CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-896

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

APR 15 1999

NDA#: 20-896

Applicant: Hoffmann-La Roche Inc.

Name of Drug: XELODA (capecitabine) Tablets 150mg & 500mg

Indication: Advanced or metastatic breast cancer patients who had failed or were resistant to paclitaxel

Documents Reviewed: Vols. 110 - 226 of submission dated on 10/28/97, and supplement analyses and data sets submitted on 12/23/97, 01/09/98, 01/27/98, 01/28/98, 02/04/98, 2/24/98, 03/04/98, and 03/05/98.

Medical Officer: Alison Martin, M.D.

Major Statistical Issues:

(i) Longitudinal analysis of the clinical benefit response variable

A clinical benefit variable was defined to evaluate QOL. This clinical benefit was based on repeated measurements of pain, analgesic consumption, and performance status. These continuous variables were categorized as positive, negative, or stable, by prespecified criteria. Then, the clinical benefit variable was dichotomized as response or nonresponse. This categorization could cause non robust results. In addition, about 60% of patients dropped out of study before week 18 (the treatment period). In this review, a longitudinal data analysis was applied to pain, analgesic consumption, and performance status separately to investigate QOL time trends and dropout patterns, i.e., missing data mechanism (ignorable vs nonignorable).

Section 1 contains a brief background on XELODA. Section 2 contains a description of the Study SO14697. Section 3 contains the Sponsor's results and this reviewer's comments. Section 4 contains longitudinal data analyses of clinical benefit variables. Section 5 contains the conclusions regarding this

submission.

I. Background

In this NDA the sponsor seeks approval of XELODA for the treatment of patients with advanced or metastatic breast cancer who had failed or were resistant to pacitaxel.

XELODA will be given orally twice a day at 2510 mg/sqm/day for two weeks followed by one week rest period.

II. Description of Study

Study SO14697 was an open-label, multicenter, single-arm phase II study for patients with breast cancer who had failed previous paclitaxel therapy. XELODA was given twice daily at 2510 mg/sqm/day for two weeks followed by one week rest period and repeated in three week cycles. The study consisted of three periods. The first period was called "treatment period" (18 weeks). During this period tumor respose was assessed for the first time at week 6. Patients with complete or partial responses or stable disease could continue further treatment in courses of three weeks, up to a total of 18 weeks. The second period was called "maintenance period" (additional 30 weeks). During this period "tumor assessments were to be repeated at six-week intervals, and at the time of withdrawal from study." Patients with an objective tumor response or stable disease were allowed to stay in the trial for an additional 30 weeks using the same dosing regimen. The third period was called a "continuation period". After 48 weeks, responding patients or patients who still had stable disease were allowed to stay on treatment.

The primary objective of the study was to assess the overall response rate of "patients with measurable metastatic breast cancer" and secondary objectives were (i) to demonstrate the safety and tolerability of the drug as an outpatient treatment, (ii) to determine the duration of response, time to treatment failure, and overall survival, and (iii) to evaluate the effect on "pain intensity, analgesic consumption, and performance status as measured by a Clinical Benefit Response assessment."

One hundred fifty patients were to be accrued. This study was powered (94% power) by the assumption that the true response rate was 20% and the lower bound of the 95% confidence interval was greater than 10%. One hundred and sixty three patients were accrued in this study.

III. Results and Reviewer's Comments

(A) Primary Variable (Response Rate)

Reviewer's Table 2.A.1 shows the response rate analysis for patients with measurable disease and with measurable and evaluable disease. Results were derived from data sets submitted to this reviewer by the sponsor.

Reviewer's Table 2.A.1 Response Rate in Each Category

	Measurable	Measurable + Evaluable
Sample Size	135	163
# of Responders	27 (3,24)*	32
Response Rate	20.0%	19.6%
95% CI	13.6% - 27.8%	13.8% - 26.6%

*three patients were complete responders and 24 patients were partial responders.

The estimated response rate was 20.0% and 19.6% with 95% CIs (13.6% - 27.8%) and (13.8% - 26.6%)in both populations, respectively.

Based on the Medical Reviewer's assessment of objective response, there were 25 responders among the measurable disease patients and the estimated response rate was 18.5 % with 95% CI (12.4%, 26.1%).

Reviewer's Table 2.A.2 shows results of the response rate in the "standard population" with measurable disease and in the IRC reviewed population. Details about this can be found in the Medical Review.

Reviewer's Table 2.A.2 Response Rate in Each Category

	Standard Population (measurable)	IRC*
Sample Size	128	101
# of Responders	27 (3,24)**	18
Response Rate	21.1%	17.8%
95% CI	14.4% - 29.2%	10.9% - 26.7%

*Independent Review Committee
**three patients were complete responders and 24 patients were partial responders.

The response rate was 21.1% and 17.8% with 95% CIs (14.4% - 29.2%) and (10.9% - 26.7%) in the "standard population" and the IRC reviewed population, respectively. These results were derived from SAS data sets submitted to this reviewer by the sponsor. The Medical reviewer's assessment of objective response can be found in the Medical review of this NDA.

(B) Secondary Variables

1. Duration of Overall Response (Measurable Disease only)

Duration of response was defined (WHO criteria)as the time between treatment start and disease progression for partial responses and as the time between onset of response and progression of disease for complete responses. In this analysis all measurable responded patients were evaluated. Reviewer's Table 2.B.1 shows the results of the duration of response analysis and the number of responders who progressed during the study. Eleven responders had not progressed during the trial. This reviewer confirmed the sponsor's results.

Reviewer's Table 2.B.1 Duration of Response for Measurable Disease Patients

# of Responders	27
# of Progressed Patients	16
Median (days)	241

The Medical Reviewer includes duration of overall response, where partial response was calculated as the time from onset of response to disease progression.

2. Time to Disease Progression

Patients who dropped out with no documented progressive disease were counted as being censored for the time to disease progression. Reviewer's Table 2.B.2 shows the results of time to disease progression analysis. One hundred thirty five patients progressed during the entire study. One hundred fifteen patients progressed among patients with measurable disease. This reviewer confirmed the sponsor's results in the following table.

Reviewer's Table 2.B.2 Time to Disease Progression

	All Patients (Measurable + Evaluable)	All Patients (Measurable only)
Sample Size	163	135
# of Progressed Pts	135*	115
Median (days)	93	92
95% CI	84 - 106	70 - 101

*135 patients were counted in the treatment and follow-up periods (10 patients progressed in the follow-up period).

3. Time to Treatment Failure

Patients who dropped out with no documented progressive disease were counted as beening events for the time to treatment failure analysis. Reviewer's Table 2.B.3 shows the TTF analysis results. Comparing to Reviewer's Table 2.B.2, seven patients dropped out of the study for reasons other than disease progression.

Reviewer's Table 2.B.3 Time to Treatment Failure (All Patients)

Sample Size	162
# of treatment failures	142
Median (days)	89.5
95% CI	75 -100

These results were summarized on page 35, Module V-35 of the NDA submission. This reviewer confirmed the sponsor's results.

4. Survival Analysis

Survival time was calculated from start of treatment to the date when the patient died or was last known to be alive. All patients (measurable plus evaluable patients) were evaluated. Reviewer's Table 2.B.4 shows the results. Seventy patients died during the entire study.

Reviewer's Table 2.B.4 Time to Death

# of Deaths	70 (22 in the treatment period and 48 in the follow-up period)
Median Survival (days)	384

These results were summarized on page 36, Module V-36 of the NDA submission. This reviewer confirmed the sponsor's results.

IV. Clinical Benefit Response

Clinical benefit variables were assessed by all patients on a daily (pain and analgesic consumption) or weekly schedule (Karnofsky performance score). The sponsor defined prospectively a clinical benefit variable by combining pain score, Karnofsky performance score and analgesic consumption. Details describing this endpoint are not included in this review.

Patients categorized prospectively by the sponsor as either "responders" or "nonresponders" with regards to the clinical benefit variable. Duration (a minimal 4 weeks) was also used in the determination of the clinical benefit response. If this duration criterion was not met, then subjects were classified as "Stable". Because the dropout rate was very high (Reviewer's Appendix 1 - by the end of a treatment period, 65.8% of the subjects dropped out of the study), the observed treatment effect may not reflect a true effect.

The clinical benefit response is based on repeated measurements of pain score, analgesic consumption, and performance status -- all defined as continuous variables. Potentially, information regarding the individual components of the clinical benefit response may be lost by categorizing and combining them to a single benefit variable. In addition, the derived results are depended on the predefined criteria. For example, improvement of 50% or more in pain score over baseline is required for someone

to be a responder. Thus, results might be sensitive to the predefined criteria.

This reviewer investigated the time profile of the three components of the clinical benefit response (pain, analgesic consumption, and performance status) using an exploratory longitudinal data analysis and investigated the missing mechanism by applying the concept of "Pattern-Mixture Model"(Little, 1995).

4.1 Notes on Longitudinal Analyses

The purposes of a longitudinal data analysis are (i) to characterize patterns of responses and changes over time, and (ii) to investigate the effect of baseline values and dropouts on time trends. The approach employed in this review is known as a growth curve analysis. Details are in Reviewer's Appendix 2.

The advantages of this approach are: (i) it enables us to investigate each of the individual components of the clinical benefit response, (ii) it treats outcomes as continuous variables, rather than imposing a binary structure, and (iii) it provides information on the temporal patterns of change. We utilize all available observed data for each component on each patient.

In general, there are two challenges in repeated measurements analysis. The first challenge is to address the unknown within-subject correlation of observations. This reviewer compared estimated standard errors between a model-based (an inverse of Fisher's information) and a sandwich (derived from a model, known as GEE approach) estimator taking the Akaike's information value into account. The second challenge is the problem with missing data. Typically, in clinical trials patients drop-out for a variety of reasons, e.g., death, adverse events, progression of disease, etc. The common univariate analyses -- observed cases (OC) analysis, last observation carried forward (LOCF) analysis, or repeated measurements ANOVA -- depend on strong missing mechanism assumptions. This reviewer employed the concept of "Pattern-Mixture Model" to investigate the missing mechanism. A brief description can be found in reviewer's Appendix 3.

