

Format of Animal Tumor Data Set.

Record 1 to Record 12 contain header information of the data set (identifications and descriptions of the experiment from which the data set was generated).

<u>Record Number</u>	<u>Variable Name</u>	<u>Description</u>
1	SPONNAME	Name of sponsor
2	LABNAME	Name of laboratory that conducted the study.
3	STRTDATE ENDDATE	Date of start of study: MMDDYYYY Date of end of study: MMDDYYYY
4	INDNUM NDANUM PROTONUM STUDYNUM	IND number NDA number Protocol number Study number
5	GENNAME TRADNAME	Generic name of the drug Trade name of the drug
6	SPECIES STRAIN	Species name Strain name
7	ROUTEADM	Route of administration
8	DOSEUNIT	Dose unit (mg/kg/day, etc.)
9	NUMGRPS	Number of treatment groups
10	DOSLEVL	Dose levels for controls and treated Groups - As many values as indicated in Item 9
11	NUMANMLS	Numbers of animals in each dose/sex group - As many Values as indicated in Item 9
12	NUMORGAN	Numbers of organs/tissues to be examined for pathology observations in this study

Record 13 to last record of this data set contain tumor data of individual animals.

<u>Record Number</u>	<u>Variable Name</u>	<u>Description</u>
13	ANIMLNUM	Animal number
	SEX	Sex: M = Male F = Female
	DOSEGP	Dose Group: 0 = Control group 1 = Low dose group 2 = Medium dose group 3 = High dose group  Or Use 0, 1, 2, 3, 4, . . . for different groups if there are more than four groups
	DTHSACTM	Time (day or week) of death or sacrifice
	DTHSACST	Death or sacrifice status: 1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Intermittent sacrifice 4 = Accidental death
	ANIMLEXM	Animal microscopical examination code 1 = At least one tissue was examined 2 = No tissues were examined
	RECORDS	Number of records for the animal (See the note below)
	TUMORCOD	Tumor type code
	ORGNCODE	Organ Tissue code
	DETECTTM	Time (day or week) of detection

**MALIGNST**

**Malignancy status**

- 1 = Malignant
- 2 = Benign
- 3 = Undetermined

**DEATHCAU**

**Cause of death:**

- 1 = Tumor caused death
- 2 = Tumor did not cause death
- 3 = Undetermined

**ORGANEXM**

**Organ/Tissue microscopical examination code**

- 1 = Organ/Tissue was examined and was usable
- 2 = Organ/Tissue was examined but was not usable (e.g. autolyzed tissue)
- 3 = Organ/Tissue was not examined

End of Record # 13.

Record # 14 (Same format as Record # 13).

Record # 14 is for either next animal data or data of second tumor or data of an unusable examined, or unexamined organ/tissue of the same animal. In the case of a repeated record for the same animal, repeat the information contained in the first 7 variables of Record # 13 for the animal, and add the data of the second tumor or data of the unusable examined, or unexamined organ/tissue to the last 6 variables.

**Note:** The variable RECORDS (number of records) for each animal with tumors, and/or unusable examined, and/or unexamined organs/tissues is the sum of the number of tumors, and the numbers of unusable examined, and of unexamined organ/tissues. There will be one record for each animal with zero or one tumor and without unusable examined, and unexamined organs/tissues.

There will be no data for the last 6 variables of the record of an animal with no tumors on a usable examined organ/tissue. For an animal with unusable examined, and/or unexamined organs/tissues, a record should be generated for each such tumor-organ/tissue combination identified by the TUMORCOD, ORGNCODE, and ORGANEXM variables. A missing value should be given for the variable TUMORCOD of an unexamined organ/tissue.

### II.2.2. Format of Tumor Type Code Data Set - Group A

(One record for each tumor type).

<u>Variable Name</u>	<u>Description</u>
TUMORCOD	Tumor type code
TUMORNAM	Tumor type name

### II.2.3. Format of Organ/Tissue Code Data Set - Group A

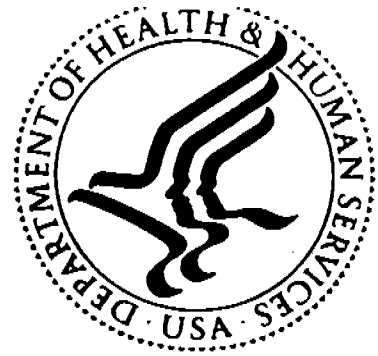
(One record for each organ/tissue).

<u>Variable Name</u>	<u>Description</u>
ORGNCODE	Organ/Tissue code
ORGNAME	Organ/Tissue name

**REFERENCES:**

- (1) Cox, D. (1972). Regression models and life tables, *Journal of Royal Stat. Soc. B*, 34, 187-200.
- (2) Gehan, E. (1965). A generalized Wilcoxon test for comparing arbitrarily singly censored samples, *Biometrika*, 52, 203-223.
- (3) Thomas, Breslow, and Gart (1977). Trend and homogeneity analyses of proportions and life table data, *Computers and Medical Research*, 10, 373-381.
- (4) Peto et al. (1980). Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, long term and short term screening assays for carcinogens: A critical appraisal, *International Agency for Research Against Cancer Monographs, Annex to Supplement*, WHO, Geneva, 311-426.
- (5) StatXact-3 for Windows (1996). Statistical Software for Exact Nonparametric Inference, Cytel Software Corporation, Cambridge, Massachusetts.
- (6) Haseman (1984). Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, *Environmental Health Perspectives*, Vol. 58, 385-392.
- (7) Chu, Cueto, Ward. (1981). Factors in the evaluation of 200 National Cancer Institute carcinogen bioassays, *J. Of Toxicology and Environmental Health*, Vol. 8, 251-280.
- (8) Bart, Chu, Tarone. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity, *J. Of the National Cancer Institute*, 62, 957-974.
- (9) McConnell, Solleveld, Swenberg, Boorman (1986). Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies, *J. Of the National Cancer Institute*, 76, 283-289.
- (10) Lin (1997). Formats and Specifications for Submission of Animal Carcinogenicity Study Data, OEB document.

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Candice Shepherd

Maureen Pelosi

Fax: 973-562-3700

Fax: 301-827-4590

Phone: 973-562-3695

Phone: 301-594-5778

Pages, including cover sheet: 7

Date: 11 - 29 - 99

Re: NDA 20-896 SE-1/006

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● Candice,

Please refer to the attachments from the statistical reviewer of the carcinogenicity data regarding the format that is needed. I received the actual review today, and it contains other information as well as the cover sheet I sent by Email last week.

Regards,

Maureen Pelosi

ELECTRONIC MAIL MESSAGE

Date: 26-Nov-1999 11:16am EST  
From: Maureen Pelosi  
PELOSIM  
Dept: HFD-150 WOC2 2092  
Tel No: 301-594-2473 FAX 301-594-0498

TO: CANDICE SHEPHERD

( CANDICE.SHEPHERD@roche.com@Internet

Subject: Carcinogenicity reformat

Candice:

Please refer to attached message regarding a reformat of the carcinogenicity data sent as Excel spreadsheets.

FOR EXPEDITED STATISTICAL REVIEW OF CARCINOGENICITY DATA PLEASE PROVIDE THE FOLLOWING:

Three (3) ASCII files, one for the tumor codes and names, one for the organ codes and names, and one for the animal data allowing for SAS list input, e.g. input values have to be separated from each other by at least one blank (by at least two blanks for character input values with one or more single imbedded blanks), and periods rather than blanks for missing values. The period should always be separated by two blanks. The format is know as the old 'OEB' format (attached) and is similar to the one specified in the Electronic Submission Guidance with the exception that the tumor and organ names are not with the animal data but in separate files.

At the end of each line of organ/tumor code and names there should be a string of blanks, so that there will be no wrap around when reading the data into SAS.

When an animal has no tumors and all organ/tissues were examined, there should be only one record for this animal.

For animals with tumors, there should be as many records as there were tumor/tissue combinations.

In addition, there should be one record for each organ/tissue that was 'unusable examined' or 'unexamined'.

The codes for the variables should be exactly those specified in the OEB format.

Please provide the results of a PROC CONTENTS run.

Please perform at least the following statistical analyses: Survival trend tests, adjusted Cox and Kruskal-Wallis tests, all pair-wise comparisons of groups (adjusted Cox and Kruskal-Wallis), and Kaplan Meier survival curves. Weigh doses by actual dose levels used. Tumor analysis: Perform exact permutation trend tests and exact pair-wise comparisons on fatal, incidental or

palpable tumors as defined by Peto and asymptotic tests when fatal and incidental tumors fall in the same time interval. We suggest the following fixed intervals: weeks 0-52, 53-78, 79-91, 92-104. If there are two control groups, perform the tests with each control group separately and combined (if control groups are identical). Certain tumors should also be grouped and analyzed, according to McConnell et al (1986) or through discussion with reviewing pharmacologist.

For questions please call Ms. Kelly (301) 827-1547.

thanks, maureen



November 24, 1999

Dr. Gerston Turner  
Food and Drug Administration  
Division of Scientific Investigations  
7520 Standish Place, Room 125  
Rockville, Maryland 20855

Dear Dr. Turner:

**Re: NDA 20-896 - XELODA™ (capecitabine) Tablets**  
**Response to Request for Information**

As requested, enclosed please find CRFs and CRTs for every third patient in center 17801 and 17802 participating in Protocol SO14695 entitled, "An open-label randomized phase 3 study comparing capecitabine with 5-fluorouracil in combination with leucovorin as first-line chemotherapy in patients with advanced and/or metastatic colorectal carcinoma". Also included are adverse event listings for every patient in centers 17801 and 17802. Details of this submission follow.

