase II study,

H3S-MC-GGGN     A Comparison of Raloxifene HCl and Placebo in the Treatment of Osteoporosis in Postmenopausal Women by Assessment of Bone Mineral Density.

From this data, a linear open 1-compartment mammalry model with first order absorption was fit to the data using a population approach. Due to the limited number of samples during the absorption phase the fraction absorbed (Fabs) and the absorption rate constant (ka) were fixed, with the values based upon estimates from previous classical and population pharmacokinetic studies.

#### 2. Model Verification - Phase II Studies

The model was verified by using the estimated population pharmacokinetic parameters to provide individual bayesian estimates of clearance and volume of distribution based upon two raloxifene concentrations from the second 12 months (months 13 - 24) of this study (Study H3S-MC-GGGN). The model was also used to provide individual bayesian estimates of clearance and volume of distribution in another smaller 24 month study in postmenopausal women (Study H3S-MC-GGGP) that also utilized sparse sampling (4 samples over 24 months),

H3S-MC-GGGP     A Comparison of Raloxifene HCl and Placebo in the Treatment of Osteopenia in Postmenopausal Women by Assessment of Bone Mineral Density.

<sup>2</sup> Item 6; Vol 3 of 11; page 55

From these individual parameter estimates of clearance and volume of distribution, raloxifene concentrations were predicted and the predicted concentrations were compared to the observed concentrations.

Concentration data was also summarized by descriptive statistics (mean, CV, and number of observations) as well as presented graphically. This was also done for data from subjects who initially received placebo and were re-randomized to receive raloxifene during a later phase of the study.

Other procedures taken to verify the model included the following analyses:

1. Parameter sensitivity analysis (Study H3S-MC-GGGN 0 - 12 month data)
2. Leverage analysis (Study H3S-MC-GGGN 0 - 12 month data)
3. Statistical Analysis
  - MPE, MSPE, MRE of predicted concentrations to observed concentrations
  - Nonparametric comparison of probability distributions of individual clearances from each study

### 3. Model Development and Verification - Phase III Studies

The phase III study (Study H3S-MC-GGGK) was a 36 month study, and was composed of two substudies with slightly difference inclusion criteria (See Table 4).

**Table 4 Study H3S-MC-GGGK Substudies**

| Sub-study        | Study H3S-MC-GGGK  |   |
|------------------|--|---|
|                  | I  | II  |
| Study Population | Post-menopausal women with Osteopenia (p/a lumbar spine BMD 1 s.d. below mean) | Post-menopausal women with Osteoporosis (at least 1 non-traumatic vertebral fracture) |

Demographic and information on study design is included in Table 5.

**Table 5 Study Design - PK Substudy H3S-MC-GGGK**

|                         |  |
|-------------------------|--|
| Age                     | 45 - 81  |
| Study Locations         | US<br>UK<br>Argentina<br>Netherlands<br>Norway |
| Concurrent Therapy      | Vitamin D & Calcium                            |
| Raloxifene Dosages      | PBO, 60 mg qd, 120 mg qd                       |
| Formulations            | 60, 120 mg                                     |
| Blood Sampling (Months) | 3, 6, 12, 18, 24, 36                           |
| Drug Species Examined   | Raloxifene; TRHP                               |

Only a small fraction of the total number of subjects in the phase III efficacy study were included in the population pharmacokinetic substudy (H3C-MC-GGGK). Details of the number of subjects in the substudy and the sampling for these subjects are included in Table 6. Due to the large size of phase III trial, the absolute number of subjects in the population PK substudy is quite large (n = 1712)

**Table 6 Plasma Sampling - PK Substudy H3S-MC-GGGK**

|   | Number of Subjects | Number of Observations |
|---|--------------------|------------------------|
| Potential Data Available from Pop PK Study  | 1820               | 9982                   |
| Number of Subjects by Study Arm   |                    |                        |
| Placebo   | 923                | —                      |
| 60 mg   | 910                | —                      |
| 120 mg  | 910                | —                      |
| Usable Data<br>(quantifiable raloxifene concentrations,<br>adequate dosing and sampling data) | 1712               | 8914                   |
| Mean # of Usable Observations / Subject<br>Claimed by sponsor                                 | 5.2                |                        |
| Range   | 1 - 6              |                        |

The population pharmacokinetic model for this study was developed and validated in the following manner. The data from the first 24 months of this 36 month study was divided into 2 datasets, a model development dataset and a model verification dataset. The model development dataset contained data from ¾ of the subjects and is also known as the index dataset. The Model Verification Dataset contained data from the remaining ¼ of the subjects with 0 - 24 month data (See APPENDIX 2 - PROTOCOL SUMMARY - Study H3S-MC-GGGK 36-Month Data).