4.2 Results

This reviewer applied three different "working" correlation structures -- independent, compound symmetry, and Auto Regressive of order 1 -- to investigate the correlation issue. As mentioned

before, model-based and sandwich estimators are compared using the Akaike's information.

This reviewer used week 6 (period 1), week 12 (period 2), week 18 (period 3), and week 18+ (period 4) as time cut-off points to investigate the missing data mechanism based on a homogeneity criteria from a patern-mixture model. For example, patients who dropped out of the study before week 6 were analyzed in period 1 and patients who stayed on study at least 6 weeks and dropped out before week 12 were analyzed in period 2. In this sense, we had 4 different cohorts of patients. These time cut-off points come from the study design. Recall that tumor assessments were made at six weeks intervals (week 6, week 12, and week 18) or when patients came off study.

4.2.1 Pain Intensity

Pain score is a weekly mean of daily pain intensity scores, measured by the "Memorial Pain Assessment Card". The pain intensity score was reported for each week of the study period.

Reviewer's Summary 1 displays the results of the analyses. Based on these analyses, it is reasonable to assume that the missing mechanism is nonignorable. We have three possible time profiles (Reviewer's Figure 1).

The pain score was stable for patients who dropped out of the study in period 1. On the other hand the pain score decreased for some time for patients who stayed on study beyond week 6. The pain score decreased until week 9 and started to increase for patients who dropped out of study in period 2 and 3. For patients who stayed on study beyond week 18, the pain score decreased until week 12 and started to increase.

4.2.2 Analgesic Consumption

Analgesic consumption is a weekly mean of daily analgesic consumption (morphine equivalent). This reviewer analyzed "the analgesic consumption with amended 0 for missing analgesics records per week when a pain score was available". Therefore, the results might be optomistic.

Note that this reviewer observed many outlier data points (15,000 score), which could influence the results completely. Patients whose baseline values were more than 300 were deleted. Scores more than 300 during the study were also deleted.

Based on this Reviewer analyses (Reviewer's Summary 2) it is reasonable to assume that the missing mechanism is nonignorable. We see two possible time profiles in Reviewer's Figure 3.

Figure 3 shows that the analgesic consumption increased at a constant rate for patients who dropped out of study in period 1. On the other hand, the analgesic consumption was stable for patients who could stay in the study beyond week 6.

4.2.3 Karnofsky Performance Status

Karnofsky performance status was assessed on a weekly basis.

Based on this Reviewer's analyses (Reviewer's Summary 3) it is reasonable to assume that the missing mechanism is nonignorable. We see two possible time profiles in Reviewer's Figure 2.

Figure 2 shows that the Karnofsky performance status was stable for patients who dropped out of study in periods 1,2 and 3. On the other hand, the score increased at a constant rate (better Karnofsky performance score) for patients who stayed in the study beyond 18+ weeks.

V Conclusions

Six endpoints: response rate, duration of response, time to disease progression, time to treatment failure, survival time, and clinical benefit response, were evaluated in this review.

This reviewer confirmed the sponsor's reported results on response rate, duration of response, time to disease progression, time to treatment failure, and survival time.

This reviewer investigated the time trend of three clinical benefit response components (pain, analgesic consumption, and performance status) and the missing data mechanism. This reviewer concluded that the missing data mechanism was nonignorable.

For patients who stayed in the study for at least 18 weeks (the treatment period, N=50), the pain score decreased over time with no change in the analgesic consumption, and the karnofsky score increased over time. On the other hand, for patients who were resistant to both paclitaxel and anthracyclines (N=43), the pain score, the analgesic consumption, and the Karnofsky score did not change over time. These findings were presented at the

Oncological Advisory Committee Meeting on March 19, 1998.

Due to the lack of a control group and the high dropout rate in this trial, it is hard for this reviewer to draw any definitive conclusions about the QOL data.

/S/ 4/15/98

Masahiro Takeuchi Sc.D
Mathematical Statistician

Concur: Dr. Koutsoukos 4/15/98
Dr. Chi

4/15/98

cc:
NDA#20-896
HFD - 150 / Division File
HFD - 150 / Dr. Beitz
HFD - 344 / Dr. Barton
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HFD - 710 / Chron
Takeuchi / 03-03-98 / WP6.1 - Stat_Review
This review consists of 10 pages of text, 3 Appendices (Appendix 1-3), 3 Summaries (Summary 1-3), and 3 figures (Figures 1-3).

Reviewer's Appendix 1: Sample Size Over Time in Pain Score

Time	Number of Patients
baseline	155
week 1	148
week 2	145
week 3	138
week 4	134
week 5	133
week 6	124
week 7	102
week 8	91
week 9	93
week 10	86
week 11	82
week 12	79
week 13	68
week 14	60
week 15	61
week 16	58
week 17	55
week 18	53

Reviewer's APPENDIX 2: A Summary of Longitudinal Linear Models

We briefly outline longitudinal linear models, which can be applied under an ignorable missing assumption or within a homogeneity group under a nonignorable missing assumption.

In a general longitudinal analysis, Zeger *et al* (1988) make a distinction between two types of longitudinal analyses: a "subject-specific (SS) model" (a type of mixed effects model) and a "population-averaged (PA) model". In the SS model, we are mainly concerned with individuals' response over time, and the heterogeneity of the data from each individual can be explicitly modeled. On the other hand, the PA model focuses on the average response and the heterogeneity of individuals is not considered in the model.

The SS model focuses on the between-subject variability in a data set. The variance can be modeled explicitly, and will contribute to the marginal covariance structure and/or the marginal mean functions in the SS models. This is the approach used in the linear mixed effects model. However, if the analysis is not focused on accounting for between subject variability, a PA model approach, with relaxed assumptions, can be applied. This is a Generalized Estimating Equations (GEE) approach. As noted by Zeger *et al* (1988), a marginal covariance structure, which is one of challenges in a repeated measurement setting, can be explained by the two approaches in a different fashion. On the other hand, a marginal means, in our case, intercept and a slope, will not be affected by the two approaches.

1. Subject-Specific Linear Models

The linear mixed effects models have been investigated by a number of researchers (Harville, 1976 and 1977, and Rao, 1965, 1967, and 1975). As described above, by introducing distributional assumptions for each individual's random variability, a marginal covariance structures can be explained explicitly. Of particular interest in the regulatory context, Laird and Ware (1982) have described the application of these models to unbalanced (in general we have a balanced design in a clinical trial setting) and incomplete data based on the assumption that a missing mechanism is defined as "missing at random" (MAR), belonging to an ignorable missing mechanism. The model can be defined as

$$\mathbf{y}_i = \mathbf{X}_i\beta + \mathbf{Z}_i\mathbf{b}_i + \varepsilon_i$$

where Z_i is a known design matrix of random effects, $\mathbf{b}_i$, and $\mathbf{b}_i$ and ε_i are N (0, Ω) and N (0, $\sigma^2 I_i$) respectively. Note that we assume that $\mathbf{b}_i$ and ε_i are independent of each other. To estimate the fixed effects parameters (population parameters), we need to know the marginal means and marginal covariance matrix. Applying the independence assumption of $\mathbf{b}_i$ and ε_i with the corresponding expectation equal to 0, we will obtain

$$E(\mathbf{y}_i) = \mathbf{X}_i\beta \text{ and } \operatorname{cov}(\mathbf{y}_i) = \mathbf{Z}_i\Omega\,\mathbf{Z}_i^T + \sigma^2\mathbf{I}_i = \mathbf{V}_i$$

Then the estimated fixed effects parameters can be obtained by

$$\hat{\beta} = \left(\sum_{i=1}^{K_j} \mathbf{X}_i^T \hat{\mathbf{V}}_i^{-1} \mathbf{X}_i \right)^{-1} \left(\sum_{i=1}^{K_j} \mathbf{X}_i^T \hat{\mathbf{V}}_i^{-1} \mathbf{y}_i \right) \text{ and } \operatorname{cov}(\hat{\beta}) = \left(\sum_{i=1}^{K_j} \mathbf{X}_i^T \hat{\mathbf{V}}_i^{-1} \mathbf{X}_i \right)^{-1}$$

Note that (i) the random effects only contribute to the marginal covariance matrix, and not to the marginal means, I.e., $\mathbf{V}_i$ is the only function of random efects, and that the covariance structure will depend on a choice of random effects, Z_i, and that (ii) the misspecification of the marginal covariance matrix due to a incorrect choice of the random effects, Z_i, may lead to an underestimate of the variance of the estimated parameters.

The second approach is called a "random coefficient models". This approach is similar to a linear mixed effects model. The model can be defined as

$$\mathbf{y}_i = \mathbf{X}_i \beta_i + \varepsilon_i$$

where β_i and ε_i are $N(\beta, \Sigma_{\beta\beta})$ and $N(0, \sigma^2 \mathbf{I}_i)$ respectively, and we assume that β_i and ε_i are independent each other.

Then a simple unweighted estimator can be defined as

$$\mathbf{b}_u = \frac{1}{K_j} \left(\sum_{i=1}^{K_j} \hat{\beta}_i \right), \quad \text{where } \hat{\beta}_i = (\mathbf{X}_i^T \mathbf{X}_i)^{-1} (\mathbf{X}_i^T \mathbf{y}_i) \text{ and } \operatorname{cov}(\hat{\beta}_i) = \Sigma_{\beta\beta} + \sigma^2 (\mathbf{X}_i^T \mathbf{X}_i)^{-1} = \mathbf{W}_i$$

And a weighted estimator can be defined as

$$\mathbf{b}_w = \frac{1}{\sum_{i=1}^{K_j} \mathbf{W}_i^{-1}} \left(\sum_{i=1}^{K_j} \mathbf{W}_i^{-1} \hat{\beta}_i \right)$$

Note that for a balanced and a complete design we have $\mathbf{b}_u = \mathbf{b}_w$.

