Enoxacin is a quinolone antibiotic marketed under the tradename Penetrex. Enoxacin is indicated for the treatment of infections caused by susceptible strains of microorganisms. The usual adult dosage is 200 mg to 400 mg every 12 hours. *Enoxacin* and *Eloxatin* may also sound similar when spoken. Both names have four syllables. The first two syllables "Enox" vs. "Elox" differ in only one letter, "n" vs. "l". The letter "n" may sound similar to the letter "l" since they are both formed by placing the tip of the tongue on the alveolar region of the mouth. The last two syllables "acin" vs. "atin" also differ in only one letter and sound very much alike. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between these products including differences in route of administration (oral vs. intravenous), dosage form (tablet vs. powder for injection), dosing regimen (every 12 hours vs. one dose every 2 weeks) and strength (200 mg and 400 mg vs. 50 mg and 100 mg).

ELOXATINE

Loxapine is a dibenzoxazepine compound from a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Loxapine is marketed under the tradename Loxitane and is also marketed generically. Loxapin is indicated for the treatment of schizophrenia. The recommended dosage of Loxapin is 60 mg to 100 mg per day by mouth and 50 mg every 4 to 6 hours by the intramuscular route of administration. Both the established name, Loxapine, and the proprietary name Loxitane may potentially be confused with Eloxatine. *Loxapine* and *Eloxatine* may sound similar when spoken. Although Eloxatine has an extra syllable compared to Loxapine (the "E" at the beginning), that syllable could be misunderstood as a separate word or as verbal hesitation during a telephone order, e.g., "eh...loxatine". In fact, one study participant responded "Loxetin" to the verbal order for Eloxatin. Except for the questionably distinct "E", the two names are virtually indistinguishable. In fact, "loxatine" and "loxapine" differ only by the similar sounding plosive* consonants "t" vs. "p". It is worth noting that one study participant responded "Aloxapin" to the verbal order for Eloxatin, substituting the "t" for a "p". The two drug products have additional similarities. Both are available as injectable dosage forms and the products share a common strength, 50 mg. Postmarketing experience has shown medication errors occurring as a result of common dosage forms and overlapping strengths. The drug products also have differences most notably, differences in usual dosage (unlike Loxapine, Eloxatine is dosed on a mg/m^2 basis), dosing intervals (Loxapine, every 4 to 6 hours vs. Eloxatine, every 2 weeks), and routes of administration (Loxapine, IM vs. Eloxatine IV). These differences may decrease the risk of confusion.

Loxitane is the proprietary name for Loxapine (see above). *Loxitane* and *Eloxatine* may also sound similar when spoken and may look similar when written. Except for the "E" as the first syllable of Eloxatine, the names sound very much alike ("loxitane" vs. "loxatine"). When written, the names look very much alike and have 8 of 9 possible letters in common (see writing sample on page 9). The two drug products have additional similarities. Both are available as injectable dosage forms and the products share a common strength, 50 mg. Postmarketing experience has shown medication errors occurring as a result of common dosage forms and overlapping strengths. The drug products also have differences most notably, differences in usual dosage (unlike Loxapine, Eloxatine is dosed on a mg/m^2 basis), dosing intervals (Loxapine, every 4 to 6 hours vs. Eloxatine, every 2 weeks), and routes of administration (Loxapine, IM vs. Eloxatine IV). These differences may decrease the risk of confusion.

* A good reference for phonetic terminology can be found at: http://www.unil.ch/ling/phonetique/api-eng.html

loxitane loxatine

In the original review of the proposed proprietary name, Eloxatine, there was concern regarding confusion with Loxitane (Loxapine). However, the name was found acceptable at that time due to differences in route of administration (Eloxatine is given IV and Loxitane is given IM), usual dosage, dosing intervals, and differences in indications of use. Although DMETS has concerns with confusion between these two products, the concerns do not warrant reversal of the earlier decision.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary names Eloxatin. However, DMETS has no objections to the use of the proprietary name, Eloxatine. The names thought to have the greatest potential for confusion with Eloxatin are discussed below.

ELOXATIN

Loxapine is a dibenzoxazepine compound from a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Loxapine is marketed under the tradename Loxitane. Loxapin is indicated for the treatment of schizophrenia. The recommended dosage of Loxapin is 60 mg to 100 mg per day by mouth and 50 mg every 4 to 6 hours by the intramuscular route of administration. Both the established name, Loxapine, and the proprietary name Loxitane may potentially be confused with Eloxatin. *Loxapine* and *Eloxatin* may sound similar when spoken. Although Eloxatin has an extra syllable compared to Loxapine (the "E" at the beginning), that syllable could be misunderstood as a separate word or as verbal hesitation during a telephone order, e.g., "eh...loxatin". In fact, one study participant responded "Loxetin" to the verbal order for Eloxatin, omitting the "E". Except for the questionably distinct "E", the two names are very similar in sound. The syllables, "loxa" are identical in both names. The syllables "tin" and "pine" start with the similar sounding plosive* consonants "t" and "p" and "in" may be pronounced the same as "ine". It is worth noting that one study participant responded "Aloxapin" to the verbal order for Eloxatin, substituting the "t" for a "p". The two drug products have additional similarities. Both are available as injectable dosage forms and the products share a common strength, 50 mg. Postmarketing experience has shown medication errors occurring as a result of common dosage forms and overlapping strengths. Differences between the drug products include different usual dosage, and different dosing intervals, however, given the similarities such as the sound-alike/ look-alike properties, the fact that these are both injectable products, and overlapping strengths, there is potential for confusion. If Loxapine was given instead of Eloxatin, the patient would not receive the benefits of chemotherapy. The patient would also be exposed to risk of Neuroleptic Malignant Syndrome as well as unnecessary side effects such as dyskinesias, drowsiness, and other unwanted anticholinergic effects. If Eloxatin was given rather than Loxapine, the patient's mental illness