**I. Case Report Forms**

◆ **London Regional Cancer Centre** (CRTN 17801, Dr. Walter Kocha)  
Patient #: 1081, 1084, 1087, 1090, 1093, 1096, 1099, 1336, 1339, 1342

◆ **Ottawa Regional Cancer Centre** (CRTN 17802, Dr. Jean Maroun)  
Patient #: 1121, 1124, 1127, 1130, 1133, 1136, 1139, 1321, 1324, 1327, 1330, 1333, 1446

**II. Case Report Tabulations**

◆ **London Regional Cancer Centre** (CRTN 17801, Dr. Walter Kocha)  
Patient #: 1081, 1084, 1087, 1090, 1093, 1096, 1099, 1336, 1339, 1342

◆ **Ottawa Regional Cancer Centre** (CRTN 17802, Dr. Jean Maroun)  
Patient #: 1121, 1124, 1127, 1130, 1133, 1136, 1139, 1321, 1324, 1327, 1330, 1333, 1446

### III. Adverse Event Listings

- ◆ **London Regional Cancer Centre** (CRTN 17801, Dr. Walter Kocha)  
Capecitabine Patient #: 1082, 1083, 1085, 1086, 1089, 1090, 1093, 1094, 1097, 1099, 1343
- ◆ **Ottawa Regional Cancer Centre** (CRTN 17802, Dr. Jean Maroun)  
Capecitabine Patient #: 1121, 1122, 1127, 1128, 1130, 1132, 1133, 1134, 1140, 1322, 1323, 1325, 1326, 1329, 1331, 1333, 1334, 1335, 1446
- ◆ **London Regional Cancer Centre** (CRTN 17801, Dr. Walter Kocha)  
5-FU/LV Patient #: 1081, 1084, 1087, 1088, 1091, 1092, 1095, 1096, 1098, 1100, 1336, 1337, 1338, 1339, 1340, 1341, 1342
- ◆ **Ottawa Regional Cancer Centre** (CRTN 17802, Dr. Jean Maroun)  
5-FU/LV Patient #: 1123, 1124, 1125, 1126, 1129, 1131, 1135, 1136, 1137, 1138, 1139, 1321, 1324, 1327, 1328, 1330, 1332

If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

*Candice Shepherd for*

Jennifer Dudinak, Pharm.D.  
Program Manager  
Drug Regulatory Affairs  
Phone: (973) 562-2930  
Fax: (973) 562-3554/3700

Attachments  
HLR No. 1999-2832

**DESK COPY: Ms. Maureen Pelosi, Division of Oncology Drug Products (Letter Only)**

## Electronic Mail Message

**Date:** 10/20/99 10:26:42 AM  
**From:** Shepherd, Candice PDRG-Nutley ( CANDICE.SHEPHERD@ROCHE.COM )  
**To:** 'Maureen Pelosi 301-594-2473 FAX 30 ( PELOSIM@A1 )  
**Subject:** Re: Xeloda info request

Hello Maureen,

I have forwarded the request to our toxicologist and we should get back to you by the end of the week with any questions and a proposed timeframe for submission.

Also, we tracked the 2nd Fed-Ex box that contained the copies of vol. 37 (appendix to the ISS) and it was signed for by William Kopp. However, we are also sending out additional copies of these volumes (one archival and three desk copies), just in case. Please let me know if you have any problems receiving these additional copies.

Thanks so much,  
Candice

> -----Original Message-----

> From: Maureen Pelosi 301-594-2473 FAX 301-594-0498

> [SMTP:PELOSIM@cder.fda.gov]

> Sent: Tuesday, October 19, 1999 2:16 PM

To: CANDICE.SHEPHERD@ROCHE.COM

Subject: FWD: Xeloda info request

> Sensitivity: Confidential

>

> Candice,

>

> Attached is a request from Pharm/tox. Dave's number is 301-827-1534 in  
> case you wish to speak directly with him. However, he often works at  
> home and you may have difficulty contacting him.

>

> maureen

> << Message: Xeloda info request >>

## Electronic Mail Message

**Date:** 9/28/99 10:55:59 AM  
**From:** Shepherd, Candice PDRG~Nutley ( CANDICE.SHEPHERD@ROCHE.COM )  
**To:** 'PELOSIM@cder.fda.gov' ( PELOSIM@a1 )  
**Subject:** Xeloda Colorectal Supplement

Hello Maureen,

We just encountered an issue with the annotations in the right hand margin of the revised PI that is contained in the Application Summary (vol. 2). We have a new computer system that we are using to publish our NDAs which can electronically insert the annotations to the PI. The problem that we found is that the system hiccuped when publishing the PI and has annotated to pages that don't exist, etc. We are correcting this problem right now in order to provide you with an annotated PI that is correct. This problem has not effected the text of the revised PI, just the annotations.

By tomorrow, we will send to you a revised version of the Application Summary (vol. 2) that has the corrected PI. I plan to send in the corrected volume to NDA 20-896 and will send you 10 desk copies. Please let me know if this is OK. I deeply apologize about this inconvenience.

The disks containing the PI in your desk copy are not affected, however, the application summary on the review aid is. Would you like us to send a CD with the corrected Application Summary and Bill can work with Gary to fix this on the \_\_\_\_\_ etc.?

We have checked other parts of the sNDA for similar problems and found 2 other small problems the system created:

- \* Master Index (vol 1). Parts of the overall index for the Application Summary have replicating page numbers (on pages 42-45 of volume 1). We would also be happy to fix this volume and send the corrected version to the NDA and desk copies to you.
- \* Volume 37 (appendices to the ISS)- Appendix 83 and 92 had incorrect files inserted by the system. Would you like us to only send you the correct appendices (total of approximately 20 pages) or correct the entire volume and re-send it?

Again, I am very sorry about these problems and we will do everything possible to correct them. Thanks so much for your help and understanding.

Kind Regards,  
Candice

November 15, 1999

Food and Drug Administration  
Division of Oncology Drug Products, HFD150  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Woodmont II Building  
1451 Rockville Pike, Room 2063  
Rockville, Maryland 20852

Dear Dr. Turner:

Re: **NDA 20-896 - XELODA® (capecitabine) Tablets**  
**Response to Request for Information**

DSI

As requested, enclosed is patient enrollment information for Dr. Weaver's site (CRTN# 17715) participating in study SO14695 entitled, "An open-label randomized phase 3 study comparing capecitabine with 5-fluorouracil in combination with leucovorin as first-line chemotherapy in patients with advanced and/or metastatic colorectal carcinoma".

If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

*Jennifer Dudinak*

Jennifer Dudinak, Pharm.D.  
Program Manager  
Drug Regulatory Affairs  
Phone: (973) 562-2930  
Fax: (973) 562-3554/3700

Attachments

JD:eh

HLR No. 1999-2736

Desk Copy: Dr. Gerston Turner, Division of Scientific Investigations  
**DESK COPY: Ms. Maureen Pelosi, Division of Oncology Drug Products (Letter Only)**

September 8, 2000

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



Ladies and Gentlemen:

**Re: NDA 20-896 – Supplement 006 – Xeloda® (capecitabine, Ro- 09-1978) Tablets  
 Supplement 006 – Xeloda® (capecitabine, Ro- 09-1978) Tablets  
 Complete Survival Data – Standard Population**

Reference is made to Hoffmann La-Roche Inc.'s New Drug Application 20-896 – Supplement 006- Xeloda Tablets, for the proposed indication of metastatic colorectal cancer. As requested in your fax of September 7, 2000, here are the updated survival results for standard population from studies SO14695 and SO14796 (cut-off date May 15<sup>th</sup>, 2000).

**SO14695**

Since the last survival update for SO14695 (September 15<sup>th</sup>, 1999) there were 47 new events, 15 in the capecitabine arm and 32 in the 5-FU/LV arm. The median survival of the 4-month Safety Update and of the new survival update is the same. The hazard ratio (HR) has changed from 1.09 to 0.98 due to the high number of new events in the 5-FU/LV arm. The upper limit of the HR confidence interval is now 1.17 and therefore below the 1.25 limit.

	Number of events	Median Survival [CI]	HR [CI]	Log rank test p value
<b>4-month Safety Update</b>				
Capecitabine (N=269)	216	392 [350; 442]		
5-FU/LV (N=266)	205	421 [366;468]	1.09 [0.90; 1.33]	0.36
<b>New Survival Update</b>				
Capecitabine (N=269)	231	392 [350; 442]		
5-FU/LV (N=266)	237	421 [366; 468]	0.98 [0.82; 1.17]	0.81

## SO14796

Since the last survival update for SO14796 (September 15<sup>th</sup>, 1999) there were 36 new events, 15 in the 5-FU/LV arm and 21 in the capecitabine arm. The median survival of the 4-month Safety Update and the new survival update are very close. The change in the median survival of the 5-FU arm from 395 to 391 days is explained by two additional deaths in this treatment arm occurring on study days 268 and 252, respectively. The HRs and the upper limits of the confidence intervals are also similar. Overall, the new survival update results on standard population are similar to the 4-month Safety Update.

	Number of events	Median Survival [CI]	HR [CI]	Log rank test p value
<b>4-month Safety Update</b>				
Capecitabine (N=265)	207	415 [373;469]		
5-FU/LV (N=273)	230	395 [356;459]	0.89 [0.74; 1.08]	0.23
<b>New Survival Update</b>				
Capecitabine (N=265)	228	415 [373; 464]		
5-FU/LV (N=273)	245	391 [354;450]	0.91 [0.76; 1.09]	0.29

## Pooled Data

In accordance with the agreement reached at the end-of-phase 2 meeting (held on September 9, 1996) for pooled data analysis and in order to be consistent with the sNDA and the 4-month Safety Update, the survival data has again been pooled.