The main difference between the two approaches is that (I) a weighted least squares (a generalized least squares) is applied to each subject in a linear mixed effects model, and a simple least squares is applied to each subject in a random coefficient model, and (ii) the weighting scheme is different.

2. Population-Averaged Linear Models

In the PA approach to linear models we are interested in a model which is only a function of covariates without introducing subject to subject heterogeneity in the marginal covariance matrix. Therefore the model can be simply defined as

$$\mathbf{y}_i = \mathbf{X}_i \beta + \varepsilon_i$$

In the SS model, random effects variables are employed to describe the covariance structure. This unknown correlation structure depends on the selection of $\mathbf{Z}_i$ matrix. Thus the selected covariance structure can be viewed as one of a number of possible alternatives. In applying the PA approach, Jennrich and Schluchter (1986) investigated a number of covariance structure (independent observations, compound symmetry, random-effects, first-order autoregressive structure, and so on), in a variety of situations (unbalanced and incomplete designs). They used a likelihood-based approach to the linear model. Therefore the only restriction required for the covariance matrix is a positive definite matrix. Note that the misspecification of of the covariance matrix may lead to an underestimate of the variance of the estimated parameters.

Another approach to the linear model, not requiring distributional assumptions on the error term, is the application of an estimating equation. Invoking M-estimation theory (Huber 1967, White 1982, Liang and Zeger, 1986), the estimating equation can be defined as

$$U(\beta) = \sum_{i=1}^{K} \mathbf{X}_i^T \mathbf{V}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i\beta) = 0$$

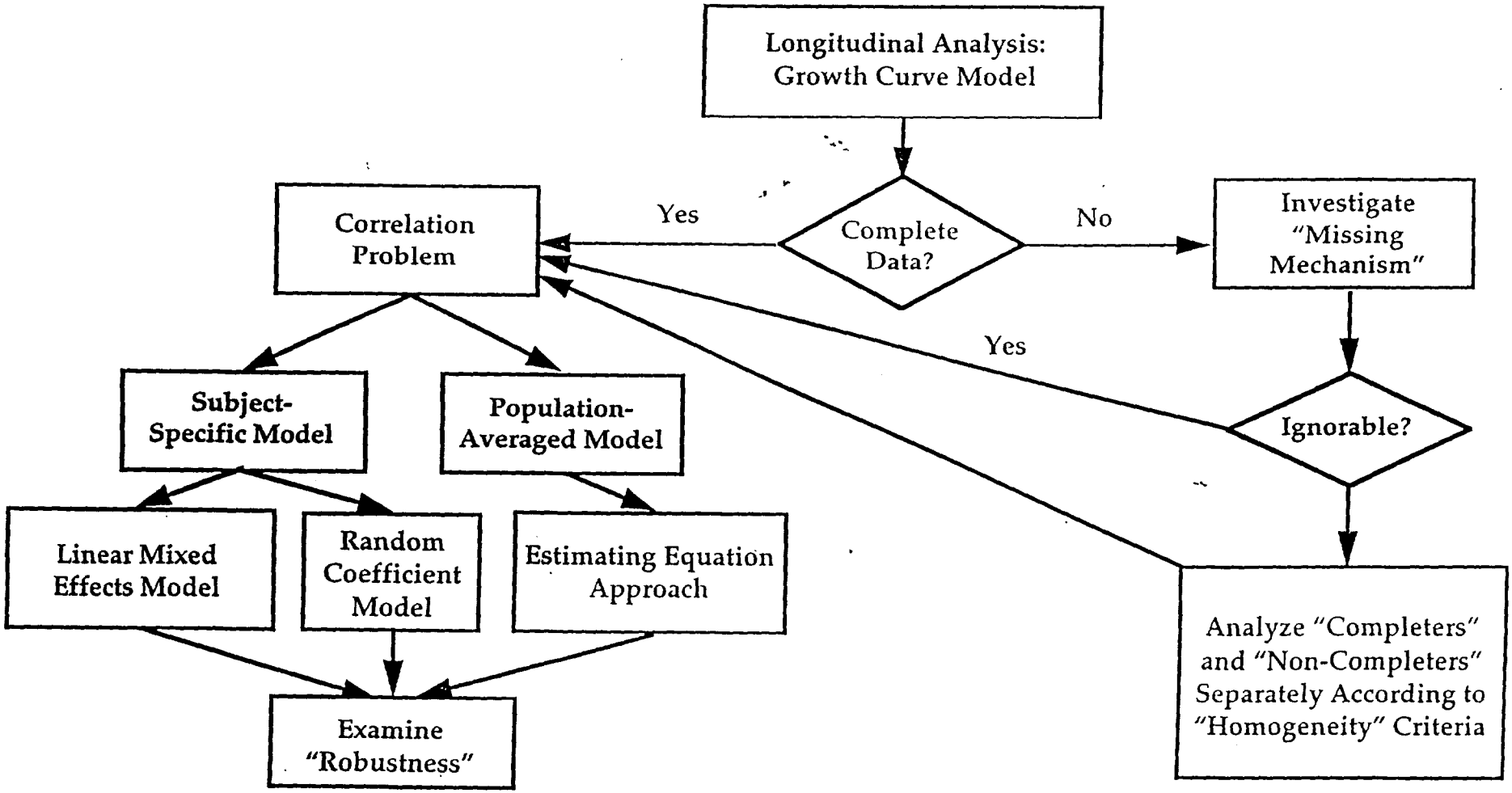
where $\mathbf{V}_i$ is known as a "working" covariance matrix. Note that the solution of the equation is consistent even if $\mathbf{V}_i$ is misspecified as long as the expected value of the estimating equation equal to 0. Liang and Zeger (1986) introduced the notion of a "working" correlation in the estimating equation --a parsimonious covariance structure. In addition, we can protect the underestimation of the variance of the estimators of the population parameters by introducing "sandwich" estimators of the variance, derived from M-estimation theory (Serfling, 1980). This is an important fact in a regulatory context in a sense that the variance estimator will be robust. The sandwich variance estimate of the parameters of interest can be given as

$$\hat{\mathbf{V}}_\beta = (\sum_{i=1}^{K} \mathbf{X}_i^T \hat{\mathbf{V}}_i^{-1} \mathbf{X}_i)^{-1} (\sum_{i=1}^{K} \mathbf{X}_i^T \hat{\mathbf{V}}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i\hat{\beta})(\mathbf{y}_i - \mathbf{X}_i\hat{\beta})^T \hat{\mathbf{V}}_i^{-1} \mathbf{X}_i) (\sum_{i=1}^{K} \mathbf{X}_i^T \hat{\mathbf{V}}_i^{-1} \mathbf{X}_i)^{-1}$$

Note that the asymptotic results will depend on having a large number of subjects, not on having a large number of data points per subject.

Reviewer's Appendix 3

Overview: A Longitudinal Approach



Reviewer's Summary 1: Pain Score

Pain Score			
Period 1*: # of subjects:50			
Mean: 17.86			
Period 2* + Period 3*: # of subjects: 58 Working Correlation: AR-1			
Parameter	Estimated Value	SE(Sandwich)	P-value
intercept	20.668	2.738	0.0001
linear	-1.465	0.432	0.0007
quadric	0.118	0.0277	0.0001
Period 4*: # of subjects:50 Working Correlation: AR-1			
Parameter	Estimated Value	SE(Sandwich)	P-value
intercept	17.393	2.943	0.0001
linear	-1.229	0.494	0.0131
quadric	0.0490	0.0186	0.0086
Note1: Pain score was stable for patients who dropped out of the study in period 1. Note2: No difference in time trends between period 2 and 3 was found (homogeneity criterion was met). Therefore, the two periods were combined. Note3: The time trend (quadratic term) was found to be different between periods2+3 and period 4. Note4: There exist three possible distinct time trend in pain score.			
Possible Missing Mechanism			
Nonignorable			

Note*: Period 1,2,3, and 4 are the time periods from baseline to week 6, from week 7 to week 12, from week 13 to week 18, and after week 18, respectively.