* A good reference for phonetic terminology can be found at: http://www.unil.ch/ling/phonetique/api-eng.html

might not be controlled and they would be exposed to risk of allergic reactions and unwanted side effects such as thrombocytopenia, neutropenia, nausea, vomiting, and diarrhea.

Loxitane (Loxapine) is a dibenzoxazepine compound from a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Loxitane is indicated for the treatment of schizophrenia. The recommended dosage of Loxitane is 60 mg to 100 mg per day by mouth and 50 mg every 4 to 6 hours by the intramuscular route of administration. *Loxitane* and *Eloxatin* may sound similar when spoken and may look similar when written. Except for the "E" as the first syllable of Eloxatin, the names sound very much alike ("loxitane" vs. "loxatin"). When written the names look very much alike (see writing sample below). The two drug products have additional similarities. Both are available as injectable dosage forms and the products share a common strength, 50 mg. Postmarketing experience has shown medication errors occurring as a result of common dosage forms and overlapping strengths. Differences between the drug products include different usual dosage, and different dosing intervals, however, given the similarities such as the sound-alike/ look-alike properties, the fact that these are both injectable products, and overlapping strengths, there is potential for confusion. If Loxitane was given instead of Eloxatin, the patient would not receive the benefits of chemotherapy. The patient would also be exposed to risk of Neuroleptic Malignant Syndrome as well as unnecessary side effects such as dyskinesias, drowsiness, and other unwanted anticholinergic effects. If Eloxatin was given rather than Loxitane, the patient's mental illness might not be controlled and they would be exposed to risk of allergic reactions and unwanted side effects such as thrombocytopenia, neutropenia, nausea, vomiting, and diarrhea.

Cefoxitin is a semi-synthetic, broad-spectrum cepha antibiotic for intravenous administration. It is marketed under the tradename Mefoxin. Cefoxitin is indicated for the treatment of serious infections caused by susceptible strains of microorganisms in, lower respiratory tract infections, urinary tract infections, intra-abdominal infections, gynecological infections, septicemia, bone and joint infections, and skin and skin structure infections. The usual dosage is 1 g to 2 g every 4 to 8 hours. *Cefoxitin* and *Eloxatin* may sound similar when spoken. Each name has four syllables. The first syllables "Cef" vs. "El" sound similar since they share the short "e" sound. The last three syllables of each name ("oxitin" vs. "oxatin") are virtually indistinguishable, differing only in the first vowel the short "i" vs. the short "a". The two products have additional similarities. The products share a common route of administration, intravenous and both are available in vials as sterile powder for reconstitution. The products also have similar numeric strengths [1 g (Cefoxitin) vs. 100 mg, which can be written 0.1 g, (Eloxatin)]. Postmarketing experience has shown medication errors occurring as a result of a numerical similarity in strengths. The drug products differ in their dosing intervals, however, given the similarities such as the sound-alike properties, common routes of administration, dosage forms, and strengths which share the number "1", the likelihood of confusion is high. If Cefoxitin was given instead of Eloxatin, the patient would not receive the benefits of chemotherapy and would be exposed to

risk of allergic reaction. If Eloxatin was given rather than Cefoxitin, the patients' infection would be untreated and they would be exposed to risk of allergic reactions and unwanted side effects such as thrombocytopenia, neutropenia, nausea, vomiting, and diarrhea.

In addition, DMETS reviewed the container labels, carton, and insert labeling of Eloxatin/ Eloxatine. DMETS has focused on safety issues relating to possible medication errors and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER

We suggest the use of contrasting colors, boxing, or some other means to more clearly differentiate the strengths of these products.

B. CARTON

See comment under CONTAINER.

C. PACKAGE INSERT

Please ensure that the conditions of 21 CFR 201.10(g)(1) are met.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name Eloxatin. However, DMETS has no objections to the use of the proprietary name, Eloxatine.

B. DMETS recommends the labeling revisions as outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Hoppes
7/16/02 01:22:06 PM
PHARMACIST

Carol Holquist
7/16/02 01:37:29 PM
PHARMACIST

DDMAC. Review

Labeling

21 pages redacted from this section of the approval package consisted of draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Grillo
7/2/02 04:01:44 PM
UNKNOWN

54 pages redacted from this section of the approval package consisted of draft labeling

N/A

Applicant proposed labels are acceptable.