In the pooled data, there were 83 new events, 36 in the capecitabine arm and 47 in the 5-FU/LV. Median survival shows only a 2-day difference. The hazard ratio has changed in favor of capecitabine (0.94 vs. 0.99), and the upper limit of the HR is now 1.07.

	Number of events	Median Survival [CI]	HR [CI]	Log rank test p value
<b>4-month Safety Update</b>				
Capecitabine (N=534)	423	404 [378; 440]		
5-FU (N=539)	435	407 [369; 441]	0.99 [0.86; 1.13]	0.86



Division of Oncology Drug Products, HFD-150  
September 8, 2000  
Page 3 of 3

	Number of events	Median Survival [CI]	HR [CI]	Log rank test p value
New Survival Update				
Capecitabine (N=534)	459	404 [379; 440]		
5-FU (N=539)	482	406 [366; 439]	0.94 [0.83; 1.07]	0.37

With the updated data, each individual study and the pooled data analyses clearly indicate also on the standard population that capecitabine is at least equivalent to 5-FU/LV in terms of survival. The apparent difference in directionality of survival outcome observed with previously submitted data does not exist any more as well for the standard population with the most recent survival data.

Sincerely,

HOFFMANN LA-ROCHE INC.

Murad Husain  
Program Director  
Drug Regulatory Affairs  
(973) 235-4578 (phone)  
(973) 562-2777 (fax)

Desk-copy: Ms. Maureen Pelosi, Senior Project Manager

MH/emd  
HLR No: 2000-2235





PHARMACIA

May 15, 2000

Food and Drug Administration  
Division of Oncology Drug Products, HFD-150  
Office of Drug Evaluation and Research  
1451 Rockville Pike, Woodmont II Building  
Rockville, MD 20852

Ladies and Gentlemen:

Re: IND \_\_\_\_\_ Capecitabine (Ro 09-1978), S-299  
**Information Amendment: Cross Reference to NDA 20-896 (S-006)**  
**24 Month Oral Carcinogenicity Study of Ro 09-1978 in Mice**  
**and Additional Analyses Requested by the FDA**

Reference is made to Hoffmann-La Roche Inc.'s Investigational New Drug Application( \_\_\_\_\_ ) for Capecitabine (Ro 09-1978) Tablets. We are submitting by way of cross-reference the following information which was submitted to the supplemental New Drug Application (sNDA), S#006, for metastatic colorectal cancer either at the time of filing in September 20, 1999 or in subsequent communications as outlined below.

- ◆ *24 Month Oral Carcinogenicity Study of Ro 09-1978 in Mice* submitted in the sNDA S#006 in research reports J-146'816 [section 5, volume 11, page 1] and J-146'848 [section 5, volume 16, page 1]
- ◆ *Response to Request for Information: Carcinogenicity Datasets-OEB Format* submitted to the sNDA S#006 on January 26, 2000
- ◆ *Response to Request for Information: Carcinogenicity Data-Analysis Package* submitted to the sNDA S#006 on May 15, 2000

For additional information, please reference communications documented in the sNDA S#006 between the FDA and the Sponsor regarding agreements for the carcinogenicity data- analysis package. Included in these communications are the FDA fax (November 29, 1999) requesting additional analysis on the 24 month oral carcinogenicity study of Ro 09-1978 in mice submitted in the sNDA in research reports \_\_\_\_\_ ] and \_\_\_\_\_ submission of the Sponsor's proposal for the requested data analysis on February 25, 2000; and telephone discussions (April 25, 2000) with the FDA regarding the Sponsor's analysis plan for the carcinogenicity data.



Division of Oncology Drug Products. HFD-150  
May 15, 2000  
Page 2 of 2

If you have any questions regarding this submission, please contact the undersigned.

Sincerely,

**HOFFMANN-LA ROCHE, INC.**

A handwritten signature in cursive script that reads "Robyn B. Konecne".

Robyn B. Konecne, Pharm.D.  
Program Manager  
Drug Regulatory Affairs  
Phone: 973-562-5567  
Fax: 973-562-3700

RK:emd  
HLR No. 2000- 1183

Desk Copy: Ms. Pelosi - HFD-150

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Tom Watson

Maureen Pelosi

Fax: 973-562-3700

Fax: 301-827-4590

Phone: 973-235-34578

Phone: 301-594-5778

Pages, including cover sheet: 4

Date: 03 - 20 - 00

Re: MedWatch Report for Xeloda

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● Dear Tom,

Last week we received the attached MedWatch Report regarding a life threatening event involving Xeloda in pancreatic cancer. We would like to request a follow-up, specifically, whether or not a liver biopsy was performed.

Regards,

Maureen A. Pelosi  
Regulatory Project Manager

# MEDWATCH

For use by user-facilities,  
distributors and manufacturers for  
MANDATORY reporting.

APPROVED BY FDA ON 03/06/98

Mfr report #	225906
UF/Dist. report #	
FDA Use only	

Page 1 of 3

## FDA MEDICAL PRODUCTS REPORTING PROGRAM

### A. Patient information

1. Patient Identifier	2. Age at time of event: or Date of birth:	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight 110.9 lbs or 50.3 kgs
-----------------------	--	---	--

### B. Adverse event or product problem

1.  Adverse event and/or  Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

<input type="checkbox"/> death	<input checked="" type="checkbox"/> disability
<input checked="" type="checkbox"/> life threatening	<input type="checkbox"/> congenital anomaly
<input type="checkbox"/> hospitalization initial or prolonge	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
	<input type="checkbox"/> other:

3. Date of event (m/d/yyyy)	4. Date of this report (m/d/yyyy)
JAN / 10 / 2000	FEB / 29 / 2000

5. Describe event or problem

A FEMALE PATIENT, AGE UNSPECIFIED, DEVELOPED LIVER CIRRHOSIS DURING THE USE OF XELODA (CAPECITABINE) FOR AN UNSPECIFIED INDICATION.

THE PATIENT'S MEDICAL HISTORY WAS NOT PROVIDED. UNKNOWN DATES: THE PATIENT COMMENCED ORAL XELODA. SHE DEVELOPED CIRRHOSIS OF THE LIVER. AT THE TIME OF THE REPORT, IT WAS NOT SPECIFIED IF XELODA WAS MAINTAINED OR IF THE EVENT WAS PERSISTING.

THE COMPANY ASSESSED THE SERIOUSNESS CRITERIA AS MEDICALLY SIGNIFICANT.

FURTHER INFORMATION WAS RECEIVED ON 17 FEB 00 STATING THE PATIENT WAS 69 YEARS OF AGE AND EVENTS OF ASCITES, BACK PAIN, PALMAR-PLANTAR ERYTHRODYSAESTH, DIARRHOEA AND TIREDNESS. THE DRUG RELATIONSHIP FOR CIRRHOSIS WAS CHANGED FROM NOT RELATED TO RELATED FOR XELODA. THE SERIOUS CRITERIA FOR CIRRHOSIS WAS CHANGED TO LIFE THREATENING AND DISABILITY.

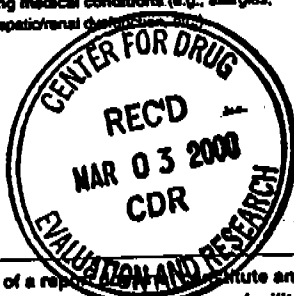
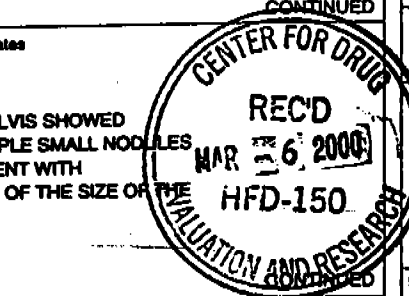
THE PATIENT HAD A HISTORY OF DIAGNOSIS OF LIVER METASTASES (15 FEB 99), SHE UNDERWENT A BILARY

6. Relevant tests/laboratory data, including dates

CT SCAN  
28-JUN-1999  
CT SCAN OF THE ABDOMEN AND PELVIS SHOWED INTERVAL DEVELOPMENT OF MULTIPLE SMALL NODULES IN THE RIGHT LUNG BASE CONSISTENT WITH METASTASES AND PROGRESSION OF THE SIZE OF THE HEPATIC METASTASES.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction)

Medical History Terms  
STENT INSERTION NOS 5-AUG-1999  
ANOREXIA  
ICTERUS



### C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)	
#1 XELODA (CAPECITABINE)	#2 NA
2. Dose, frequency & route	
#1 1800 MG 2 per DAY ORAL	#2 NA
3. Therapy dates (if unk. give duration) from/to (or best estimate)	
#1 14-OCT-1999 / 07-JAN-2000 E	#2 NA
4. Diagnosis for use (indication)	
#1 PANCREATIC CANCER	#2 NA
5. Event abated after use stopped or dose reduced	
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
6. Lot # (if known)	
#1 UNK	#2 NA
7. Exp. date (if known)	
#1 UNK	#2 NA
8. NDC # for product problems only (if known)	
#1 NA	#2 NA
10. Concomitant medical products and therapy dates (exclude treatment of event)	
GEMZAR 22-APR-1999 / 15-AUG-1999 E (GEMCITABINE HYDROCHLORIDE)	
COUMADIN 15-OCT-1999 E / UNK	

### G. All manufacturers

1. Contact Office-name/address		2. Phone Number
GLOBAL DEVELOPMENT HOFFMANN-LA ROCHE INC. 340 KINGSLAND STREET NUTLEY, NJ 07110-1199		(973) 562-3523
4. Date received by manufacturer		5. (ANDA# 20-896)
FEB / 17 / 2000		IND # _____ PLA # _____ pre-1938 <input type="checkbox"/> yes OTC <input type="checkbox"/> yes product <input type="checkbox"/> yes
6. If IND, protocol #		3. Report source (check all that apply)
NA 1		<input type="checkbox"/> foreign <input type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer <input checked="" type="checkbox"/> health professional <input type="checkbox"/> user-facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:
Type of report (check all that apply)		8. Adverse event term(s)
<input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> periodic <input type="checkbox"/> initial <input checked="" type="checkbox"/> follow-up # 1		CIRRHOSIS LIVER +++ ASCITES -ABDOMINAL DISCOMFORT DIARRHOEA BACK PAIN PALMAR-PLANTAR ERYTHRODYSAESTH. +++ adverse event that generated submission -comanifestation
9. MFR report number		
225906		

### E. Initial reporter

1. Name, address & phone #			
2. Health professional?		3. Occupation	
<input checked="" type="checkbox"/> yes <input type="checkbox"/> no			
4. Initial reporter also sent report to FDA			
<input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> unk.			