Reviewer's Summary 2: Analgesic Consumption

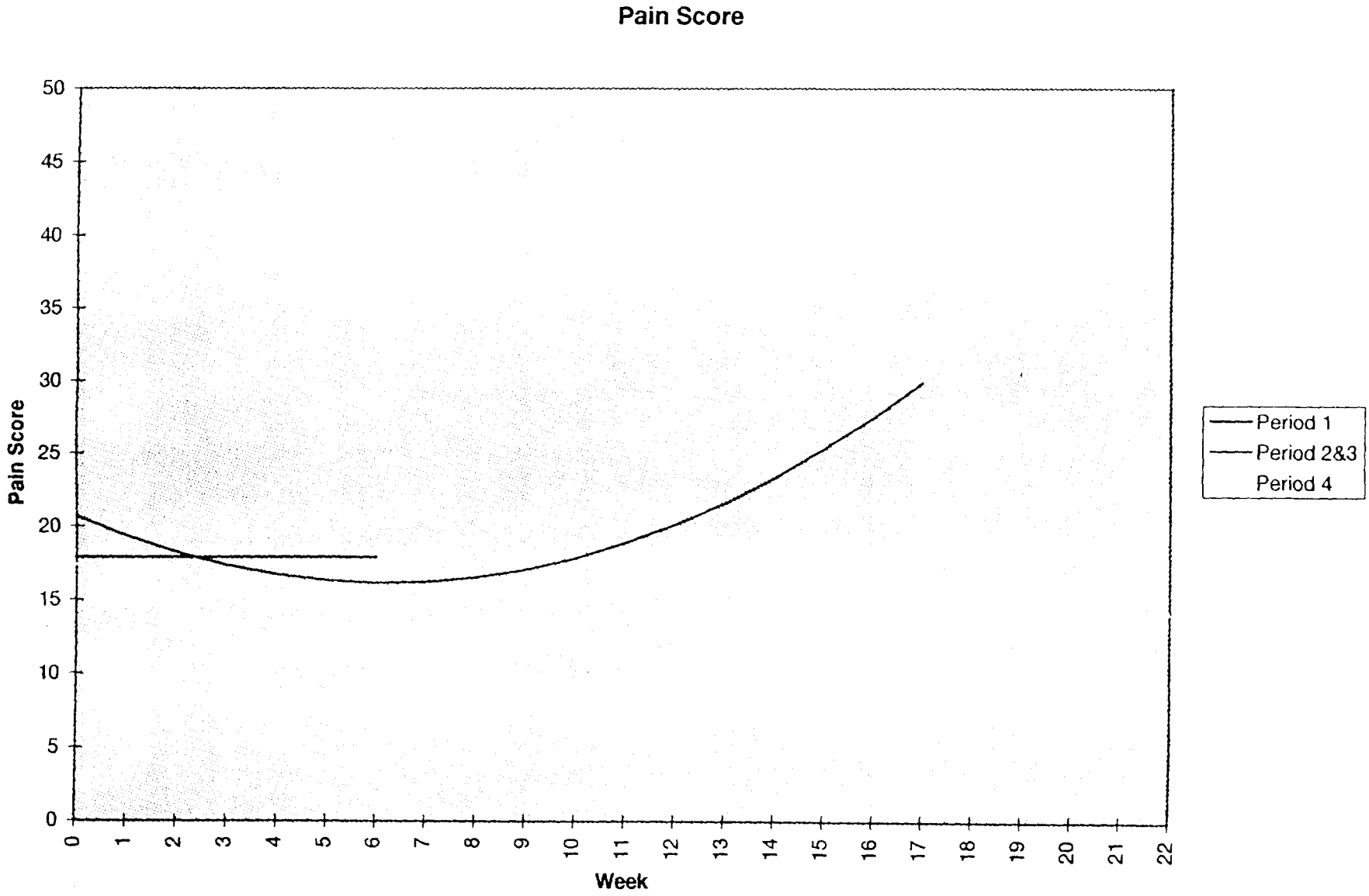
Analgesic Consumption			
Period 1*: # of subjects: 36 Working Correlation: AR-1			
Parameter	Estimated Value	SE(Sandwich)	P-value
intercept	38.440	12.017	0.0029
linear	8.279	4.064	0.044
Period 2* + Period 3* + Period 4: # of subjects:84			
Mean: 45.309			
Note1: In this analysis, patients who had more than 300 baseline score were deleted. In addition, more than 300 morphine equivalent week scores during the study period were deleted. Note2: Analgesic consumption (morphine equivalent week) was increased in period 1 for patients who dropped out of the study. Note3: Analgesic consumption (morphine equivalent week) was stable in periods 2,3, and 4 for patients who dropped out of the study. Note4: A drived result was found to be very sensible to a 'working' correlation structure applied in periods 2,3 and 4. In periods 2 and 3, a weak time trend (decresing analgesic consumption over this period) was detected. In period 4, a quadratic time trend was found using AR-1 'working' correlation, but this result was unstable because this reviewer observed a totally different result derived using the compound symmetry 'working' correlation. Note5: There exist two possible distinct time trends in analgesic consumption.			
Possible Missing Mechanism			
Nonignorable			

Note*: Period 1,2,3, and 4 are the time periods from baseline to week 6, from week 7 to week 12, from week 13 to week 18, and after week 18, respectively.

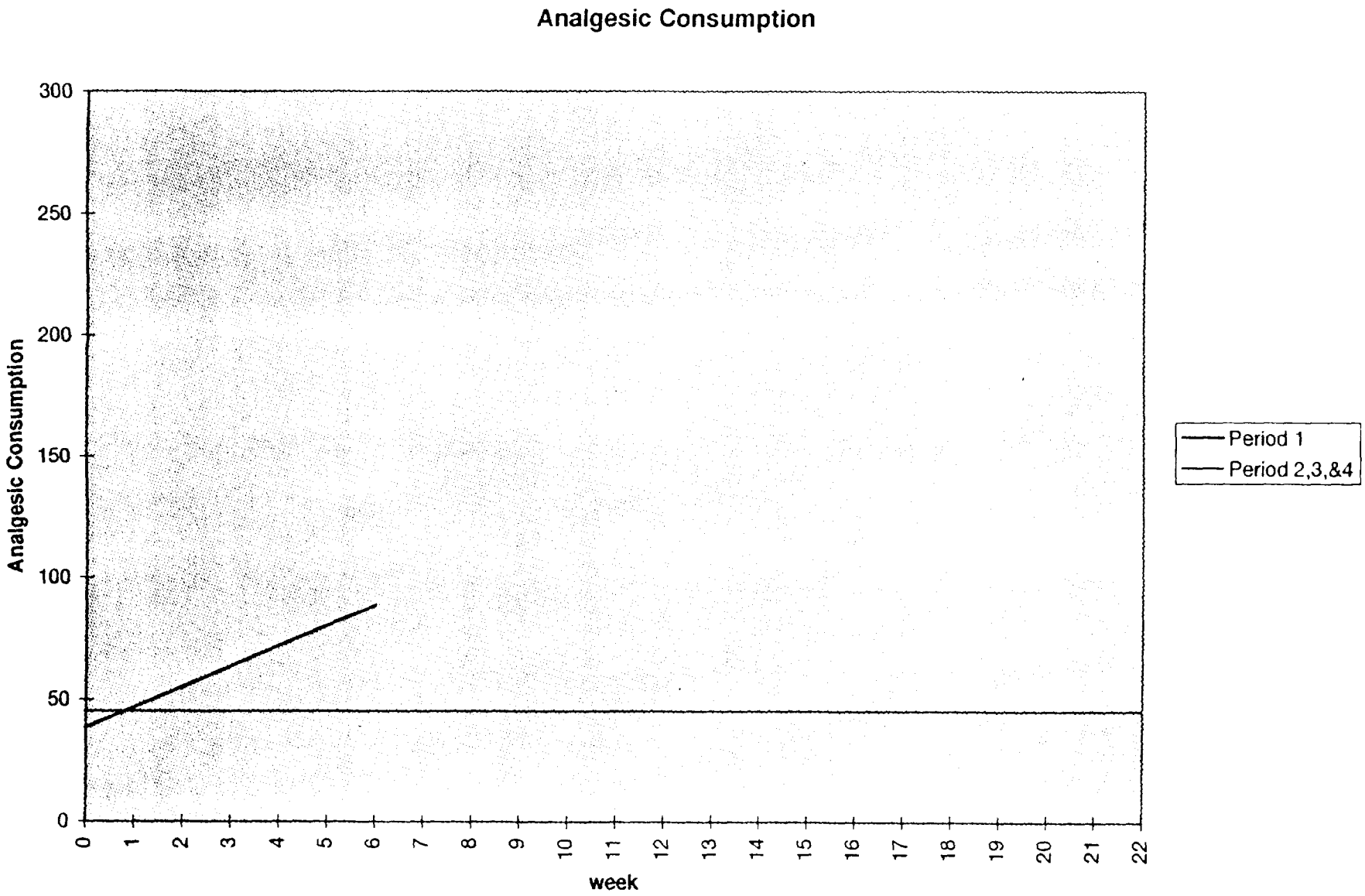
Reviewer's Summary 3: Karnofsky Score

Karnofsky Score			
Period 1* + Period 2* + Period 3*: # of subjects:109			
Mean: 81.220			
Period 4*: # of subjects: 38 Working Correlation: AR-1			
Parameter	Estimated Value	SE(Sandwich)	P-value
intercept	83.914	1.874	0.0001
linear	0.199	0.087	0.0220
Note1: No time trend was found in period 1,2,and 3. The mean Karnofsky score was 77.939 in period 1, 81.690 in period 2 and 82.727 in period 3. This indicates that Karnofsky score was stable for patients who dropped out of the study. Note2: Karnofsky score was increasing for patients who stayed in the study over the treatment period. Note3: There exist two possible time trends in Karnofsky score.			
Possible Missing Mechanism			
Nonignorable			

Note*: Period 1,2,3, and 4 are the time periods from baseline to week 6, from week 7 to week 12, from week 13 to week 18, and after week 18, respectively.