**Table 7 Model Development and Verification - Phase III Study GGGK - 0 - 24 month Data**

| Data-set                    | Fraction of Subjects | Other Names    |
|-----------------------------|----------------------|----------------|
| Model Development Data-set  | ¾ subjects           | Index Data-set |
| Model Verification Data-set | ¼ subjects           | —              |

As with the phase II studies' population pharmacokinetic analysis a one-compartment model with fixed first order absorption was used as the structural model. Model validation procedures were similar to those used with the phase II studies.

### **C. Linearity and Time Invariance**

The results from the phase II studies do not show any evidence of nonlinearity over the dose range studied (60 to 150 mg daily) nor any time invariance (See Table 8, Table 9 and Figure 1). (Time invariance indicates a lack of change in pharmacokinetics over time.) Due to the limitations of the study design (this will be addressed later when discussing the phase III studies), the lack of evidence cannot be taken as a firm conclusion of linearity or time invariance.

**Table 8 Mean Observed Raloxifene Steady-State Concentrations by Duration of Therapy (GGGN)**

| Raloxifene HCl Dose | 1 Month | 6 Months | 12 Months | Overall <sup>a</sup> Raloxifene |
|---------------------|---------|----------|-----------|---------------------------------|
| <b>60 mg</b>        |         |          |           |                                 |
| Mean (ng/mL)        | 1.07    | 1.14     | 0.97      | 1.06                            |
| CV (%) <sup>b</sup> | 53.9    | 53.8     | 46.7      | 52.2                            |
| n <sup>c</sup>      | 45      | 44       | 39        | 128 <sup>d</sup>                |
| <b>120 mg</b>       |         |          |           |                                 |
| Mean (ng/mL)        | 1.79    | 1.76     | 1.92      | 1.82                            |
| CV (%) <sup>b</sup> | 46.6    | 46.0     | 58.2      | 50.3                            |
| n <sup>c</sup>      | 46      | 43       | 37        | 126 <sup>d</sup>                |

a May include analytical results obtained at an unscheduled visit.

b Statistics from UNIVARIATE procedure in SAS.

c Number of patients for whom plasma concentrations, as well as dose and sample draw times, were available.

d The overall number (n) represents the total number of blood samples and may be greater than the sum of patient number for 1, 6, and 12 months.

**Table 9 Overall Mean Raloxifene Steady-State Plasma Concentrations in Studies GGGN & GGGP**

| Raloxifene HCl Dose                          | GGGN <sup>a</sup> (0- 12 months) |        | GGGN <sup>a</sup> (13- 24 months) |        | GGGN <sup>a</sup> Re-randomized to raloxifene from Placebo |        | GGGP <sup>a</sup> (0- 24 months) |        |
|--|----------------------------------|--------|-----------------------------------|--------|--|--------|----------------------------------|--------|
|  | 60 mg                            | 120 mg | 60 mg                             | 120 mg | 60 mg  | 120 mg | 60 mg                            | 150 mg |
| <b>Raloxifene Mean (ng/mL)<sup>b</sup></b>   | 1.06                             | 1.82   | 1.06                              | 2.00   | 1.02   | 2.11   | 0.76                             | 1.88   |
| <b>CV (%)</b>                                | 52.2                             | 50.3   | 53.5                              | 54.4   | 42.2   | 50.9   | 52.1                             | 55.1   |
| <b>n<sup>c</sup></b>                         | 128                              | 126    | 67                                | 67     | 33   | 37     | 148                              | 139    |
| <b>Ratio of Means; High Dose to Low Dose</b> |                                  | 1.72   |                                   | 1.87   |  | 2.07   |                                  | 2.47   |

a Statistics from UNIVARIATE procedure in SAS

b Mean of all visits during time interval which may include analytical results obtained at an unscheduled visit

c (n) represents the total number of plasma concentrations.