Submission of a report constitutes an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

E-Indicates estimated date, P-Indicates partial date

**3.5. Describe event or problem - continued**

STENT ON 5 AUG 99 WITH BILARY DRAINAGE PERFORMED. THE PATIENT ALSO EXPERIENCED A POOR APPETITE AND MILD SCLERAL ICTERUS. A CT SCAN ( 28 JUN 99) SHOWED INTERVAL DEVELOPMENT OF MULTIPLE SMALL NODULES IN THE RIGHT LUNG BASE CONSISTENT WITH METASTASES. THERE WAS ALSO SLIGHT PROGRESSION OF THE SIZE OF THE HEPATIC METASTASES. THE PATIENT WAS PREVIOUSLY TREATED WITH GEMZAR ( GEMCITABINE) FROM 22 APR 99 DISCONTINUED IN AUG 99. A BASELINE CBC, COMPREHENSIVE METABOLIC PANEL AND CA 19-9 LEVEL WERE PENDING ( RESULTS NOT PROVIDED).

14 OCT 99: THE PATIENT COMMENCED XELODA 2.500 MG /M2 (1800 MG BID) PO FOR 14 DAYS WITH 1 WEEK OFF. THE PATIENT ALSO COMMENCED LOW DOSE COUMADIN (WARFARIN) 1 MG QD FOR PROPHYLACTIC THROMBOSIS OF THE PORTACATH.

28 OCT 99 (EST): THE PATIENT COMPLETED THE 1ST CYCLE OF XELODA. THE PATIENT EXPERIENCED VERY MILD DIARRHOEA DURING THE END OF THE TWO WEEKS OF XELODA THERAPY. HER STOOL FREQUENCY DID NOT INCREASE ABOVE THREE STOOLS A DAY.

10 NOV 99 (EST): THE PATIENT LIFTED A HEAVY OBJECT AND EXPERIENCED LOW BACK PAIN (NO FURTHER INFORMATION PROVIDED).

UNKNOWN DATES: THE PATIENT WAS LATE RESTARTING HER XELODA CYCLE DUE TO A HOLIDAY. THE PATIENT RESTARTED XELODA.

23 NOV 99: THE PATIENT COMPLETED THE SECOND CYCLE OF XELODA.

29 NOV 99: THE PATIENT PRESENTED WITH WORSENING ABDOMINAL DISCOMFORT. SHE DESCRIBED FULLNESS AND EARLY SATIETY BUT NOT PAIN. ON EXAMINATION THE ABDOMEN WAS DISTENDED WITH FLUID WAVE AND SHIFTING DULLNESS. THE PATIENT HAD INCREASING GIRTH AND THE REPORTER STATED PROBABLE MALIGNANT ASCITES. THE PATIENT WAS TREATED WITH ALDACTONE (SPIROLACTONE) 25 MG TID ( UNKNOWN ROUTE).

4 JAN 00 (EST): THE PATIENT EXPERIENCED MILD PAIN INVOLVING THE PALMS OF HER HANDS.

7 JAN 00: THE PATIENT UNDERWENT A THERAPEUTIC PARACENTESIS WHICH YIELDED FOUR LITRES OF SEROUS FLUID.

10 JAN 00: AN AXIAL CT SCAN OF THE ABDOMEN AND PELVIS REVEALED AN INTERVAL DEVELOPMENT OF MARKED CIRRHOSIS OF THE LIVER AS WELL AS VARICES AND A DECREASE IN THE SIZE AND NUMBER OF HEPATIC METASTASES. THE PATIENT UNDERWENT A CT SCAN OF THE CHEST, ABDOMEN AND PELVIS. THE CHEST SCAN SHOWED INTERVAL IMPROVEMENT OF THE BILATERAL LOWER LOBE METASTASES. THE REPORTER STATED THAT THE CIRRHOSIS WAS OF UNKNOWN AETIOLOGY.

UNKNOWN DATE: A CYTOLOGY OF THE SEROUS FLUID REVEALED THE ACIDIC FLUID WAS MALIGNANT. THE TOTAL PROTEIN CONTENT OF THE ASCITIC FLUID WAS LOW AT (APPROX) 500 MG PER DECILITRE. CBC, COMPREHENSIVE METABOLIC PANEL AND CA 19-9 LEVELS PENDING (RESULTS NOT PROVIDED).THE XELODA WAS DISCONTINUED.

26 JAN 00: THE PATIENT UNDERWENT A LEVEEN SHUNT FOR MALIGNANT ASCITES. MORE THEN 6000 CC'S OF FLUID WAS REMOVED.

UNKNOWN DATE: HEPATITIS B AND C SEROLOGIES , SERUM FERRITIN AND CERULOPLASMIN TESTS WERE PENDING.

AT THE TIME OF THE REPORT THE OUTCOME OF THE ASCITES WAS WORSENERD. THERE WAS INSUFFICIENT INFORMATION CONCERNING THE OUTCOME OF THE DIARRHOEA, BACK PAIN, PALMAR-PLANTER ERYTHRODYSAESTH AND TIREDNESS. THE REPORTER STATED THAT THE PATIENT'S ASCITES WAS REFRACTORY TO DIURETIC TREATMENT WITH RAPID RE-ACCUMULATION OF FLUID FOLLOWING TWO PARACENTESES.

THE COMPANY ASSESSED THE ASCITES AS MEDICALLY SIGNIFICANT.

**B.6. Relevant tests/laboratory data - continued**

CT SCAN  
31-AUG-1999  
RESULT NOT PROVIDED.

CT SCAN  
10-JAN-2000  
AXIAL CT SCAN OF ABDOMEN AND PELVIS SHOWED AND INTERVAL DEVELOPMENT OF MARKED CIRRHOSIS OF THE LIVER AS WELL AS THE VARICES. DECREASE IN SIZE AND NUMBER OF HEPATIC METASTASES.

CT SCAN

10-JAN-2000

A CHEST SCAN SHOWED INTERVAL IMPROVEMENT OF THE BILATERAL LOWER LOBE METASTASES.

CYTOLOGY

CYTOLOGY OF PARACENTESIS SEROUS FLUID SHOWED THE ACIDIC FLUID WAS MALIGNANT AND POSITIVE FOR ADENOCARCINOMA.

TEST\_METHOD

CA 19-9 LEVEL - (RESULTS NOT PROVIDED).

TEST\_METHOD

THE TOTAL PROTEIN CONTENT OF THE ACIDIC FLUID WAS LOW AT APPROX 500 MG PER DECILITER.

COMPLETE\_BLOOD\_CNT

BASELINE (RESULTS NOT PROVIDED).

COMPLETE\_BLOOD\_CNT

RESULTS NOT PROVIDED.

CHEMISTRY\_PANEL

BASELINE COMPREHENSIVE METABOLIC PANEL (RESULTS NOT PROVIDED).

CHEMISTRY\_PANEL

COMPREHENSIVE METABOLIC PANEL (RESULTS NOT PROVIDED).

HEPATITIS\_SCREEN

HEPATITIS B AND C SEROLOGIES PENDING.

FERRITIN

SERUM FERRITIN PENDING.

FERRITIN

SERUM FERRITIN TEST PENDING.

C.10. Concomitant medical products and Therapy Dates - continued

(WARFARIN SODIUM)

TYLENOL UNK

(ACETAMINOPHEN)

LASIX UNK

(FUROSEMIDE)

ZANTAC UNK

(RANITIDINE)

LORTAB UNK

(ACETAMINOPHEN/HYDROCODONE BITARTRATE)

E.1. Initial reporter (Name, address & phone #) - continued

PHONE [ ]

G.8. Adverse event term(s) - continued

TIREDFNESS



February 25, 2000

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

Ladies and Gentlemen:

**Re: NDA 20-896 – XELODA® (capecitabine) Tablets**  
**Response to Request for Information: Carcinogenicity Data-Analysis Plan**

Reference is made to Hoffmann-La Roche Inc.'s approved New Drug Application 20-896 for the treatment of patients with paclitaxel and anthracycline resistant metastatic breast cancer and supplemental New Drug Application S#006 (September 20, 1999) for metastatic colorectal cancer. Reference is also made to FDA fax (November 29, 1999) regarding the format of the carcinogenicity data submitted in the sNDA. Further to submitting the transformed carcinogenicity datasets to FDA on January 27, 2000 and discussions with the Agency, the sponsor has prepared the analysis plan for the carcinogenicity data. We would greatly appreciate the Division's review of our analysis plan in order to verify that we have correctly interpreted their requests and addressed their concerns. As agreed with the Division, we will submit the entire package, including all statistical analysis, to FDA by end of March 2000.