8 pages redacted from this section of the approval package consisted of draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Haripada Sarker
7/19/02 05:42:54 PM
CHEMIST

Richard Lostritto
7/22/02 05:23:42 PM
CHEMIST

Christy Wilson
7/23/02 08:46:35 AM
CSO

MEMORANDUM OF TELECON

DATE OF TELECON: July 19, 2002

APPLICATION NUMBER: NDA 21-492, Eloxatin (oxaliplatin) for Injection

BETWEEN:
Dr. Donna Przepiorka, ODAC consultant

AND
Dr. Richard Pazdur, Director
Dr. Grant Williams, Deputy Director
Dr. Donna Griebel, Medical Team Leader
Christy Wilson, Consumer Safety Officer

SUBJECT: Accelerated approval of NDA 21-492 for Eloxatin (oxaliplatin) for Injection

BACKGROUND:

The draft Medical Officer review was sent to Dr. Przepiorka for her review prior to the teleconference.

DISCUSSION:

On July 19, 2002, the review team called Dr. Przepiorka to discuss response rates, time to progression, study durations, and safety data for NDA 21-492 for Eloxatin.

Dr. Pazdur briefly summarized the contents of the application and stated that the Division was pursuing accelerated approval of the NDA.

Dr. Przepiorka agreed with the Division's decision to approve this NDA for the stated indication.

/S/

Christy Wilson
Consumer Safety Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
7/31/02 11:28:40 AM

Donna Griebel
7/31/02 11:44:39 AM

MEMORANDUM OF TELECON

DATE OF TELECON: July 26, 2002

APPLICATION NUMBER: NDA 21-492, Eloxatin (oxaliplatin) for Injection

BETWEEN:
Dr. Jean Grem, ODAC consultant

AND
Dr. Richard Pazdur, Director
Dr. Grant Williams, Deputy Director
Dr. Donna Griebel, Medical Team Leader
Dr. Martin Cohen, Medical Officer
Christy Wilson, Consumer Safety Officer

SUBJECT: Accelerated approval of NDA 21-492 for Eloxatin (oxaliplatin) for Injection

BACKGROUND:

The draft Medical Officer review was sent to Dr. Grem for her review prior to the teleconference.

DISCUSSION:

On July 26, 2002, the review team called Dr. Grem to discuss response rates, time to progression, study durations, and safety data for NDA 21-492 for Eloxatin.

Dr. Pazdur briefly summarized the contents of the application and stated that the Division was pursuing accelerated approval of the NDA.

Dr. Grem agreed with the Division's decision to approve the NDA based on response rates, but noted a safety concern regarding chronic cumulative sensory neuropathy. Dr. Grem noted that the cumulative neurotoxicity she has seen has resulted in functional disability (i.e., writing, driving, interfering with work and daily activities). Dr. Grem suggested neuropathy follow-up as a potential Phase 4 commitment.

/S/

Christy Wilson
Consumer Safety Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
7/31/02 11:25:57 AM

Donna Griebel
7/31/02 11:47:24 AM

MEMORANDUM OF TELECON

DATE OF TELECON: July 26, 2002

APPLICATION NUMBER: NDA 21-492, Eloxatin (oxaliplatin) for Injection

BETWEEN:
Carol Holquist, Deputy Director, Division of Medication Errors and Technical Support

AND
Dr. Richard Pazdur, Director
Christy Wilson, Consumer Safety Officer

SUBJECT: Tradename review for NDA 21-492 for Eloxatin (oxaliplatin) for Injection

BACKGROUND:

In a review dated July 16, 2002, Charles Hoppes, reviewer in the Division of Medication Errors and Technical Support, did not recommend the use of the tradename Eloxatin due to the potential confusion with Cefoxitin and Loxitane, but had no objections to the name Eloxatine.

In prior discussions, the sponsor noted a preference for the use of Eloxatin, in order to maintain global consistency.

DISCUSSION:

On July 25, 2002, Dr. Pazdur called Ms. Holquist to discuss DMETS' disapproval of the tradename Eloxatin. He explained that the Division did not feel strongly that there was a great potential for medication errors with Cefoxitin and Loxitane. He informed Ms. Holquist that the Division plans to let the sponsor use the tradename Eloxatin rather than Eloxatine (as suggested by DMETS). The Division was willing to incorporate a Phase IV commitment (similar to that used for the approval of Faslodex) requiring the sponsor to follow-up on and report any medication errors that occur due to the tradename. Ms. Holquist agreed with the Division's proposal for the tradename Eloxatin and the Phase IV commitment.

/S/

Christy Wilson
Consumer Safety Officer

/S/

Richard Pazdur, M.D.
Division Director

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
7/30/02 04:19:43 PM

Richard Pazdur
7/30/02 04:35:35 PM

MEETING MINUTES

MEETING DATE: December 12, 2000 **TIME:** 8:30 am **LOCATION:** E

IND/NDA: IND [redacted]

Meeting Request Submission Date: 11-16-00
Briefing Document Submission Date: 12-4-00
Additional Submission Dates: N/A

DRUG: Oxaliplatin

SPONSOR/APPLICANT: Sanofi-Synthelabo

TYPE OF MEETING:

1. End-of-Phase 2 meeting #4

2. **Proposed Indication:** First line colorectal cancer

FDA PARTICIPANTS:
Dr. Richard Pazdur, Division Director
Dr. John Johnson, Medical Team Leader
Dr. Amna Ibrahim, Medical Officer
Dr. Mark Rothmann, Statistics Reviewer
Dr. Atik Rahman, Biopharmaceutics Reviewer
Dr. Nancy Sher, Medical Officer
Christy Wilson, Consumer Safety Officer
Patricia Delaney, Office of Special Health Issues
Janelle Ernat, Office of Special Health Issues