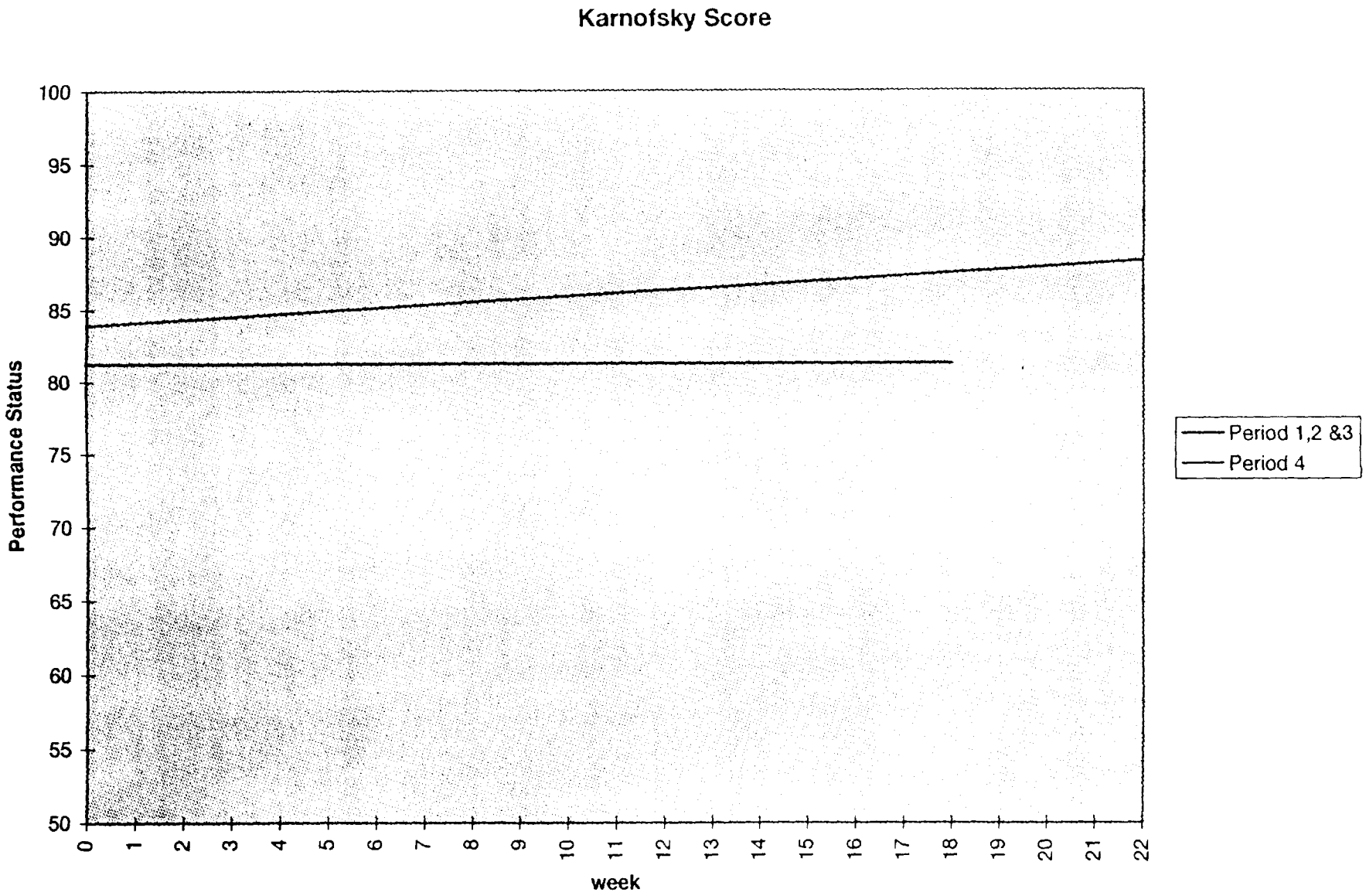


Reviewer Figure 1. Pain Score



Reviewer's Figure 2. Analgesic Consumption

Chart1



Reviewer's Figure 3. Karnofsky Score

Statistical Review and Evaluation

Review of Stability Data

MAR 18 1998

NDA #: **20-896**

APPLICANT: **Hoffmann-La Roche Inc.**

NAME OF DRUG: **Xeloda (capecitabine) Tablets, 150mg and 500mg.**

DOCUMENTS REVIEWED: **Results of Stability Studies, Pages 1-80.**

CHEMISTRY REVIEWER: **Cheng Yi Liang, Ph.D.**

1. Background

This section contains the sponsor's write up of the stability studies, the listings of the raw data, and the graphs where zero-order kinetics were fit to the data of each of the supportive lots. These lots have stability data for one or two years resulting in five to seven data points at the 25 degrees Celsius, but only in three or four data points when stored at the 30 degrees Celsius. There were four lots of the 150 mg strength and three lots of the 500 mg strength. No analysis was performed on the data of the primary lots because the sponsor considered the data too sparse. When stored at 25 degrees C, two lots had four data points for the first nine months of storage, the remaining lots had three data points for the first six months of storage. When stored at 30 degrees C, there was only one data point (six months) available after the initial assay. For the product intended for market there are three lots of the 150 mg strength and four lots of the 500 mg strength. These strengths were packaged in varying size bottles with two closure systems, all with silica.

2. Sponsor's Results

The sponsor is requesting a two year expiration dating period. In support the sponsor applied a zero-order kinetic model to the data of the supportive batches and estimated the expiration dating period by the intersection of the lower 95% confidence band with the 90% label claim limit. The data came from both the 25 degrees and 30 degree C storage because a statistical analysis of means and variances reportedly showed no significant differences between the product being stored at either temperature (Sponsor's Table 1). Considering only the regression lines with negative slope estimates, the shortest expiration dating period observed was 33 months (Sponsor's Table 2).

3. Reviewer's Results

This reviewer has the following comments on the sponsor's statistical approach:

- The use of only supportive data to set the expiration dating period is insufficient as there are minimal data of the proposed market batches available for analysis.

- The sponsor's use of the one-sided 95% confidence band is equivalent to using two-sided 90% confidence bands around the regression lines, which are narrower than recommended by FDA and estimate longer expiration dating periods.

- Using only regression lines with negative slopes in setting expiration dating periods is inappropriate. Positive slope estimates can occur due to random variation in assay results and can even represent true positive slopes caused by loss of moisture in liquid products. In addition, high initial fill and large variation in the assay determinations can force the upper confidence band to intersect with the upper specification limit before the lower band crosses the lower specification limit. As potency assays have upper and lower specification limits, it stands to reason to use either one in setting the expiry period.

- In the analysis of the supportive data the sponsor combined the findings observed under 25 degrees Celsius with those observed under 30 degrees C. There was no real statistical analysis to support this grouping beyond the listing of assay means and standard deviations for lots stored at 25 degrees C and for the combined data of 25 degrees C and 30 degrees C. Since the recommended storage condition ranges from 15-30 degrees Celsius, it is not clear why assaying from 30 degrees storage was done only every six months and not at the full schedule as it was done with the 25 degrees C condition. Combining the data from both conditions will tend to overestimate the expiration dating period based on 30 degrees C data only.

- The sponsor did not perform a regression analysis on the batches with the proposed market formulations. Though the data points are few, they are sufficient to form a regression line. In particular, the three or four batches of a given strength may regress to a common line or at least to parallel lines, and an early estimate of the stability performance of the product can be obtained.

- The sponsor apparently did not test whether slopes or intercepts of a group of batches, which theoretically should have the same degradation pattern, were similar and hence whether batches could be pooled. Besides providing narrower confidence bands around the regression line(s), a common slope or intercept suggests a more stable manufacturing process than when only individual regression lines can be fit to each batch.

This reviewer reanalyzed the data in the following way: Batches of a given strength and packaged in a given size bottle are tested for poolability of slopes and intercepts at $\alpha = 0.25$. The first intersection of either confidence band around any of the regression line(s) with the specification limit estimates the expiration dating period for this group of batches. The results of all these analyses are summarized in Table 3.

For the product with the proposed market formulations the 25 degree C data were used, because only two data points were available from the 30 degree storage condition. Therefore,

the estimated expiration dating periods may be optimistic. However, the 150 mg tablets bottled into 120 count bottles represented a problem, though the same product bottled into 60 count or 1000 count bottles supported a two year expiration dating period. From a statistical point of view, the extremely short expiration dating periods are due to the fact that these data could not be pooled to parallel lines. It is too early to speculate whether the problem lies with the product /packaging or with the sparsity of data. For the 500 mg tablets one batch estimated only 20 months for an expiration dating period when the product was bottled in 120 count bottles despite the fact that this group of batches regressed to parallel lines. All other findings supported extrapolated expiration dating periods of at least 24 months.

For the supportive lots, the 30 degree data were analyzed. As mentioned above, it seems appropriate to analyze the 30 degree data separately when enough information is available. With this approach this reviewer found that both the 150 mg and the 500 mg batches of the research lots estimated expiration dating periods of well beyond 24 months.

4. Summary

There is one area of real concern with the product proposed for market: the 150mg tablets packaged in 120 tablet bottles, where the estimated expiration dating periods ranged from zero (Upper confidence band lies completely above upper specification limit) to six months. The same three lots packaged in 60 count or 1000 count bottles showed acceptable stability. The data for the 120 count bottles did not regress to parallel lines and the individual regression lines based on three or four close data points have wide confidence bands. Additional data should correct this situation but these lots should be monitored closely. Similarly, the 20 months estimated expiry period of lot CWS-253960-96 of the 500 mg tablet bottled into 120 count bottles will probably increase when additional data become available. As soon as there are sufficient data available for the 30 degree C condition, they should be properly analyzed and the expiration dating period should be set on these data only.

Taking a worst case scenario (only 30 degrees C data) with the supportive batches resulted in estimated expiration dating periods of well over two years.

/S/

Roswitha Kelly, M.S.

Mathematical Statistician

/S/ 3/13/98

Tony Koutsoukos, Ph.D.

Acting Team Leader

/S/ 3/18/98

George Chi, Ph.D.