If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

Jennifer Dudinak, Pharm. D.  
Program Manager  
Drug Regulatory Affairs

Phone: (973) 562-2930  
Fax: (973) 562-3700/3554  
JD:eah

HLR No. 2000-494  
Desk Copy: Ms. M. Pelosi, Project Manager



Pharmaceuticals

November 3, 1999

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

Ladies and Gentlemen:

**Re: NDA 20-896 - Supplement 006 - Xeloda® (capecitabine, Ro 09-1978) Tablets  
4 Month Safety Update Proposal**

Reference is made to Hoffmann-La Roche Inc.'s approved New Drug Application 20-896 for the treatment of patients with paclitaxel and anthracycline resistant metastatic breast cancer and Xeloda supplement #006 (September 20, 1999) for the first line treatment of metastatic colorectal cancer. Pursuant to 21 CFR 314.50 (d)(5)(iv)(a) the Sponsor will be providing a 4 Month Safety Update to the Xeloda supplement #006 in January 2000. Prior to submission of this report the Sponsor would appreciate the opportunity to consult with the Division on details of its format and content and is, therefore, submitting this 4 Month Safety Update Proposal for FDA consideration.

The following is an outline of this proposal:

- I. Safety Update on Pivotal Colorectal Cancer Trials
- II. Survival Update for Pivotal Colorectal Cancer Trials
- III. Safety Update on Ongoing Studies
  - a) Studies Conducted Under the US IND
  - b) Studies Not Conducted Under the US IND
- IV. Additional Questions to the Division

- I. Safety Update on Pivotal Colorectal Cancer Trials

For the pivotal colorectal cancer trials, SO14695 and SO14796, new data is available on approximately 50 patients and will be integrated into the existing safety database for these trials. We will repeat all major safety analyses from the sNDA and include in this update. Also we will provide CRFs for any additional patients who died or dropped out due to an adverse event and narratives for these patients and patients with related SAEs since the NDA clinical-cut-off.

- ◆ Does the Division concur?
- ◆ Does the Division want any additional analyses for the pivotal colorectal trials?





Food and Drug Administration  
Division of Oncology Drug Products, HFD-150  
November 3, 1999  
Page 2

Pharmaceutical Division

**II. Survival Update for Pivotal Colorectal Cancer Trials**

The Sponsor will perform all survival analyses included in the sNDA. In addition, as agreed at the July 13, 1999 meeting with the Division, the Sponsor will perform the bayesian survival analysis recommended by Dr. Simon. This analysis will be performed on the updated survival data and provided in the 4 Month Safety Update.

**III. Safety Update on Ongoing Studies**

The Sponsor will provide an update of ongoing studies both conducted under the US IND and not conducted under the US IND. Please refer to attachment 1 for a summary of these studies.

**a) Studies Conducted Under the US IND**

As indicated in the June 15, 1999 FDA comments to Roche's content and format questions the Sponsor will provide safety listings for the ongoing post-marketing capecitabine studies. Examples of the type of safety listings to be included are provided in attachment 2. We will also include CRFs for patients who died within 28 days or dropped out due to adverse events.

We propose to submit narratives only for patients who died within 28 days or dropped out due to an adverse event.

- ◆ Does the Division concur?

The Sponsor plans to submit as an IND submission in 1Q2000 the final study reports for \_\_\_\_\_ (listed in Attachment 1). Therefore, we propose not to include these studies in the safety update since they will be submitted in final form in 1Q2000.

- ◆ Does the Division concur?

**b) Studies Not Conducted Under the US IND**

For the studies not conducted under the US IND we will provide data listings for serious adverse events.

- ◆ Does the Division concur?



Food and Drug Administration  
Division of Oncology Drug Products, HFD-150  
November 3, 1999  
Page 3

**V. Additional Questions to the Division**

- 1. Are there any content and format issues the Division would like the Sponsor to address during preparation for the 4 Month Safety Update?

If you have any questions regarding this submission please do not hesitate to contact the undersigned.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

Candice A. Shepherd, Pharm. D.  
Program Director  
Drug Regulatory Affairs  
Phone: (973) 562-3695  
Fax: (973) 562-3700/3554

JD/TN  
Attachments  
HLR No. 1999-2632

Desk Copies: Ms. M. Pelosi, Project Manager (1)

November 2, 1999

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

Ladies and Gentlemen:

**Re: NDA 20-896, Supplement 006 – Xeloda® (capecitabine, Ro 09-1978) Tablets**  
**Teleconference Package: Bayesian Survival Analysis**

Reference is made to Hoffmann-La Roche Inc.'s approved New Drug Application 20-896 for the treatment of patients with paclitaxel and anthracycline resistant metastatic breast cancer and Xeloda supplement #006 (September 20, 1999) for the first line treatment of metastatic colorectal cancer. Reference is also made to the teleconference request to discuss Bayesian Survival Analysis (October 26, 1999). As a follow-up to the teleconference request we are herein providing the teleconference package.

The following is an outline of this teleconference package:

- I. Analysis Interpretation and Plan for Analysis; Questions for the Division
- II. Proposed Prior Information from the Literature
- III. Proposed Agenda
- IV. List of Roche Attendees with Titles/Functions
- V. Suggested FDA Members to Attend

#### **I. Analysis Interpretation and Plan for Analysis**

The analysis interpretation and plan, which includes the questions to the Division is included in Attachment 1.

#### **II. Proposed Prior Information from the Literature**

To perform the bayesian analysis as proposed in the analysis interpretation and plan, the choice of the prior information for  $\beta$  and  $\gamma$  is required. The proposed prior information from the literature to be used as the basis for the selection of  $\beta$  and  $\gamma$ , i.e. the log hazard rates for 5-FU/LV and capecitabine, respectively, when compared to previous controls is from the article by M.A. Poon et al. (1989) "Biochemical Modulation of Fluorouracil: Evidence of Significant Improvement of Survival and Quality of Life in Patients With Advanced Colorectal Carcinoma" JCO 7, 1407-1418. Hard copies of the referenced literature from the analysis interpretation and plan are provided in Attachment 2.



Division of Oncology Drug Products, HFD-150  
November 2, 1999  
Page 2

**III. Proposed Agenda with Timeline**

**Introductions**  
5 minutes

**Address FDA Questions on teleconference package and the Bayesian Survival Analysis**  
20 minutes

**Address Questions Outlined by Roche**  
20 minutes

**Final Agreement and Next Steps**  
15 minutes

**IV. List of Roche Attendees with Titles/Functions**

1. Dr. Bruno Osterwalder, Clinical Science Leader Oncology
2. Dr. Dvorit Samid, Clinical Science Oncology
3. Dr. Hans Ulrich Burger, Biometrics
4. Dr. Olga Rutman, Biometrics
5. Dr. Candice Shepherd, Regulatory Affairs
6. Dr. Jennifer Dudinak, Regulatory Affairs
7. Dr. Peter Teuber, Project Leader
8. Dr. Stefan Frings, International Medical Director

**V. Suggested FDA Members to Attend**

We recommend the following FDA attendees: Ms. Maureen Pelosi, Dr. Robert Justice, Dr. Julie Beitz, Dr. Alison Martin, Dr. Gang Chen, Dr. Claire Gnecco and Dr. Richard Simon, ODAC Member.

We look forward to scheduling this teleconference with the Division if you have any questions, please do not hesitate to contact the undersigned or Dr. Jennifer Dudinak at (973) 562-2930.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

Candice A. Shepherd, Pharm. D.  
Program Director  
Drug Regulatory Affairs  
Phone: (973) 562-3695  
Fax: (973) 562-3700/3554

HLR No. 1999-2623  
Desk Copies: Ms. M. Pelosi, Project Manager (10)

**22 PAGE(S)  
COPYRIGHT  
MATERIAL -  
REMOVED  
FROM THIS  
SECTION**

**Poon, M. A., et al., Biochemical Modulation of Fluorouracil: Evidence of Significant Improvement of Survival and Quality of Life in Patients With Advanced Colorectal Carcinoma, Journal of Clinical Oncology, Vol. 7, No. 10 (October), 1989, pp. 1407-1418**

**Poon, M. A., et al., Biochemical Modulation of Fluorouracil With Leucovorin: Confirmatory Evidence of Improved Therapeutic Efficacy in Advanced Colorectal Cancer, Journal of Clinical Oncology, Vol. 9, No. 11 (November), 1991, pp. 1967-1972**

**Simon, R., Bayesian Design and Analysis of Active Control Clinical Trials, Biometrics, 55, (June) 1999, 484-487**

Roche

October 14, 1999

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

Ladies and Gentlemen:

Re: **NDA 20-896 – XELODA® (capecitabine) Tablets**  
**Replacement Volumes for Efficacy Supplement Submitted on September 20, 1999**

Reference is made to our Efficacy Supplement to NDA 20-896 for Xeloda® (capecitabine) tablets, that was submitted to the Agency on September 20, 1999 to support an indication for the first line treatment of metastatic colorectal cancer.

As discussed with Maureen Pelosi, Project Manager, please find enclosed replacement copies of Volumes 1, 3 and 37 (Index, Application Summary and ISS appendices, respectively) of the NDA 20-896 efficacy supplement submitted on September 20, 1999. Our electronic publishing system encountered problems with these volumes, which resulted in clerical errors that were discovered post-filing. Also, enclosed is a replacement CD with the corrected files. Mr. Bill Repasy, E-Sub Manager, will contact Mr. Gary Gensinger of the Division to replace the corresponding files on the reviewers' laptops.