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Figure 1 Mean Plasma Raloxifene and TRHP Concentrations in Study GGGN

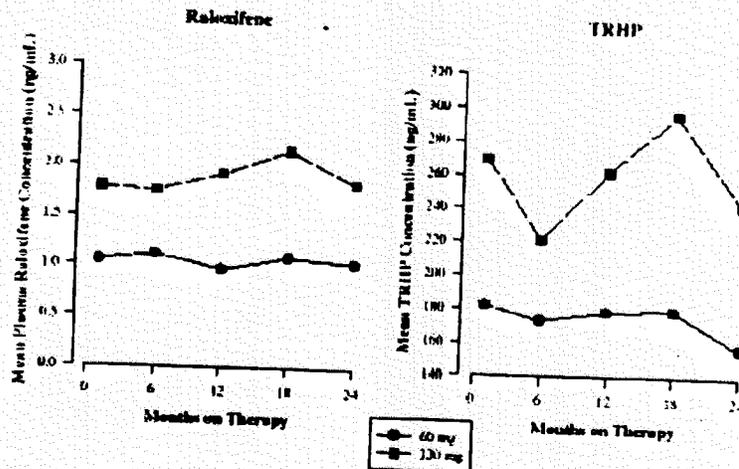


Figure 5.7. Mean plasma raloxifene and TRHP concentrations in Study GGGN.

**D. Estimates of Population Pharmacokinetic Parameters**

Estimates of pharmacokinetic parameters are included in Table 10.

Table 10 Estimated Pharmacokinetic Parameters for Raloxifene as Determined From the Interim Analysis of Study GGGN

| Parameter Description           | Population Estimate (%SEE) <sup>a</sup> | Between-Patient Variability (%SEE) <sup>a</sup> |
|---------------------------------|---|---|
| Clearance (Liters/hour)         | 46.2 (5.4)                              | 38.1% (15.2)                                    |
| Volume of Distribution (Liters) | 2970 (27.5)                             | - <sup>b</sup>                                  |
| Residual Error                  | 25% (12.4)                              |   |

Abbreviations: %SEE = standard errors of the NONMEM estimates expressed as % of estimate  
<sup>a</sup> From Final Report: Interim Analysis of Population Pharmacokinetic and Pharmacodynamic Analyses of Selected Efficacy Studies.  
<sup>b</sup> Allowing for between-patient variability in V did not improve the model.

According to the sponsor there was a slight difference in the distribution of clearance estimates in the phase II studies GGGN and GGGP, although there was still a 77% overlap of the two distributions. The sponsor attributed this difference to a combination of variability in the estimates (38.1% between patient CV for clearance in Study GGGN) and since each study examined a slightly different patient population (See Table 11).

**Table 11 Patient Populations - Phase II Studies**

| Study | Country | Patient Population  |
|-------|---------|---|
| GGGN  | USA     | Post-menopausal women with Osteoporosis<br>(1 non-traumatic vertebral fracture)   |
| GGGP  | France  | Post-menopausal women with Osteopenia<br>(p/a lumbar spine BMD 1 s.d. below mean) |

Both of these explanations are plausible. However, it should be remembered that both studies, and study GGGP in particular, had very small sample sizes and this alone could explain the difference.

### **E. Patient Specific Factors**

#### **1. Introduction**

Patient specific factors were not evaluated in the phase II studies GGGN and GGGP.

They were evaluated in the 36 month phase III study H3S-MC-GGGK 'A Comparison of Raloxifene HCl and Placebo in the Treatment of Postmenopausal Women With Osteoporosis'. Study GGGK was composed of 2 sub-studies with slightly different patient populations. (See Table 12 for additional information)

**Table 12 Study H3S-MC-GGGK**

|                         |   |
|-------------------------|---|
| H3S-MC-GGGK<br>(N=7705) | A Comparison of Raloxifene HCl and Placebo in the Treatment of Postmenopausal Women With Osteoporosis |
| Substudy I<br>(n=5064)  | Femoral neck or lumbar spine BMD > 2.5 standard deviations below normal peak bone mass                |
| Substudy II<br>(n=2641) | At least one prevalent vertebral fracture, determined by a baseline semiquantitative assessment       |

A schematic including the methods used for identification and evaluation of covariates is included on the next page (See Figure 2 General Process for Pharmacokinetic and Pharmacodynamic Modeling). Individual patient specific factors that were evaluated for inclusion in the final model are listed on the following page in Table 13.

Regardless of the results of covariate identification analysis the following patient specific factors were identified *a priori* to be evaluated for their influence on raloxifene concentrations based upon clinical or demographic significance.