Director, Division of Biometrics 1

cc: Archival NDA #20-896 Xeloda , Hoffmann-La Roche
HFD-150/Ms. Pelosi , CSO
HFD-150/Dr. Liang
HFD-150/Dr. Zhou
HFD-710/Dr. Chi
HFD-710/Dr. Koutsoukos
HFD-710/Ms. Kelly
HFD-710/Chron.
This review consists of 4 pages and 3 tables. 03/13/98. MS Word: xeloda

Table I. Summary of the Statistical Evaluation of Capecitabine 150 mg and 500 mg Tablet Stability Data*
Investigational Formulation F#5, F#6, F#7 and F#8

Lot No.	Formulation No.	Dosage Strength	Storage Temperature	Package	Assay Mean (%)	Minimum (%)	Maximum (%)	Standard Deviation
CP-26084-253B	F#5	150 mg	25°C	OHDPE bottle of 50	99.9			1.03
CP-26084-253B	F#5	150 mg	25°C and 30°C	OHDPE bottle of 50	99.8			0.92
C-183025	F#5	150 mg	25°C	OHDPE bottle of 50	99.1			0.57
C-183025	F#5	150 mg	25°C and 30°C	OHDPE bottle of 50	98.8			0.72
C-184465	F#5	150 mg	25°C	OHDPE bottle of 50	99.9			0.29
C-184465	F#5	150 mg	25°C and 30°C	OHDPE bottle of 50	99.8			0.49
C-185536	F#7	150 mg	25°C	OHDPE bottle of 50	96.7			0.47
C-185536	F#7	150 mg	25°C and 30°C	OHDPE bottle of 50	96.7			0.40
CP-26084-253A (with silica)	F#6	500 mg	25°C	OHDPE bottle of 50	99.3			1.55
CP-26084-253A (with silica)	F#6	500 mg	25°C and 30°C	OHDPE bottle of 50	99.4			1.13
CP-26084-253A (without silica)	F#6	500 mg	25°C	OHDPE bottle of 50	98.2			0.70
CP-26084-253A (without silica)	F#6	500 mg	25°C and 30°C	OHDPE bottle of 50	98.2			0.63
C-183595	F#6	500 mg	25°C	OHDPE bottle of 50	98.7			0.71
C-183595	F#6	500 mg	25°C and 30°C	OHDPE bottle of 50	98.8			0.63
C-185526	F#8	500 mg	25°C	OHDPE bottle of 100	96.2			0.97
C-185526	F#8	500 mg	25°C and 30°C	OHDPE bottle of 100	96.2			0.81

*up to 24 months stability data are included

Table II. Summary of the Linear Regression Analysis of Capecitabine 150 mg and 500 mg Tablet Stability Data*
Investigational Formulation F#5, F#6, F#7 and F#8

Lot No.	Storage Temperature	Package	$k_o \times 10^3$ (% per month)	t_{90} (months)	$k_{\alpha=0.05} \times 10^3$ (% per month)	Shelf-Life (months)
CP-26084-253B	25°C and 30°C	OHDPE bottle of 50	-30.2	331	-104.5	96
C-183025	25°C and 30°C	OHDPE bottle of 50	-26.7	375	-78.9	127
C-184465	25°C and 30°C	OHDPE bottle of 50	32.3	**	**	**
C-185536	25°C and 30°C	OHDPE bottle of 50	-32.6	307	-169.2	59
CP-26084-253A (with silica)	25°C and 30°C	OHDPE bottle of 50	80.3	**	**	**
CP-26084-253A (without silica)	25°C and 30°C	OHDPE bottle of 50	0.6	**	**	**
C-183595	25°C and 30°C	OHDPE bottle of 50	-13.5	741	-62.4	160
C-185526	25°C and 30°C	OHDPE bottle of 100	-55.7	180	-303.9	33

*Initial test data and 3, 6, 9, 12, months stability data are included, 18 and 24 months data are included if they are available.
**Due to a positive slope of the regression line, t_{90}, $k_{\alpha=0.05}$ and shelf-life were not calculated for this group.

Reviewer's Table 3: Expiration Dating Periods of Market Formulations and Research Batches

Type of Batch	Bottle Size	Strength	Batch Number	Slope Estimate	Est. Expiry Period
Market Formulation	60 Count	150 mg	CWS-25396-097	- 0.0926	52 mos
			CWS-25396-108	- 0.0926	57 mos
			CWS-25396-110	- 0.0926	52 mos
Market Formulation	120 Count	150 mg	CWS-25396-097	- 0.5333	6 mos
			CWS-25396-108	+ 0.0833	0 mos
			CWS-25396-110	+ 0.0500	5 mos
Market Formulation	1000 Count	150 mg	CWS-25396-097	- 0.0704	24 mos
			CWS-25396-108	- 0.0704	25 mos
			CWS-25396-110	- 0.0704	27 mos
Market Formulation	120 Count	500 mg	CWS-25396-096	- 0.0318	20 mos
			CWS-25396-109	- 0.0318	27 mos
			CWS-25396-111	- 0.0318	25 mos
			CWS-25396-112	- 0.0318	29 mos
Market Formulation	240 Count	500 mg	CWS-25396-096	+ 0.0061	29 mos
			CWS-25396-109	+ 0.0061	25 mos
			CWS-25396-111	+ 0.0061	24 mos
			CWS-25396-112	+ 0.0061	25 mos

Table 3 con'd:

Market Formulation	**1000 Count**	**500 mg**	**CWS-25396-096**	**- 0.0167**	**30 mos**
			CWS-25396-109	**- 0.0167**	**37 mos**
			CWS-25396-111	**- 0.0167**	**40 mos**
			CWS-25396-112	**- 0.0167**	**40 mos**
Research	**50 Count**	**150 mg**	**CP-26084-253B**	**- 0.0422**	**93 mos**
			C-183025	**- 0.0422**	**80 mos**
			C-184465	**- 0.0422**	**81 mos**
			C-185536	**- 0.0422**	**65 mos**
Research	**50 Count**	**500 mg**	**CP-26084-253A**	**+ 0.0026**	**80 mos**
			C-183595	**+ 0.0026**	**74 mos**
			C-185526	**+ 0.0026**	**86 mos**

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-896 Submission Dates: April 9, 1998

Drug Name: **Capecitabine (XELODA™) Tablets, 150 mg and 500 mg**

Sponsor: Hoffmann-La Roche Inc., Nutley, New Jersey

Comments

1. The biometrics reviewer recommends a sandwich estimator in addition to a model-based standard error derived from a Cox model when a treatment effect is tested.

2. The biometrics reviewer believes that a mixed effect model with intercept as a random factor is equivalent to a marginal model with a compound symmetry structure.

/S/ 4/14/98

Maureen A. Pelosi

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-896

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-896 Submission Dates: October 28, 1997
January 27, 1998
February 9, 1998

Drug Name: **Capecitabine (XELODA™) Tablets, 150 mg and 500 mg**

Dose: 2500 mg/m^2/day (Given in divided doses b.i.d)

Sponsor: Hoffmann-La Roche Inc., Nutley, New Jersey

Comments

1. In the bioequivalence study [#BP15572], although Cmax for all species (except for FBAL) and AUC for capecitabine did not pass the acceptance criteria of 80-125%, the 500-mg commercial tablet is considered to be equivalent to the 500-mg clinical tablet based on the extent of exposure ($AUC_{0-\infty}$) to 5'-DFUR and 5-FU. Exposure ($AUC_{0-\infty}$) to 5'-DFUR and 5-FU is expected to be the primary parameter related to the safety and efficacy of capecitabine.

2. The exploratory meta-analyses performed by the sponsor in this submission are considered inappropriate for labeling purposes since the models used in these analyses have not been validated and results might be biasd. Roche should (i) justify the assumptions for the appropriateness of the models satisfactorily (any model-based meta-analysis is sensitive to assumptions about the patients); (ii) check the sensitivity of their models to their assumptions; (iii) justify the "alpha=0.01 for exploratory purposes" and decide which analyses are "formal" and therefore "spend" alpha accordingly.

Presently, the information obtained from these exploratory meta-analyses is considered inadequate to support the claim made in the labeling regarding the use of Xeloda™ in the elderly and in renal patients and it should not be included in the labeling for Xeloda™. Roche should conduct prospective studies to examine the effect of age, gender, ethnicity, and renal disease on the pharmacokinetics of capecitabine and its metabolites. The results of these studies will provide proper recommendations for dosage adjustment required in these patient populations.

3. The drug interaction studies between capecitabine and paclitaxel and between capecitabine and leucovorin remain inconclusive since a limited number of patients were used (n=3-5 patients/dose and n=5 patients/dose, respectively) in these studies.

Presently, the information obtained from these two studies is considered inadequate to support the claim made in the labeling regarding the presence or absence of pharmacokinetic interaction between capecitabine and paclitaxel and capecitabine and leucovorin; and it should not be included in the labeling for Xeloda™.

4. It is mentioned in the Monograph for leucovorin under the Warnings and Precautions sections that "leucovorin may enhance the toxicity of 5-fluorouracil. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil." In light of this information, it is suggested that Roche incorporate this information in the Warnings section in the labeling for Xeloda™ .

5. Based on individual dissolution data submitted for the **commercial** 150 mg and 500 mg tablets (three batches each), we request that Roche adopt the following dissolution methodology and specification for Xeloda™ tablets:

Apparatus:	USP Apparatus 2 (Paddle)
Paddle Speed:	50 rpm
Medium:	900 mL of water at 37"0.5 °C
Specification:	% dissolved in minutes

6. The sponsor has mentioned that a study in cancer patients is Please submit the study report and results for review.

6. Drug interaction studies between capecitabine and docetaxel or interferon-alpha 2 are being conducted. Please submit the study reports and results for review.

7. A population PK study cancer patients is Please submit the results of this analysis for review.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-896 Submission Dates: October 28, 1997
ßß: January 27, 1998
ßß: February 9, 1998

Drug Name: **Capecitabine (XELODA™) Tablets, 150 mg and 500 mg**

Dose: 2500 mg/m^2/day (Given in divided doses b.i.d)

Sponsor: Hoffmann-La Roche Inc., Nutley, New Jersey

Reviewer: Safaa Ibrahim, Ph. D.

Type of Submission: New Drug Application (NME)

Drug Classification: 1P

1. SYNOPSIS

Xeloda™ (Capecitabine, Ro 09-1978) is a novel antineoplastic agent (prodrug) belonging to the fluoropyrimidine carbamate class. It is rationally designed as an orally administered precursor of 5'-deoxy-5-fluorouridine (5'-DFUR) which is activated to the cytotoxic moiety, 5-fluorouracil (5-FU), by thymidine phosphorylase. Xeloda™ is being proposed for the treatment of advanced or metastatic breast cancer after failure of paclitaxel and an anthracycline-containing chemotherapy regimen. The sponsor is proposing to market Xeloda™ as 150 mg and 500 mg immediate-release, film-coated tablets for oral administration. The proposed dose of Xeloda™ is 2500 mg/m^2 given daily in two divided doses (b.i.d) within 30 minutes after the end of a meal. This daily dose is given in 3-week cycles with 2 weeks administration period followed by one week rest period.