We apologize for any inconvenience this has caused and appreciate the Division's understanding. If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

*Candice A. Shepherd*

Candice A. Shepherd, Pharm. D.  
Program Director  
Drug Regulatory Affairs  
Phone: (973) 562-3695  
Fax: (973) 562-3700/3554

CAS/TN  
Attachments  
HLR No. 1999-2414



Food and Drug Administration  
Rockville MD 20857

NDA 20-896

SEP 23 1999

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

Attention: Candice Shepherd, Pharm.D.  
Program Director

Dear Dr. Shepherd:

Reference is made to your correspondence dated September 9, 1999, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Xeloda for metastatic breast cancer and metastatic colorectal cancer for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have any questions, please contact Maureen A. Pelosi, Project Manager at (301) 594-5778.

Sincerely yours,

9/22/99

MRJ

Robert Justice, M.D.  
Acting Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research



Pharmaceuticals

October 5, 1999

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
12229 Wilkins Avenue  
Rockville, Maryland 20859

Ladies and Gentlemen:

**RE: NDA 20-896 - XELODA® (capecitabine) Tablets**  
**Amendment to Efficacy Supplement - Colorectal Cancer**

Reference is made to the September 20, 1999 submission by Hoffmann-La Roche Inc., as agent of HLR Technology Corporation sponsor of NDA 20-896, of an efficacy supplement to NDA 20-896 for the use of Xeloda (capecitabine) Tablets in the first line treatment of patients with metastatic colorectal cancer. Reference is also made to the September 23, 1999 telephone call from Maureen Pelosi, Regulatory Project Manager, requesting additional information regarding Chemistry, Manufacturing, and Controls for this supplement.

The efficacy supplement does not contain Chemistry, Manufacturing, and Controls information because that information remains unchanged from that submitted in the original NDA and supplements thereto. However, because approval of this efficacy supplement will result in increased use of Xeloda Tablets, an evaluation of the effect on the quality of the environment was required. This submission provides the requested evaluation, which is a claim for categorical exclusion from the environmental assessment requirement.

In addition to the waiver, this submission also includes updated establishment information for the manufacturing sites, and a DMF cross-reference list, as requested. The DMF list reflects the change in ownership of DMF \_\_\_\_\_ from \_\_\_\_\_ A letter authorizing Roche to cross-reference this DMF is also included.

Please contact me at (973) 562-3519 if you require any additional information.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

Ms. Duane Voss  
Program Director  
Drug Regulatory Affairs

Phone: (973) 562-3519

Fax: (973) 562-3700

DV/tn  
Attachments  
HLR No. 1999-2380



Redacted 4

pages of trade

secret and/or

confidential

commercial

information



Food and Drug Administration  
Rockville MD 20857

NDA 20-896/S-006

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

SEP 23 1999

Attention: Candice A. Shepherd, Pharm.D.  
Program Director  
Drug Regulatory Affairs

Dear Dr. Shepherd:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: XELODA (capecitabine) Tablets

NDA Number: 20-896

Supplement Number: 006

Date of Supplement: September 20, 1999

Date of Receipt: September 20, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 19, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

(if via courier)

FDA/CDER  
Division of Oncology Drug  
Products, HFD-150  
5600 Fishers Lane  
Rockville, Maryland 20857

FDA/CDER  
Division of Oncology Drug Products,  
HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852

Sincerely,

1/23/99

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products, HFD-150  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

DUPLICATE

SUPPL NEW CORRESP  
SNC to S-006



Pharmaceuticals

September 22, 1999

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



Ladies and Gentlemen:

**Re: NDA 20-896 – XELODA® (capecitabine) Tablets**  
**Interactions Between FDA and Therapeutic Products Directorate**

Reference is made to our Efficacy Supplement to NDA 20-896 for Xeloda® (capecitabine) tablets, that was submitted to the Agency on September 20, 1999 to support an indication for the first line treatment of metastatic colorectal cancer. The Sponsor of NDA 20-896 has no objections to interactions between the FDA and the Therapeutic Products Directorate of Canada concerning the review of this Supplemental NDA.

If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

Candice A. Shepherd, Pharm. D.  
Program Director  
Drug Regulatory Affairs  
Phone: (973) 562-3695  
Fax: (973) 562-3700/3554

CAS/TN  
HLR No. 1999-2279



September 20, 1999

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
12229 Wilkins Avenue  
Rockville, Maryland 20859

Ladies and Gentlemen:

**RE: NDA 20-896 - XELODA® (capecitabine) Tablets  
Supplemental New Drug Application 20-896**

In accordance with 21 CFR Part 314.50, Hoffmann-La Roche Inc. herewith submits, as agents of HLR Technology Corporation sponsors of NDA 20-896, an efficacy supplement to NDA 20-896 for the use of Xeloda (capecitabine) Tablets in the first line treatment of patients with metastatic colorectal cancer. Xeloda has been the subject of IND ( ) sponsored by Hoffmann-La Roche Inc., Nutley, New Jersey.

Xeloda is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. Xeloda is currently approved for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated.

This efficacy supplement for the first line treatment of metastatic colorectal cancer is based on the results of two identical, large, multi-center, phase 3 pivotal trials (SO14695 and SO14796) conducted in 120 centers worldwide. These two pivotal trials randomized 603 patients to Xeloda 2500 mg/m<sup>2</sup>/day in the intermittent regimen (2 weeks on and 1 week off) and 604 patients to 5-FU and leucovorin (LV) administered in the Mayo regimen. We believe these two adequate and well-controlled phase 3 trials provide substantial evidence of efficacy and safety, as compared to the standard first line treatment of metastatic colorectal cancer, to support Xeloda in this indication. Supportive efficacy data from a phase 2 trial of Xeloda in metastatic colorectal cancer is also provided in this sNDA. A comprehensive clinical trial safety database, as well as description of the post-marketing safety data, are provided to established the safety of Xeloda when used to treat a large population of colorectal and breast cancer patients.

The primary colorectal cancer safety data is based on 596 patients enrolled in the two pivotal phase 3 colorectal cancer trials who received a dose of 2500 mg/m<sup>2</sup>/day for 2 weeks followed by a 1 week rest period. The overall clinical trial safety database is comprised of 875 patients enrolled in clinical therapeutic trials (phase 3 colorectal studies- 596 patients, phase 2 colorectal study- 34 patients, phase 2 breast cancer studies- 245 patients) treated with the approved dosage regimen of Xeloda.



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Central Document Room  
 September 20, 1999  
 Page 2

**FDA/Roche Key Meetings/Teleconferences:**

Please note the clinical development program supporting this colorectal cancer indication has been discussed with the Division of Oncology and recommendations of the Division have been incorporated. We refer you to the following teleconferences/meetings: End of Phase 2 Meeting on September 9, 1996, Phase 3 Analysis Plan Teleconference on September 15, 1998, Pre-sNDA meetings on February 16, 1999 and July 13, 1999. Analysis of the phase 3 population pharmacokinetics data was discussed with the Division in a teleconference on March 17, 1999. In addition, sNDA format and content questions were answered by the Division in the minutes from the February 16<sup>th</sup> Pre-sNDA meeting and in correspondence dated June 15, 1999.

The sNDA is organized as follows:

<b><u>Overall sNDA Content:</u></b>	<b><u>Volume(s)</u></b>
Section 1 - Index	1
Section 2 - Labeling	2
Section 3 - Application Summary	3-4
Section 5 - Nonclinical Pharmacology and Toxicology	5-21
Section 6 - Human Pharmacokinetics and Bioavailability	22-29
Section 8/10 - Clinical and Statistical	30-180
Location of Documents	30
Clinical Background and Overview	30
Clinical Pharmacology	30
Integrated Summary of Efficacy	31-33
Integrated Summary of Safety	34-37
Section 11 - Case Report Tabulations (CRTs)	DLT tape #1
Section 12 - Case Report Forms (CRFs)	DLT tape #1
Clinical Data Sets and Documentation	DLT tape #1

This submission consists of an archival copy of 180 paper volumes for Sections 1-10 and a \_\_\_\_\_ tape for Sections 11-12 and the clinical data sets. In addition, a paper review copy of Sections 1-10 and an electronic review aid (CD ROM 1-9) of Sections 1-12 and the clinical data sets are provided.



Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
September 20, 1999  
Page 3

**Electronic Submission and Review Aid:**

An Electronic Submission will constitute the official archive copy of Sections 11 and 12 (CRTs and CRFs) and the clinical data sets with accompanying documentation, which are provided electronically in accordance with the guidance for industry entitled, "Providing Regulatory Submissions in Electronic Format-NDAs", issued January 1999. The electronic submission will be provided on \_\_\_\_\_ and is approximately \_\_\_\_\_. The archival copy of the \_\_\_\_\_ tape will be sent directly to the FDA Document Control Room in accordance with guidance for industry entitled, "Guidance for Industry: Providing Regulatory Submissions in Electronic Format- General Considerations", issued January 1999. In addition, the entire sNDA submission will be provided to the Division electronically on CD ROM and \_\_\_\_\_

\_\_\_\_\_ computers as a review aid, as per our agreement in FDA correspondence dated July 22, 1999. Please refer to the outline of electronic review aid contents in Appendix 1 and the overall Index to the sNDA, as the review aid contains all components of the official submission. A full copy of the electronic review aid and \_\_\_\_\_ will be sent directly to the Division of Oncology (Attention of Gary Gensinger). All electronic files and equipment in this submission and review aid are certified to be Y2K compliant (IND submission S-274, August 31, 1999). In addition, all electronic files in the submission were scanned for viruses \_\_\_\_\_

No known viruses were found.

**NDA Referencing System:**

Each document in Sections 5, 6 and 8/10 has a unique reference number. Therefore, regardless of where in the sNDA a report or literature citation is referred to it will only have one unique number. Please refer to the overall Index, Volume 1, of the sNDA to determine location of a particular reference.

**Patent Information:**

Following this letter is patent information on the drug (U.S. Patent No. 5,472,949) and (U.S. Patent No. 4,966,891) for XELODA (capecitabine).