- 1) Dose
- 2) Age
- 3) Weight
- 4) Chronic Alcohol Use
- 5) Smoking Status
- 6) Creatinine Clearance
- 7) Ethnic Origin

The sponsor only considered factors to be clinically significant if they altered mean plasma concentrations by more than the within-subject variability of 31%.

None of the other patient specific factors were included in the final model.

Figure 2 General Process for Pharmacokinetic and Pharmacodynamic Modeling

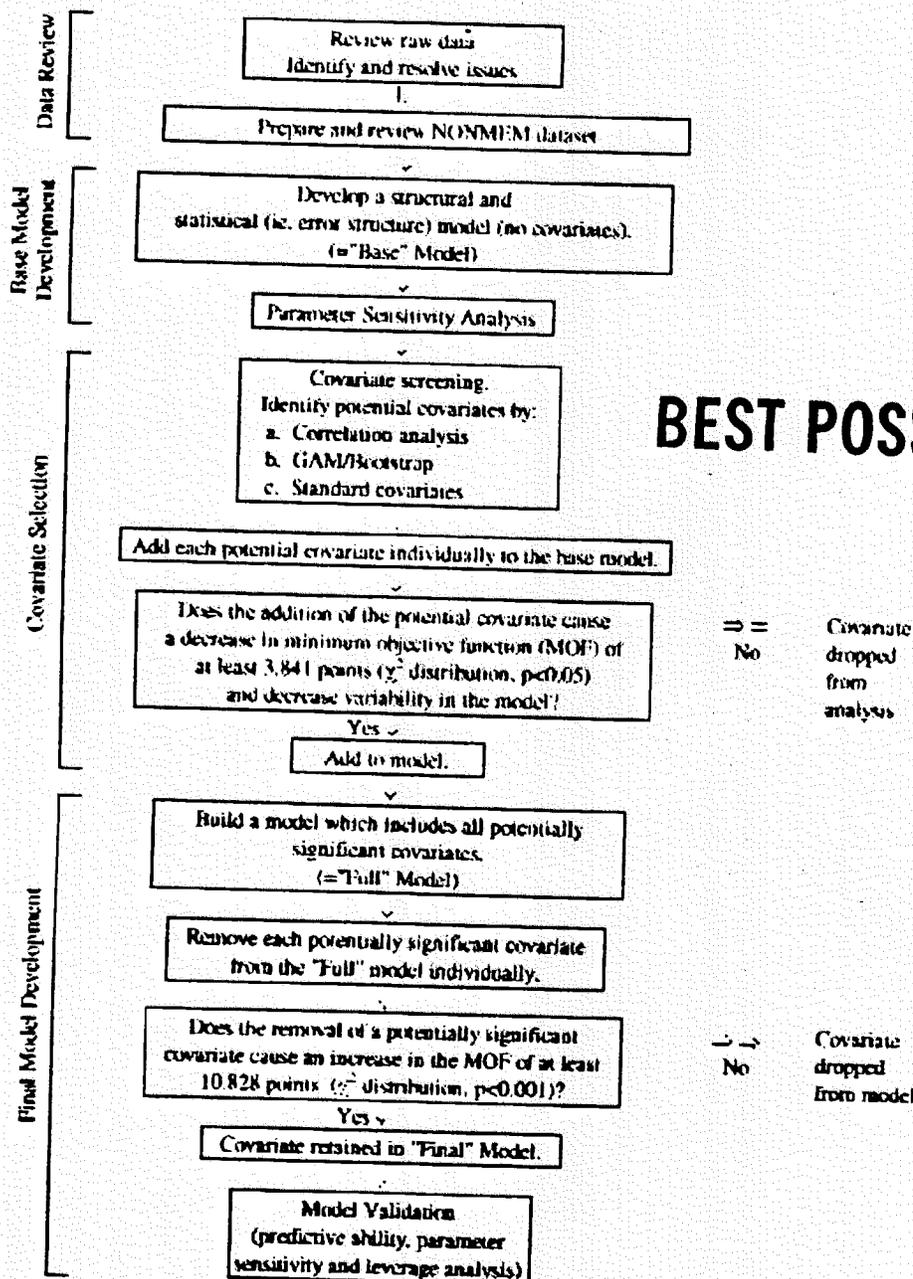


Figure 3.1. General Process for Pharmacokinetic and Pharmacodynamic Modeling