INDUSTRY PARTICIPANTS:
Dr. Martine Baysses, Clinical Research, Debiopharm
Dr. Sunil Gupta, Clinical Research
Dr. Richard Gural, Drug Regulatory Affairs
Dr. Alain Herrera, Oncology Business Unit
Dr. Nathlie LeBail, Clinical Research, Debiopharm
Mark Moyer, Drug Regulatory Affairs

MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated December 4, 2000.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **Sanofi-Synthelabo plans to suspend accrual to the compassionate use study while accrual is ongoing in the four registration studies. If the compassionate use study is reopened during the evaluation phase of the registration studies, there is a potential impact on the primary endpoint of overall survival in EFC4584 and EFC4585. Therefore, does the Division agree that the compassionate use study should not be reopened until the evaluations are completed for the primary overall survival endpoint in these two studies (EFC4584 and EFC4585)?**

   Does the Division agree that it is in the best interest of the registration studies to suspend accrual to the compassionate use study?

   FDA RESPONSE:

   - The company should use its discretion to balance accrual against continued access outside the trials. We agree that eligible patients should be enrolled in the ongoing clinical trials.

2. **Does the FDA have any comments on the proposed third line studies? (See attached protocol concept sheets).**

   FDA RESPONSE:

   - Clinical Benefit Assessment (CBA) based on Time to Symptomatic *Worsening* would not be meaningful in a non-randomized trial. However, CBA based on Symptomatic *Improvement* may be used, since it would not be expected that patients would have improvement in symptoms without response to treatment. The components of, as well as interpretation of symptomatic improvement should be defined.

     Discussion: Sponsor agrees.

   - The effect of oxaliplatin would be better demonstrated by a randomized trial of oxaliplatin + 5-FU/LV vs. 5-FU/LV (Protocol EFC4760). Primary endpoint would be response rate at a specified time period (1^{st} or 2^{nd} evaluation).

   - We suggest performing hematology and serum electrolytes more frequently than every 3 weeks.

   - Since an adverse effect of oxaliplatin may be pulmonary fibrosis which can be fatal, consider excluding patients with symptomatic pulmonary fibrosis from these third line studies.

ADDITIONAL COMMENTS

- In the two randomized trials, we suggest you include patients with both measurable and non-measurable disease. Response rate should be evaluated only in patients with measurable disease.

- Please provide your Clinical Pharmacology and Biopharmaceutics development plan for the use of oxaliplatin alone and/or in combination for your proposed indications in advanced colorectal cancer.

ACTION ITEMS

➢ Sponsor will provide a proposal for final FDA review and agreement regarding the compassionate use program prior to the meeting with the patient advocacy groups in January 2001.

The meeting concluded at 9:45 am.

/S/

Christy Wilson
Consumer Safety Officer

Concurrence Chair:

/S/

Amna Ibrahim, M.D.
Medical Officer

/s/

Christy Wilson
2/7/01 03:42:18 PM

Amna Ibrahim
2/8/01 02:17:48 PM

INTERNAL MEETING MINUTES

MEETING DATE: August 25, 2000 **TIME:** 9:30 am **LOCATION:** I

IND/NDA: IND [redacted]

Meeting Request Submission Date: 07-21-00
Briefing Document Submission Date: 07-21-00
Additional Submission Dates: N/A

DRUG: Oxaliplatin

SPONSOR/APPLICANT: Sanofi-Synthelabo

TYPE OF MEETING:

1. End-of-Phase 2 meeting #3

2. **Proposed Indication:** First line colorectal cancer

FDA PARTICIPANTS:
Dr. John Johnson, Medical Team Leader
Dr. Amna Ibrahim, Medical Reviewer
Dr. Richard Pazdur, Division Director
Dr. Gang Chen, Statistics Team Leader
Dr. Mark Rothmann, Statistics Reviewer
Christy Wilson, Consumer Safety Officer

MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated July 21, 2000.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **Does the Division agree with the proposed statistical analysis for the final analysis of survival?**

   FDA RESPONSE:

   - Yes.

   In addition, Sanofi-Synthelabo would like to know the Division's position on having all analyses performed with a one-sided test?

   FDA RESPONSE:

   - No.

2. **Does the Division agree that a comparison of the single agent oxaliplatin arm (Arm B) to the 5-FU/LV alone arm (Arm A), and the comparison of the oxaliplatin alone arm (Arm B) to the 5-FU/LV + oxaliplatin arm (Arm C) does not need to be performed to support the potential submission for conditional approval?**

   FDA RESPONSE:

   - Yes.

   - Survival is a clinical endpoint and an improvement in survival for this endpoint would suffice for full approval. Conditional approval is not anticipated.

3. **Does the Division agree with the use of this minimization technique for treatment allocation?**

   FDA RESPONSE:

   - Because a patient's known characteristics may dictate which treatment they will receive, minimization (particularly when Center is used as stratification factor) can lead to bias with respect to non-stratified factors. If a patient's characteristics dictate that they will be in the control group, they may be dissuaded from entering the study (they can always receive this treatment without being on study). As a stratification factor, we prefer country/region instead of center.