**User Fee:**

Following this letter is a copy of the check for the User Fee payment for this sNDA and a copy of the cover letter, which accompanied our payment.

**Financial Disclosure:**

Following this letter is the Financial Disclosure by Clinical Investigators information and Form 3454, as per 21 CFR part 54, for the covered clinical studies, SO14695 and SO14796.

**Roche Contacts:**

In order to facilitate the review, we encourage the Division to contact us to clarify any issues or address any questions. Please contact Dr. Candice Shepherd (973) 562-3695 or Dr. Jennifer Dudinak (973) 562-2930 with any questions or issues.



Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
September 20, 1999  
Page 4

The information contained in this New Drug Application is **CONFIDENTIAL** and should not be disclosed outside the Food and Drug Administration without the prior notification to, and written consent of Hoffmann-La Roche Inc.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

A handwritten signature in cursive script that reads "Candice A. Shepherd".

Candice A. Shepherd, Pharm. D.  
Program Director  
Drug Regulatory Affairs

Phone: (973) 562-3695  
Fax: (973) 562-3700

CAS:tn  
Attachments  
HLR No. 1999-2213

**Xeloda® (capecitabine)**  
**150 mg and 500 mf Tablets**



**Confidential Information**

### **CONFIDENTIAL INFORMATION**

Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.



September 14, 1999



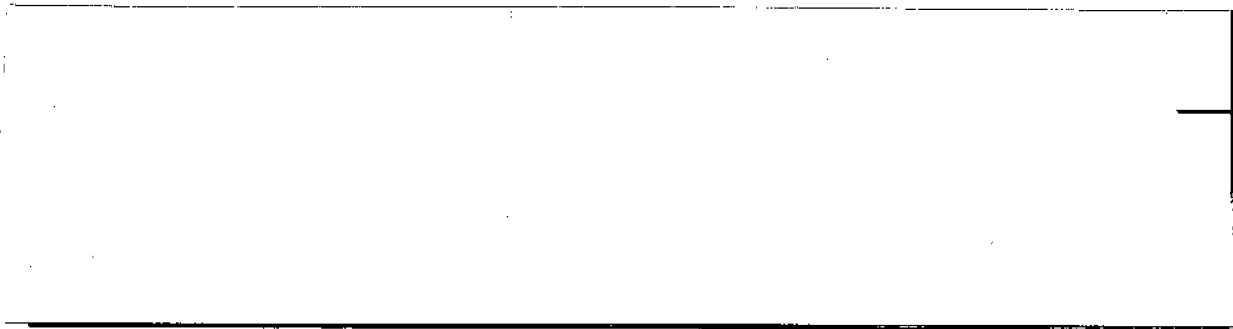
Food and Drug Administration  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research, HFD-073  
Parklawn Building, Room 8B45  
5600 Fishers Lane  
Rockville, MD 20857  
Attention: Mr. David Moss, Supervisor Computer Specialist



Ladies and Gentlemen:

Re: IND [redacted] Capecitabine (Ro 09-1978) Tablets (S-275)  
General Correspondence - Follow-Up to Letter of Intent: Summary of System Hardware

As follow-up to the Sponsor's letter of intent (S-274) submitted on August 31, 1999 we hereby provide a summary of the system hardware to be provided to the Division of Oncology for review of the Xeloda sNDA for metastatic colorectal cancer.



If there are any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE, INC.

William Repasy  
Electronic Submission Process Manager  
Hoffmann-La Roche, Inc  
Tel: 973-562-3947

WR/llb

HLR No.: 1999-2212

cc: Maureen Pelosi, Project Manager  
Ms. Debbie Lorentz  
Ms. Judith McIntyre  
Mr. Randy Levin

August 31, 1999

Food and Drug Administration  
Division of Oncology Drug Products, HFD-073  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Parklawn Building, Room 8B45  
5600 Fishers Lane  
Rockville, MD 20857  
**Attention: Mr. David Moss, Supervisor Computer Specialist**

Ladies and Gentlemen:

**Re: IND \_\_\_\_\_ Capecitabine (Ro 09-1978) Tablets (S-274)  
General Correspondence - Letter of Intent: Proposed Electronic Submission and  
Delivery Schedule (sNDA)**

---

To facilitate the review of the regulatory submission cited above, we are providing the proposed electronic submission and delivery schedule to the Center for Drug Evaluation and Research. These items will be provided for the use of Drs. Allison Martin, William McGuinn, and Claire Gnecco, Division of Oncology Drug Products, HFD-150.

The electronic archive submission of data sets, CRTs (patient profiles), and CRFs (Sections 11 and 12) will be delivered to FDA on September 15, 1999. It is our intention to deliver the electronic reviewer's aid to the Division as soon as possible after the official archive submission and at the latest within one week of the official archive submission.

The \_\_\_\_\_ of this \_\_\_\_\_ to CDER is necessary in order for reviewers to access CRF's and CRT's (case report summaries / patient profiles). As agreed with the Division of Oncology Drug Products, CRFs, CRTs, and the data sets will be submitted in electronic form only. The review aid will be submitted to the Division on either CD-ROMs or a \_\_\_\_\_ tape (depending on the Division's preference) with a copy provided on the \_\_\_\_\_. A summary of the \_\_\_\_\_ will be provided as follow-up to this correspondence ( \_\_\_\_\_ available).

Questions relating to this electronic archive submission should be addressed to Mr. Bill Repasy (973-562-3947) or Dr. Candice Shepherd (973-562-3695).

Any differences between the electronic reviewer's aid and the hardcopy submission will be clearly identified. Other than the specifics identified, the electronic reviewer's aid will be identical in content to the hard copy.

Division of Oncology Drug Products, HFD-150

August 31, 1999

Page 2

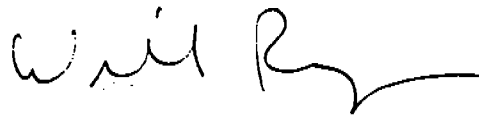
We certify and agree to the following:

- The \_\_\_\_\_ is in full compliance with the licensing agreements for that software.
- The software and computer are Y2K compliant.
- We have taken precautions to ensure that the \_\_\_\_\_ software are free from computer viruses and authorize CDER to use anti-virus software on the \_\_\_\_\_ as appropriate.
- We will arrange for the \_\_\_\_\_ when they are no longer required for the review of this specific application. We understand the data is an official part of the application and so may be retained by the Agency as an archive of the application.

If there are any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE, INC.



William Repasy  
Electronic Submission Process Manager  
Hoffmann-La Roche, Inc.  
Tel: 973-562-3947

WR/llb

HLR No.: 1999-2121

cc: Maureen Pelosi, Project Manager  
Ms. Debbie Lorentz  
Ms. Judith McIntyre  
Mr. Randy Levin

Roche

August 26, 1999

Food and Drug Administration  
Division of Oncology Drug Products, HFD-150  
Office of Drug Evaluation and Research  
1451 Rockville Pike, Woodmont II Building  
Rockville, MD 20852



Ladies and Gentlemen:

Re: IND [ ] Capecitabine (Ro 09-1978) - (S-272)  
General Correspondence: Minutes from August 18, 1999 Teleconference

Reference is made to Hoffmann-La Roche Inc.'s Investigational New Drug Application, IND [ ] for Capecitabine (Ro 09-1978) Tablets. Reference is also made to our electronic submission proposal [July 2, 1999 (S-266)] and the Division's response to our electronic submission proposal in the July 22, 1999 FDA fax. As per the Division's recommendation we requested a teleconference with Dr. Randy Levin, Associate Director for Electronic Review, to discuss the process for providing the official archive electronic submission and Y2K certification requirement. The following are minutes from our teleconference with Dr. Randy Levin on August 18, 1999.

**FDA Participants:** Randy Levin, Associate Director for Electronic review

**Roche Participants:** Jacqueline Alligood, Business Management  
Jennifer Dudinak, Regulatory  
William Repasy, Information Technology  
Candice Shepherd, Regulatory

The following are the highlights and our agreements from the teleconference:

- The electronic submission of sections 11 and 12 as the official archive is acceptable as planned with the Division.
- Discussed submission of datasets electronically as the official archive. Roche is able to submit datasets in the format as stated in the guideline, however, the sponsor is encountering difficulty in providing the accompanying documentation to the full specification of the guideline. Dr. Levin agreed that the electronic datasets would be accepted as the official archive without the accompanying documentation recommended in the guideline, however, the Sponsor should confirm with the Division the information needed for the review and should meet the Division's minimum requirement. Sponsor agreed to follow-up with the Division.

Division of Oncology Drug Products, HFD-150

August 26, 1999

Page 2

- The electronic submission for official archive should be labeled and shipped as per the 1999 Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations
  
- Send all electronic media adequately secured in a standard binder marked clearly on the outside **ELECTRONIC REGULATORY SUBMISSION FOR ARCHIVE**. The first binder with electronic media should include only a paper copy of the cover letter for the submission, a paper copy of the appropriate FDA form for the submission, and the electronic media for archiving. The labels should be attached to the CD jewel cases. Label the media with the following:
  - Submission identifier (sNDA)
  - Proprietary and generic name
  - Company name
  - Submission serial number, if applicable
  - Submission date: in the format DD-MM-YY
  - Disk/CD-ROM/tape number (the number should include the total number submitted such as Disk # of #)
  
- Shipping Address:  
Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852
  
- Submission of the electronic review aid. The sponsor should confirm with Division how the review aid CD's should be submitted. Dr. Levin suggested they be delivered directly to the Division with paper desk copies.
  
- A letter of intent for the electronic submission, including Y2K certification, should be sent to Mr. David Moss, Ms. Debbie Lorentz, Ms. Judith McIntyre and to the Division of Oncology.