Validated with detection and assay methods were used to analyze capecitabine and its metabolites in plasma. A validated method was used to analyze capecitabine and its metabolites in urine. Using these methods, the sponsor studied the biopharmaceutics and clinical pharmacology of capecitabine and its metabolites in cancer patients and provided individual study reports of their investigations. The results are summarized as follows:

1.1 Biopharmaceutics

Capecitabine is rapidly absorbed after oral administration (tmax=2 hours). Mean absolute bioavailability for 5'-DFUR, the primary precursor for 5-FU, is 42 %.

Food reduces both the rate and extent of absorption of capecitabine. Mean Cmax and $AUC_{0-\infty}$ decreased by 60 % and 35 %, respectively; tmax increased 4-fold when capecitabine was administered within 30 minutes of food intake. There is a moderate decrease in AUC and Cmax of 5'-DFCR, 5'-DFUR, and 5-FU when capecitabine was administered with food. During clinical trials, patients were instructed to administer the drug within 30 minutes of food intake.

The proposed market 500-mg tablet is considered to be equivalent to the clinical 500-mg tablet with respect to the extent of exposure ($AUC_{0-\infty}$) to 5'-DFUR and 5-FU, the primary parameter related to the safety and efficacy of capecitabine. A waiver from biostudy was granted for the lower strength proposed market 150-mg tablets. Dissolution test method for capcitabine tablets uses USP Apparatus 2 (Paddle) at 50 rpm and 900 mL of water at 37±0.5 °C. The sponsor proposes dissolution specification of % dissolved in minutes (See Comment #5, page 5).

1.2 Clinical Pharmacology and *In Vivo* Metabolism

Capecitabine and its metabolites are weekly bound to plasma proteins, 54%, 10%, 60%, and 10 % for capecitabine, 5'-deoxy-5-fluorocytidine (5'–DFCR), 5'-deoxy-5-fluorouridine (5'–DFUR), and 5-fluorouracil (5-FU), respectively. Capecitabine is primarily bound to human albumin (35 %). The ratio of concentrations in red blood cells to plasma is 0.65 and 0.84 for capecitabine and 5'-DFCR, respectively.

Plasma concentrations of capecitabine and its metabolites decline rapidly with an elimination half-life of 0.85, 1.1, 0.66, 0.76, 1.1, and 3.2 hours for capecitabine, 5'–DFCR, 5'–DFUR, 5-FU, dihydro-5-fluorouracil (FUH_2) and α-fluoro-β-alanine (FBAL), respectively. Systemic exposure ($AUC_{0-\infty}$) is higher for 5'-DFUR and FBAL than any other chemical species.

Capecitabine is rapidly and extensively metabolized to 5–FU in three enzymatic steps. First, capecitabine is converted to 5'–DFCR by carboxylesterase, an enzyme located primarily in the liver. Then, 5'–DFCR is converted to 5'–DFUR by cytidine deaminase (Cyd deaminase), mainly located in the liver and solid tumors. Finally, 5'–DFUR is converted to 5–FU by thymidine phosphorylase (dThdPase),

mainly located in liver and solid tumors (see Figure 5, page 32). Cytochrome P450 is not involved in metabolic conversion of capecitabine to 5-FU.

About 70% of the administered capecitabine dose is recovered in urine by 24 hours after dosing. The majority of the dose is recovered in urine as FBAL (about 50 %)

analyses of data from the four Phase I studies have revealed the followings:

- The pharmacokinetics of capecitabine, 5'-DFCR, 5'-DFUR, and FBAL are dose-proportional over the therapeutic range of mg/m^2 b.i.d. For 5-FU, there is a trend for its AUC to increase more than proportional with the increase of dose at therapeutic doses of mg/m^2 b.i.d. Time-dependent kinetics are only noted for 5-FU and FBAL.

- Age has no effect on the pharmacokinetics of capecitabine and its metabolites.

- No gender differences have been observed in pharmacokinetics of capecitabine and its metabolites.

- No influence of renal impairment (CLcr > 30 mL/min) has been noted on the pharmacokinetics of capecitabine, 5'-DFCR or 5'-DFUR. There is a tendency for AUC of 5-FU and FBAL to increase as CLcr decreased. The Pharmacokinetics of capecitabine and its metabolites in patients with severe renal function (Clcr < 30 mL/min) are not studied.

- Patients with breast cancer tend to have higher Cmax for 5'-DFUR and 5-FU (about 50 % and 25 %, respectively) than in patients with other types of cancer. AUC of 5'–DFUR in patients with breast cancer is also about 30% higher than in patients with other types of cancer. However, there were only 8 breast cancer patients in the database compared to 35 colon cancer patients.

In a single-dose study, it is shown that patients with mild-to-moderate hepatic dysfunction have a 60 % higher AUC and Cmax for capecitabine than patients with normal hepatic function. AUC and Cmax of 5'-DFUR increased by 20-30 % in patients with hepatic dysfunction compared to normal patients. The pharmacokinetics of other metabolites (5'-DFCR, 5-FU, FUH_2, and FBAL) slightly change between the two groups. Dosage adjustment is not recommended in

patients with mild-to-moderate hepatically impaired patients. The pharmacokinetics of capecitabine and its metabolites in patients with severe hepatic dysfunction are not studied.

No clinically significant drug-drug interactions have been noted between capecitabine and Maalox.

The drug interaction studies between capecitabine and paclitaxel and between capecitabine and leucovorin remain inconclusive since a limited number of patients was used (n=3-5 patients/dose and n=5 patients/dose, respectively) in these studies.

The concentration of 5–FU is times higher in tumor than those measured in adjacent healthy tissue and higher in tumor than in plasma. The activity of thymidine phosphorylase (dThdPase), the enzyme responsible for the formation of 5-FU from 5'-DFUR, is higher in tumor than in healthy tissue.

Using analysis, it is shown that Cmax and AUC of 5'-DFUR and FBAL are predictive of adverse effects (viz., Dose Limiting Toxicities (DLT) and Hand-Foot-Syndrome (HFS)). Exposure to either capecitabine or 5'-DFCR is not predictive of DLT and HFS. Exposure to 5-FU is not predictive of HFS and poorly predictive of DLT. No difference is noted between Cmax and AUC in their predictive ability. It is also shown that the intermittent regimen has more favorable safety profile than the continuous regimen.

2. Comments

1. In the bioequivalence study [#BP15572], although Cmax for all species (except for FBAL) and AUC for capecitabine fail to pass the acceptance criteria of 80-125%, the 500-mg commercial tablet is considered to be equivalent to the 500-mg clinical tablet based on the extent of exposure ($AUC_{0-\infty}$) to 5'-DFUR and 5-FU. Exposure ($AUC_{0-\infty}$) to 5'-DFUR and 5-FU is expected to be the primary parameter related to the safety and efficacy of capecitabine.

2. The analyses performed by the sponsor in this submission are considered inappropriate for labeling purpose since the models used in these analyses have not been validated and results might be biasd. The sponsor should (i) justify the assumptions for the appropriateness of the models satisfactorily (any model-based

analysis is sensitive to assumptions about the patients); (ii) check the sensitivity of their models to their assumptions; (iii) the sponsor needs to justify the "alpha=0.01 for exploratory purposes" and decide which analyses are "formal" and therefore "spend" alpha accordingly.

Presently, the information obtained from these analyses is considered inadequate to support the claim made in the labeling regarding the use of Xeloda™
should not be included in the labeling for Xeloda™. The sponsor should conduct prospective studies to examine the effect of age, gender, ethnicity, and renal disease on the pharmacokinetics of capecitabine and its metabolites. The results of these studies will provide proper recommendations for dosage adjustment required in these patient populations.

3. The drug interaction studies (# SO14694 and SO14798) between capecitabine and paclitaxel and between capecitabine and leucovorin remain inconclusive since a limited number of patients was used (n=3-5 patients/dose and n=5 patients/dose, respectively) in these studies.

Presently, the information obtained from these two studies is considered inadequate to support the claim made in the labeling regarding

4. It is mentioned in the Monograph for leucovorin under the Warnings and Precautions sections that

In the light of this information, it is suggested that this information should be also incorporated in Warnings section in the labeling for Xeloda™ .

5. Based on individual dissolution data submitted for the **commercial** 150 mg and 500 mg tablets (three batches each), the sponsor is requested to adopt the following dissolution methodology and specification for Xeloda™ tablets:

Apparatus:	USP Apparatus 2 (Paddle)
Paddle Speed:	50 rpm
Medium:	900 mL of water at 37±0.5 °C
Specification:	% dissolved in minutes

6. The sponsor mentions that a study in cancer patients is . The study report and results should be submitted to the Agency for review.

7. Drug interaction studies between capecitabine and docetaxel or interferon-alpha 2 are being conducted, study reports and results should be submitted for review.