4. **Does the Division agree that this is acceptable?**

   FDA RESPONSE:

   - Yes.

   Sanofi-Synthelabo plans to submit the statistical analysis plan prior to any patient entry; does the Division agree that this timing is acceptable?

   FDA RESPONSE:

   - Yes.

5. **Does the FDA agree with this change in proposed patient population?**

   FDA RESPONSE:

   - Yes.

6. **Does the Division agree that the prior dosing information does not need to be collected in this randomized Phase III study?**

   FDA RESPONSE:

   - Yes. However, the following should be collected: Start and stop dates for prior therapy, whether response was achieved and the date of response, and date of progression of disease.

7. **Does the Division have any additional comments regarding this protocol and the statistical analyses proposed?**

   FDA RESPONSE:

   - We recommend that the final analysis be performed based on a pre-specified total number of deaths between the 5-FU/LV arm and the combination arm.

   - Informative censoring (censoring subjects who receive second-line therapy) violates the censoring assumptions needed for the log-rank (Wilcoxon) test and Kaplan-Meier estimation. Such results will not be interpretable – p-values and estimates are calculated based on assumptions that do not hold.

   - Cause and effect relationships cannot be drawn from adjusting one response variable (survival) by another response variable (second-line treatment included as a time dependent covariate).

   - Subgroup analyses are strongly discouraged. All subgroup analyses should be pre-specified with multiplicity adjustments, not post-hoc – determined by baseline factors associated with higher or lower probabilities of receiving second-line therapy.

   - Definition of time to worsening for Clinical Benefit: Death without worsening should be censored and not counted as an event.

   - In Table 2, 4/8, worsening must persist for 4 weeks or until death or Disease Progression. However, improvement must persist for 4 weeks *without* death or progressive disease.

   - Each component of clinical benefit response should be analyzed separately in addition to the combined components.

   - Cross-over design will not be acceptable to review the protocol for survival as an endpoint (discussed at the meeting with NCI).

   - In the event of Grade IV diarrhea, dose modification *should* occur with the *next* cycle. (refer to section 5.1.5.1.2, page 28/102 of protocol)

- Because of propensity for diarrhea, electrolyte panel could be included in the routine laboratory blood work. Abnormal electrolytes could possibly affect performance status by causing weakness and lethargy.

- Suggest including the duration of adverse event in section 9.3.3 when evaluating safety.

8. **A) Does the Division agree with this proposal?**
   B) Does the Division have any recommendations regarding how best to address this as an alternative endpoint for full approval in the protocol and/or statistical analysis plan?

   FDA RESPONSE:

   - There can be only one primary endpoint. Classically, survival benefit has been the primary endpoint for approvability. Clinical benefit response assessment can be a secondary endpoint. Clinical benefit has not been the basis for marketing approval for any drug for this use. However, it may be used to demonstrate approvability if clinical benefit is shown in case the primary endpoint of survival is not met, provided:

     - ♦ It is supported by better RR and TTP.

     - ♦ It is a very large effect or confirmed in a 2nd randomized, controlled trial.

   - Clinical benefit is subjective and the trial is not blinded. The clinical benefit response assessment endpoints must be pre-specified in the protocol. Symptoms to be used to show this clinical benefit must also be pre-specified. These have been provided by the sponsor in the second meeting package.

9. **A) Does the Division agree that this is adequate to support this endpoint as an alternative endpoint to support full approval?**

   FDA RESPONSE:

   - The detailed analysis methods should be included in the statistical analysis plan, which is submitted prior to the randomization of the first patient to treatment.

   B) Would the Division require pre-specified null and alternative hypotheses for the clinical benefit response rate and time to worsening?

   FDA RESPONSE:

   - Yes.

10. Does the Division have any specific comments/concerns regarding the proposed case report forms?

FDA RESPONSE:

- To be given after protocol is resubmitted.

OTHER COMMENTS

- TTF should be removed as a secondary endpoint.
- Please refer to the NCI discussion where correlations for time to disease related symptom progression were addressed.

There were no action items or unresolved issues. The meeting concluded at 10:30 am.

S S

Christy Wilson
Consumer Safety Officer

Concurrence Chair:

Amna Ibrahim, M.D.
Medical Officer

/s/

Christy Wilson
2/7/01 03:30:43 PM

Amna Ibrahim
2/8/01 02:14:01 PM

COPY

MEETING MINUTES

MEETING DATE: June 8, 2000 **TIME:** 9:30 am **LOCATION:** G

IND/NDA: IND —

Meeting Request Submission Date: 04-11-00
Briefing Document Submission Date: 05-18-00
Additional Submission Dates: N/A

DRUG: Oxaliplatin (SR96669)

SPONSOR/APPLICANT: Sanofi Pharmaceuticals, Inc.