Division of Oncology Drug Products, HFD-150  
August 26, 1999  
Page 3

We appreciated the opportunity to discuss the archive electronic submission and Y2K certification with Mr. Levin. Please contact the undersigned if there are any questions regarding the minutes.

Sincerely,

HOFFMANN-LA ROCHE INC.

A handwritten signature in cursive script that reads "Candice A. Shepherd".

Candice A. Shepherd, Pharm.D.  
Program Director  
Drug Regulatory Affairs  
(973) 562-3695 (Telephone)  
(973) 562-3554/3700 (Fax)

CAS/11b  
Attachments  
HLR No. 1999-2096

Desk Copy: Mr. Randy Levin

## Electronic Mail Message

**Date:** 8/30/99 5:09:05 PM  
**From:** Shepherd, Candice PDRG-Nutley ( CANDICE.SHEPHERD@ROCHE.COM )  
**To:** 'Maureen Pelosi 301-594-2473 FAX 30 ( PELOSIM@A1 )  
**Subject:** - Electronic Archive Submission

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

Hello Maureen,

As we discussed last week regarding the official electronic archive submission, we will be submitting Sections 11 and 12 and the datasets electronically. From our discussions with Randy Levin (a copy of our minutes from our telecon was sent to the Division), everything is OK but he recommended that we check with the Division on a few things:

Submission of review aid- how should we send this? (send directly to the Division?) Also, the official archive submission will be submitted on a tape due to the size of all the files. Does the Division want the review aid also submitted on tape or on CDs as originally planned (it would amount to about 2 CDs). Bill Repasy tried to contact Gary Gensinger regarding this question, but he is out of the office until Sept. 13th. Is there someone else we should contact?  
\* Documentation to accompany datasets- Randy wanted us to communicate to the Division what documentation we will provide and confirm that this is OK.

*what maureen*

*NO*

The datasets will be submitted as per the E-sub guideline and for accompanying documentation we are planning to submit:

- \* \_\_\_\_\_ - all collected data in raw format. (Safety for all studies, efficacy separately by study for the 3 colorectal studies)
- \* Annotated CRFs which explain how CRF data is entered into \_\_\_\_\_ (for the 3 colorectal studies)
- \* \_\_\_\_\_ documentation (data sets descriptions- an example of the data sets description file that was submitted for the original NDA is attached as file datadesc.pdf)
- \* Major value-added datasets (Safety for all studies, efficacy separately by study for the 3 colorectal studies)
- \* Major programs which create value-added datasets for efficacy. These programs will provide detailed information on the algorithms behind derived data. (example programs are provided below as files \_\_\_\_\_ and oraegr.sas, which may be viewed by using \_\_\_\_\_)
- \* Programs which create major efficacy analyses, tables and graphs, such as the programs that calculate:
  - \* Cox regression for survival and time to disease progression (ttp)
  - \* kaplan meier plots for survival and ttp, time to response, duration response
  - \* CI with Shouten and Hauck Andersen corrections
  - \* chi square test
  - \* program for main time to onset of AE analysis
  - \* QoL for testing and Longitudinal analysis

<<demoext.sas>> <<oraegr.sas>> <<datadesc.pdf>>

An additional question for Dr. Gnecco regarding the datasets: According to the E-sub guidelines, the datasets should generally be less than \_\_\_\_\_. However, we have files bigger than \_\_\_\_\_ files are \_\_\_\_\_ and files are \_\_\_\_\_. We can split up the files, if Dr. Gnecco would like. Please advise.

Thank you very much for your help. Please do not hesitate to contact me at (908) 654-3882 if you have any questions.

Kind Regards,  
Candice





Pharmaceuticals

August 13, 1999

Food and Drug Administration  
Division of Neuropharmacological Drug Products, HFD-120  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
1451 Rockville Pike, Woodmont II Building  
Rockville, MD 20852  
ATTN: Dr. Randy Levin

Dear Dr. Levin:

Re: IND( ) - Capecitabine (Ro 09-1978) Tablets  
Summary of Electronic Submission Proposal and FDA Feedback

Reference is made to Hoffmann-La Roche Inc.'s Investigational New Drug Application ( ) Capecitabine (Ro 09-1978) Tablets and our approved NDA 20-896 for the treatment of patients with metastatic breast cancer resistant to Taxol and an anthracycline-containing chemotherapy regimen. The purpose of this correspondence is to provide a summary of our electronic submission proposal and FDA feedback for the upcoming colorectal cancer sNDA filing. The sNDA filing is anticipated September 15, 1999. As per the Division's recommendation in the July 22, 1999 fax; we requested a teleconference to discuss the process for providing the official archive electronic submission and Y2K certification requirement.

Summary of Electronic Submission Proposal

We intend to provide the Division with a "paper submission" (sections 1-10), with the exception of Sections 11 and 12 (Case Report Forms and Case Report Tabulations), which will be provided electronically in accordance with the guidance for industry entitled, "Providing Regulatory Submissions in Electronic Format-NDAs", issued January 1999. As per the request of the Division, the Sponsor also intends to provide an electronic review aid in PDF of Sections 1-10 for this sNDA.

Summary of Agreements with the Division of Oncology

and CD-ROMs

- ◆ FDA would accept \_\_\_\_\_ MO, Clin Pharm, and Stat.
- ◆ A CD-ROM with a copy of the programs and files on the \_\_\_\_\_ would be helpful in case of accidental deletion.

Archival Copy

- ◆ Sections 1-10 will be provided in paper. The electronic submission of Sections 11 (CRTs) and 12(CRFs) for archiving will be submitted on CD-ROM \_\_\_\_\_ as recommended by the January 1999, "Guidance for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations".
- ◆ CRF images will be submitted in PDF format as recommended in the January 1999 guidance, "Providing Regulatory Submissions in Electronic Format-NDAs".
- ◆ Data sets will be provided for the two phase III colorectal studies and one phase II colorectal study.
- ◆ We will archive the datasets as an official electronic submission using SAS transport files for both the SAS and Access files. On the review aid, SAS and Access are fine.

Division of Neuropharmacological Drug Products, HFD-120  
August 13, 1999  
Page 2

#### Review Aids

- ◆ All sNDA documents in Sections 1-10 will be provided in electronic format as a reviewer's aid.
- ◆ The Sponsor will also provide documents in Word per the Division's request.

#### User's Guide

- ◆ In order to facilitate the electronic review of our NDA, a User's Guide will be furnished in paper and electronically to provide detailed instruction on:
  - ◆ Locating and viewing documents, Case Report Forms and Case Report Tabulations (Patient Profiles)
  - ◆ Searching for specified words or phrases
  - ◆ Using the bookmarks or hypertext links to navigate through the electronic submission
  - ◆ Copy text, tables and graphics
- ◆ Training by the Division was deferred unless they experience any problems.

Thank you in advance for addressing our questions and issues surrounding the official archive of the electronic submission for the colorectal cancer sNDA September 15, 1999. We look forward to our teleconference on August 18, 1999 at 2PM. If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.



Candice A. Shepherd, Pharm.D.  
Program Director  
Drug Regulatory Affairs  
(973) 562-3695 (telephone)  
(973) 562-3554/3700 (fax)

CAS:TN

HLR No. 1999-1968

cc: Maureen Pelosi, R.Ph.

Roche

Pharmaceuticals

August 30, 1999

Mellon Bank  
Three Mellon Bank Center  
27th Floor (FDA 360909)  
Pittsburgh, Pennsylvania 15259-0001

Ladies and Gentlemen:

**RE: NDA 20-896 - XELODA (capecitabine) TABLETS  
HUMAN DRUG APPLICATION FEE - I.D. No. 3306**

Enclosed please find a check in the amount of \$\_\_\_\_\_ made payable to the U.S. Food and Drug Administration. This payment represents the user fee required for our Supplemental New Drug Application for Xeloda, which is planned for submission on September 15, 1999.

If you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.



Elisa Scordato Mandra  
Associate, Labeling  
Drug Regulatory Affairs  
(973) 562-3683 (telephone)  
(973) 562-3700/3554 (fax)

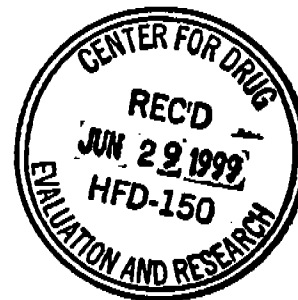
ESM:mi  
HLR No. 1999-2118

Enclosure: Check No. \_\_\_\_\_

Roche

June 28, 1999

Food and Drug Administration  
Division of Oncology Drug Products, HFD-150  
Office of Drug Evaluation and Research  
1451 Rockville Pike, Woodmont II Building  
Rockville, MD 20852



Ladies and Gentlemen:

Re: IND [redacted] Capecitabine (Ro 09-1978) - (S-265)  
Response to FDA Request for Information- Table of Protocol Information

Reference is made to Hoffmann-La Roche Inc.'s Investigational New Drug Application, IND [redacted] for Capecitabine (Ro 09-1978) Tablets and our approved NDA 20-896 for the treatment patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen. As requested in FDA's minutes of our Pre-sNDA meeting with the Division on February 16, 1999, please find attached tables for the Studies SO14695, SO14796 and SO14797. These tables provide protocol and investigator information to assist with the identification of the studies and sites to be audited.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Candice A. Shepherd, Pharm.D.  
Program Director  
Drug Regulatory Affairs

(973) 562-3695 (Telephone)  
(973) 562-3554/3700 (Fax)

CAS/ls:eh  
Attachments  
HLR No. 1999-1523

Redacted 4

pages of trade

secret and/or

confidential

commercial

information