8. A study cancer patients is The results of this analysis should be also submitted for review.

9. The sponsor is requested to incorporate the OCPB's pharmacokinetic labeling as outlined in pages # 6-12.

3. OCPB's Pharmacokinetic Labeling

[Note: Statements added are in italic. Statements deleted are strikeout]

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

/S/

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

ClinPharm/Biopharm Briefing on: March 16, 1998 (Attendees: Drs.: J. Collins, H. Malinowski, J. Hunt, A. Rahman, S. Ibrahim, J. Jenkins, J. Beitz, A. Martin, W. McGuinn, D. Smith, and L. Zhou)

RD/FT /S/

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 20-896
HFD-150/Division file
HFD-150/Pelosi, Beitz, Martin
HFD-850/Lesko
HFD-860/Malinowski, Mehta, Rahman, Ibrahim
HFD-340/Viswanathan
HFD-205/FOI
CDR/B. Murphy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-896

ADMINISTRATIVE DOCUMENTS

CLAIM FOR CATEGORICAL EXCLUSION FROM THE ENVIRONMENTAL ASSESSMENT REQUIREMENT FOR XELODA™ (CAPECITABINE) TABLETS (150 AND 500 mg) NEW DRUG APPLICATION

Hoffmann-La Roche Incorporated claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b). The proposed action, approval of an NDA, will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

PATENT INFORMATION

1.	Active Ingredient(s):	capecitabine
2.	Strength(s):	150 mg, 500 mg
3.	Trade Name	Xeloda™
4.	Dosage form and Route of Administration:	Tablet, Oral
5.	Application Firm Name:	Hoffmann-La Roche Inc.
6.	NDA Number:	20-896
7.	First Approval Date:	None
8.	Exclusivity:	Subject to patent rights, the first ANDA cannot be submitted until five years after the date of approval of the current NDA.
9.	Patent Information:	
(a)	Patent number and Expiration date:	5,472,949 12/14/2013*
	Type of Patent:	product specific claim
	Patent Owner:	Hoffmann-La Roche Inc.
(b)	Patent number and Expiration date:	4,996,891 10/30/2010*
	Type of Patent:	product specific
	Patent Owner:	Co-owned by Hoffmann-La Roche Inc. and Fuji

While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy or completeness of the information contained therein.

* Subject to patent term extension provisions of 35 USC § 156 et seq.

EXCLUSIVITY SUMMARY FOR NDA # 20-896 SUPPL # _____

Trade Name Xeloda Generic Name capecitabine

Applicant Name Roche HFD # 150

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Per patent - 5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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 /___/ NO /✓/

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

NDA# _____ _____

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 /✓/

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 8. 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 /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /___/ 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 8:

_____

_____

(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 /___/

(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 /___/

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:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

Investigation #2 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:

_____ _____

_____ _____

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 /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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"):

_____ _____

_____ _____

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 /___/ Explain: _____

! _____

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 /___/ Explain _____ ! 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 /___/

If yes, explain: _____

_____

1st

_____ 4.7.98

Signature
Title: Project Mgr.

Date

1S1

_____ 4/15/98

Signature of Office/
Division Director

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

(11)

NDA 20-896

DATE: February 2, 1998

FROM: FDA, CDER, HFD-150, Oncology

SUBJECT: Biopharm Information Request

We need the following information as quickly as possible:

For the Bioequivalancy Study BP15572 - In module 1 - 32, Table 7 (Summary of the Results of Statistical Analysis of the Primary & Secondary Parameters, 90% confidence intervals & ANOVA tables). We need tables similar to Table 7, but for Capecitabine, 5'-DFCR, and 5-FU.

Additionally, for Protocol SO 14798, Table 27, module 1-82, we need similar tables for Capecitabine and 5'-DFCR.

Thank you in advance for your assistance.

/S/

Maureen A. Pelosi

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

(NDA)/BLA # 20-896 Supplement # (NA) Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade and generic names/dosage form: (capecitabine) tablets Xeloda® Action: (AP) AE NA

Applicant Roche Therapeutic Class 5010500

Indication(s) previously approved none

Pediatric information in labeling of approved indication(s) is adequate __ inadequate X

Proposed indication in this application ~~for refractory advanced or metastatic breast cancer after~~ failure of paclitaxel + anthracycline containing) chemotherapy.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? __Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,

__ (2) Protocols were submitted and approved.

__ (3) Protocols were submitted and are under review.

__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical officer (e.g., medical review, medical officer, team leader)

/S/ 3-26-98

Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20-896
HFD-150 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 306(a) and (b), in connection with this application.

CONSULT #937

LNC TRADEMARK REVIEW

TO: HFD-150

ATTN: Chengyi Liang

PROPOSED NAME(S): XELODA

ESTABLISHED NAME: capecitabine tablets

COMMITTEE'S COMMENTS:

A review no names which sound like or look likes the proposed name.

The Committee has no reason to find the proposed name unacceptable.

/S/ 3/1/99

Dan Boring, Ph.D., Chairman
Labeling and Nomenclature Committee

12/12/97

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dr. Dan Boring, HFD-530

FROM: Division of: Oncology Drug Products HFD- 150
Attention: Chengyi Liang Phone 594-5752

DATE: 12-12-1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: XELODA **NDA:** 20-896

Company Name: Hoffmann-La Roche Inc.

Established name, including dosage form:
capecitabine tablet (150 mg and 500 mg)

Other trademarks by the same firm for companion products:
N/A

Indications for Use (may be a summary if proposed statement is lengthy):
Treat the patients with locally advanced or metastatic breast cancer.

Initial comments from the submitter: (concerns, observations, etc.)
Names that sound similar to Xeloda: none

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Orig. NDA 20-896
HFD-150 Division File
HFD-150/CLiang
HFD-150/Lzhou
HFD-150/MPelosi
HFD-810/CHoiberg/JSimmons

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-896

DEC 2 1997

Hoffman-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Attention: Cynthia Dinella, Pharm. D.

Dear Dr. Dinella:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Xeloda Tablets

Therapeutic Classification: Priority

Date of Application: October 28, 1997

Date of Receipt: October 31, 1997

Our Reference Number: 20-896

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 31, 1997 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Maureen Pelosi, Project Manager, at (301) 594-5778.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

for Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CC:
Original NDA 20-896
HFD-150/Div. Files
HFD-150/CSO/M.Pelosi
HFD-150 /Martin
/Beitz
/Liang
/Zhou
/McGuinn
/Andrews
/Ibrahim
/Rahman
/Takeuchi
/Koutsoukos

DISTRICT OFFICE

Drafted by: 11/24/97
Final: 11/26/97

ACKNOWLEDGEMENT (AC)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-896

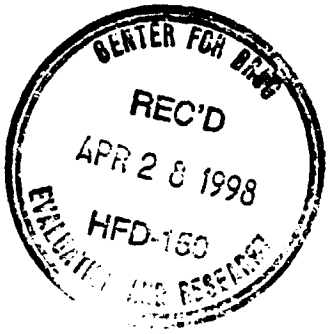
CORRESPONDENCE

Roche

Pharmaceuticals

April 23, 1998

Food and Drug Administration
Division of Oncology Drug Products, HFD-150
Center for Drug Evaluation and Research
1451 Rockville Pike, Woodmont II Building
Rockville, Maryland 20852-1448



Ladies and Gentlemen:

Re: NDA 20-896 - XELODA™ (capecitabine) Tablets
Draft Clearance Press Release

Enclosed for your review is the Xeloda draft clearance press release. Timing for dissemination of this release will be based upon FDA Press Office distribution of their "Talk Paper" concerning Xeloda. As soon as the Press Office releases their "Talk Paper" we will disseminate our press release immediately.

We would appreciate any feedback on the attached as soon as possible. If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Candia Shepherd for

Cynthia Dinella, Pharm.D.
Group Director
Drug Regulatory Affairs

Phone: (973) 562-3675
Fax: (973) 562-3700

Attachment
HLR No. 1998-1063

Desk Copy: Ms. Maureen Pelosi
Division of Drug Marketing, Advertising and Communications, HFD-240
Ms. Anne Reb

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Department of Health and Human Services
Food and Drug Administration

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

Title 21, Code of Federal Regulations, Parts 314 & 601

FOR FDA USE ONLY

Application Number

APPLICANT INFORMATION

Name of Applicant	Date of Submission
Hoffmann-La Roche Inc.	April 23, 1998
Telephone Number (Include Area Code)	**Facsimile (FAX) Number** (Include Area Code)
(973) 562-3675	(973) 562-3554/3700

Applicant Address (Number, Street, State, Country, and Zip Code or Mail Code):	Authorized U.S. Agent, Name & Address (Number, Street, State and Zip Code, Telephone & FAX Number) if applicable
Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199	Cynthia H. Dinella, Pharm.D. Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously issued) NDA 20-896

PRODUCT DESCRIPTION

Established Name: (e.g., Proper name, USP/USAN name)	Proprietary Name (trade name) if any
capecitabine	XELODA

Chemical/Biochemical Name (if any)	Code Name (if any)
(N[4]-Pentyloxycarbonyl-5'-deoxy-5-fluorocytidine)	Ro 09-1978

Dosage Form:	Strengths:	Route of Administration
Tablet	150 and 500 mg Tablets	Oral

Proposed Indications for Use:

Metastatic Breast Cancer

APPLICATION INFORMATION

APPLICATION TYPE

(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA,AADA,21 CFR 314.94)

☐ BIOLOGIC APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)

☐ Original Application ☐ Amendment to a Pending Application ☐ Resubmission ☐ Presubmission

☐ Notification ☐ Establishment Description Supplement ☐ SUPAC Supplement

☐ Efficacy Supplement ☐ Labeling Supplement ☐ Chemistry, Manufacturing & Controls Supplement

REASON FOR SUBMISSION

Draft Clearance Press Release

PROPOSED MARKETING STATUS (Check one) ☒ Prescription Product (Rx) ☐ Over-The Counter Product (OTC)

Number of Volume Submitted 1	This application is ☒ Paper ☐ Paper and Electronic

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application.

This submission contains the following items (check all that apply)	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (e.g. 21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing and control information (e.g. 21 CFR 314.50 (d) (1))
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (1))
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3))
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5))
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6))
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1))
	12. Case report forms (e.g. 21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification
	17. Field copy certification
	18. User Fee Cover Sheet (Form FDA 3397)
X	**19. Other** (Specify) Draft Clearance Press Release

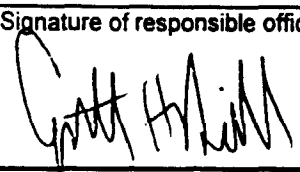
CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210, 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substance act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision. The data and information in this submission have been reviewed and are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U. S. Code, title 18, section 1001.

Signature of responsible official or agent	Typed name and title	Date
	Cynthia H. Dinella, Pharm.D. Group Director, DRA HLR No. 1998-1063	4/23/98

Form FDA 3439