TYPE OF MEETING:

1. End-of-Phase 2

2. **Proposed Indication:** First line colorectal cancer

FDA PARTICIPANTS:
Dr. Richard Pazdur, Division Director, HFD-150 (industry- only)
Dr. John Johnson, Medical Team Leader, HFD-150
Dr. Steven Hirschfeld, Medical Reviewer, HFD-150
Dr. Fumitaka Nagamura, Medical Fellow, HFD-150
Dr. Gang Chen, Statistics Team Leader, HFD-150 (industry- only)
Dr. Mark Rothmann, Statistics Reviewer, HFD-150
Christy Wilson, Consumer Safety Technician, HFD-150
Dr. Eric Duffy, Chemistry Team Leader, HFD-150
Dr. James Krook, ODAC (pre- only)

INDUSTRY PARTICIPANTS:
Dr. Robert Bigelow, Statistics, Sanofi
Dr. Richard Gural, Drug Regulatory Affairs, Sanofi
Dr. Nassir Habboubi, Clinical Research, Sanofi
Mark Moyer, Drug Regulatory Affairs, Sanofi
Dr. Nathlie LeBail, Clinical Research, Debiopharm
Dr. Martine Bayssas, Debiopharm Clinical Research
Dr. Sunil Gupta, Medical Affairs, Sanofi

Dr. Alain Herrera, Oncology Business Unit, Sanofi
Dr. Thomas Strack, Regulatory Affairs, Lilly

Dr. Percy Ivy, NCI Representative

MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated May 18, 2000.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **Since there are numerous options for study designs, does the Division agree with the proposed design?**

   FDA RESPONSE:

   - The Division agrees with the study design of a three armed randomized trial using oxaliplatin, versus oxaliplatin plus infusional 5-FU/LV versus infusional 5-FU/LV as the regimens. The primary endpoint would be survival with response rate as a secondary endpoint.

2. **Does the Division agree with the proposed response rate analysis to potentially support conditional approval if a significant difference is demonstrated with 5-FU/LV + oxaliplatin?**

   FDA RESPONSE:

   - Yes, the FDA agrees with response rate as a surrogate that may support conditional approval for second line therapy in patients with colorectal cancer who have relapsed less than 6 months following CPT-11 and 5-FU/LV. The NDA should not be submitted until all patients have been enrolled. The results should demonstrate a response rate that is clinically meaningful as well as showing a statistically significant difference over control. Approval determination would still be dependent upon a risk-benefit analysis.

3. **Does the Division agree that this proposed study would support full approval of the claim, "Eloxatine™ (oxaliplatin) is indicated for patients with advanced colorectal cancer who have progressed on first-line 5-FU/LV + CPT-11"?**

   FDA RESPONSE:

   - Yes, the proposed study could support full approval if a meaningful difference in survival were demonstrated.

   SPONSOR CLARIFICATION REQUEST:

   Due to the availability of oxaliplatin in the U.S. Compassionate Use study (LTS 7072A), do you have any advice on how to address the potential impact of crossovers to oxaliplatin on the 3-arm study?

   FDA Response:

   - FDA to discuss internally and forward response to Sanofi at a later date.

4. **Would the Division require an additional study in this patient population or another patient population to support full approval?**

   FDA RESPONSE:

   - The FDA would highly recommend an additional study to support any conclusions. An alternative additional study could be designed to enroll patients that had received 5-FU/LV as initial therapy for metastatic colorectal cancer and would randomize patients to either CPT-11 or CPT-11 plus oxaliplatin.

   SPONSOR STATEMENT:

   Sanofi-Synthelabo is committed to performing an additional study. Sanofi-Synthelabo will submit a proposed study design and synopsis within 4-6 weeks for discussion at a future meeting or teleconference.

5. **Would the Division consider inclusion of patients who have been only previously treated with 5-FU/LV + CPT-11 for metastatic disease?**

   FDA RESPONSE:

   - Yes, but the question requires explanation.

   SPONSOR CLARIFICATION AND QUESTION:

   The sponsor asked this question to determine FDA's position regarding patients who have relapsed less than 6 months following adjuvant therapy with 5-FU/LV + CPT-11. Based on discussions with external experts, Sanofi-Synthelabo proposes to exclude these patients. Does the FDA agree with this proposal?

   FDA RESPONSE:

   - Yes.

6. **Does the Division agree that clinically adjudicated progression (no scan documentation for submission) on prior therapy is adequate for enrollment to this Phase III randomized study?**

   FDA RESPONSE:

   - No, all patients who are enrolled should have scans documenting the previous response and the relapse.

SPONSOR CLARIFICATION REQUEST:

Previous response:

The proposed randomized study inclusion criteria do not include previous response.

a. Why does the FDA want this information collected?

FDA RESPONSE:

- Sponsor to submit protocol for FDA review and comment.

b. If this information is needed, will documentation on the CRF of best response with the method of determination and date be considered adequate?

FDA RESPONSE:

- Sponsor to submit protocol for FDA review and comment.

c. If FDA will require collection of the scans, will FDA also require submission of these scans for review?

FDA RESPONSE:

- Sponsor to submit protocol for FDA review and comment.

Relapse or progression:

d. Will FDA require scans to be collected, or will documentation on the CRF of the relapse or progression with method of determination and date be considered adequate?

FDA RESPONSE:

- No. Documentation on the CRF will be adequate.

e. If FDA will require collection of the scans, will FDA also require submission of these scans for review?

FDA RESPONSE:

- N/A

7. **Based on the table above, what studies and data would be required to support conditional approval of this product in a specific patient population who have progressed after 5-FU/LV + CPT-11 or after second-line CPT-11?**

   FDA RESPONSE:

   - The 3-arm randomized study may be adequate by itself to support accelerated approval. Regarding studies EFC 2970 and LTS 7072, see the response to question #9.

8. **What kind of labeling indication would this support?**

   FDA RESPONSE:

   - Labeling would be for an indication based on the population studied. Accelerated approval labeling would state that the approval is based on a surrogate marker (response rate) and that clinical benefit has not been demonstrated.

9. **If studies EFC2970 and LTS7072 are only supportive of conditional approval and/or full approval, would documentation of prior therapy and response to prior therapy still be required?**

   FDA RESPONSE:

   - All patients submitted to support an approval, whether accelerated or standard, should have full information that includes the initial regimen with doses and dates, the response to the initial regimen, the last date of therapy, and documentation of the date, sites and measurements of relapse.

   SPONSOR CLARIFICATION REQUEST:

   In the fax dated April 4, 2000, FDA raised the question regarding the 5-FU holiday and the ability to interpret the results from EFC2970 and LTS 7072.

   a. **Does FDA still consider this a concern?**

      FDA RESPONSE:

      - Yes.

   b. **Would FDA ever consider these studies as the basis of a claim in patients who have progressed on first-line 5-FU/LV and subsequent second-line CPT-11?**

      FDA RESPONSE:

      - No. Data collection not necessary since these studies will not be used to support the claim.

- Consider a study for single-agent to demonstrate benefit in third-line patients. Response and symptom improvement would be acceptable endpoints.

ADDITIONAL STATISTICAL COMMENTS

- All analyses should be based on ITT principles and include all patients as randomized.

- Fisher's exact test should be used in comparing response rates. The unadjusted log-rank tests should be used in comparing survival.

SPONSOR REQUEST FOR CLARIFICATION:

Would the Agency agree to a log rank test, stratified for prognostic factors that are also used as strata in the treatment allocation, as the primary analysis?

FDA RESPONSE:

➢ Yes. (Based on FDA's review of the protocol- to be submitted by sponsor).

- Please clarify what value for median survival of the oxaliplatin alone arm was used (8 months or 11 months) for sample size calculations. Conflicting information on this median survival time was submitted in sections 1.1 and 2.4.

SPONSOR CLARIFICATION:

The oxaliplatin single agent median survival estimate is 8 months, the 5-FU/LV is 8 months, and the 5-FU/LV + oxaliplatin is 11 months. Sample size calculations were based on these median survival estimates.

- Should both experimental arms win in their comparisons with the control arm (with respect to survival at final analysis or response rate at interim analysis), these experimental arms will need to be compared with a closed test procedure- a one-sided 0.05 level test having an alternative hypothesis that the combination arm is superior.

SPONSOR'S ADDITIONAL QUESTIONS FOR DISCUSSION

10. Does the FDA agree to the submission of scans documenting responders only?

FDA RESPONSE:

- No scans needed.

11. Does the FDA find electronic submission of scans helpful to the review process?

FDA RESPONSE:

- N/A

ACTION ITEMS

- FDA to discuss Item #3 internally and forward comments to Sanofi.
- Sanofi to submit protocol and follow-up meeting/telecon request for FDA review and comment. (Timeframe: 2-3+ weeks).

The meeting concluded at 10:45 am.

/S/
Christy Wilson 8/8/00
Consumer Safety Technician

Concurrence Chair:

/S/
Steve Hirschfeld, M.D. 8/9/00
Medical Reviewer

cc:
Original IND [redacted]
HFD-150/Div File
HFD-150/Johnson/Hirschfeld/GChen/Rothmann/Duffy/Wilson/Nagamura/Pazdur
drafted by: CWilson, 08-08-00
c:\mydocuments\ind\ [redacted] meetings\mins2ndeop2.doc

MEETING MINUTES

MEETING MINUTES

MEETING DATE: March 22, 2002 **TIME:** 2:30 pm **LOCATION:** G

IND/NDA: IND — **Meeting Request Submission Date:** 03-15-02
Briefing Document Submission Date: 03-15-02
Additional Submission Dates: 03-19-02 and 03-21-02

DRUG: Oxaliplatin

SPONSOR/APPLICANT: Sanofi-Synthelabo

TYPE OF MEETING:

1. Pre-NDA guidance meeting

2. **Proposed Indication:** Colorectal cancer

FDA PARTICIPANTS:

Dr. Richard Pazdur, Division Director
Dr. John Johnson, Medical Team Leader
Dr. Amna Ibrahim, Medical Reviewer
Dr. Raji Sridhara, Statistical Reviewer (Acting Team Leader)
Dr. Grant Williams, Deputy Director (Industry meeting only)
Patricia Delaney, Assoc. Dir., Cancer Liaison Program, OSHI (Industry meeting only)
Christy Wilson, Consumer Safety Officer

SPONSOR PARTICIPANTS:

Mark Moyer, Director, Regulatory Affairs
Dr. Sunil Gupta, Senior Director, Clinical Development, Oncology
Dr. Carlos Garay, Director, Clinical Development
Dr. Paul Juniewicz, Senior Director
Dr. Nassir Habboubi, Vice President, Clinical Research
Dr. Richard Gural, Vice President, Regulatory Affairs
Dr. Robert Bigelow, Statistician, Oncology

MEETING OBJECTIVES:

To review and discuss the positive results obtained from the ongoing oxaliplatin study EFC4584, and to discuss proposed timing of the NDA submission. To discuss sponsor's questions in the briefing document dated March 19, 2002.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **Based on the Statistical Analysis Plan, the endpoints submitted in the pre-meeting package are the only endpoints that Sanofi-Synthelabo plans to analyze for this NDA. Based on your review of these results are there any additional data displays or analyses that should be performed for inclusion in the NDA? Specifically, does the FDA want any further analysis of clinical benefit?**

   FDA RESPONSE:

   - The pre-specified analyses in the protocol regarding the clinical benefit assessment should be submitted. This includes pair-wise comparisons among the three treatment arms with the log rank test and analyses of clinical benefit comparing the three arms in terms of proportion of patients who are symptomatic at baseline and who show improvement while on treatment, using Fisher's exact test. Please submit survival data without comparative analysis.

   Discussion: The following bullet was added after discussion:

   - Submit survival data based on the cut-off date of December 18, 2001.

2. **Sanofi-Synthelabo has had all scans digitally prepared and evaluated by an independent radiology group. Does the FDA want scans submitted for all responders based on the investigator and independent assessments?**

   FDA RESPONSE:

   - Yes.

3. **Due to data collection and entry requirements for an ongoing study within Sanofi-Synthelabo, the database has data beyond the 18 December 2001 cut-off date. The data beyond the 18 December 2001 is incomplete, since it does not contain data for all patients or complete data for an individual patient. The 18 December 2001 cut-off date will be utilized for all data displays and analyses. Tumor measurements for confirmation of responders that became available after 18 December 2001 have been utilized for the response analysis and will be included in the database. Does the FDA agree with the approach for the data cut-off for data displays and analyses? Does the FDA have a preference on whether the additional data beyond 18 December 2001 remains in the database, or is removed from the database submitted with the NDA?**

   FDA RESPONSE:

   - Data after the cut-off date should not be submitted, unless it assists in confirming a response attained. This data should be provided for patients in all three arms. Please provide both confirmed and unconfirmed response rates up to December 18, 2001.

   - In the electronic datasets, especially in table NEWL, where only the visit numbers are given, please give the dates of the visits as well.

4. **Will the FDA grant Fast-Track designation to this product to allow a rolling NDA submission?**

   FDA RESPONSE:

   - Yes.

   - Please be reminded that all pre-submissions must be complete, reviewable sections of the NDA.

   Discussion: The sponsor explained that the clinical data would be ready for submission shortly. However, the Integrated Summary of Safety was the rate-limiting factor in submitting the complete clinical section of the NDA. The Division agreed to check with Randy Levin about whether the Division could accept the clinical data early (before the ISS was completed) as an incomplete clinical section of the rolling NDA. The Division also agreed to follow-up on a comprehensive Table of Contents for the electronic NDA.

OTHER COMMENTS

- As a reminder, User Fees will need to be paid for this NDA, since it provides for a new indication with new, unreviewed clinical data.

- In order to facilitate a timely review, it is suggested that questions can be sent to Sanofi-Synthelabo by e-mail (secure, if necessary), with responses sent back to the reviewer by the same route. All e-mails must be copied to the Project Manager.

- Is the NDA submission still planned for June 2002?

Discussion: The sponsor confirmed that the last section of the rolling NDA submission was still planned for June, with several sections of the NDA ready for submission immediately.

ACTION ITEMS:

- FDA to check with Randy Levin about whether the Division could accept the clinical data early (before the ISS was completed) as an incomplete clinical section of the rolling NDA. **DONE: Grant Williams- 3/26/02. The Division will accept the clinical data early as an incomplete clinical section of the rolling NDA.**

- FDA to follow-up on a comprehensive Table of Contents for the electronic NDA. **DONE: Christy Wilson- 3/28/02. The sponsor may not re-submit already submitted sections of the NDA with a comprehensive, hyper-linked Table of Contents. Each section of the rolling NDA should have its own Table of Contents, and may reference the date of submission of previous sections of the NDA instead of hyperlinking to those previous submissions.**

- Sponsor to request Fast Track designation and an NDA number prior to submission of the first section of the rolling NDA.
- Sponsor to submit tradename for preliminary review as soon as possible.
- Sponsor to provide a plan for compassionate use and for patients receiving oxaliplatin alone.

There were no unresolved issues. The meeting concluded at 4:00 pm.

/S/ /S/

Concurrence Chair:

Christy Wilson
Consumer Safety Officer

Amna Ibrahim, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
4/2/02 08:05:00 AM
Draft minutes signed by RSridhara on 3-29-02; by AIbrahim on 4-1-02

Amna Ibrahim
4/2/02 10:41:01 AM

MINUTES OF TELECONFERENCE

MEETING DATE: January 28, 2002 **TIME:** 12:00 pm **LOCATION:** A

IND/NDA: IND [redacted] **Meeting Request Submission Date:** by email on 01-11-02
Briefing Document Submission Date: by email on 01-11-02
Additional Submission Dates: N/A

DRUG: Oxaliplatin

SPONSOR/APPLICANT: Sanofi-Synthelabo

TYPE OF MEETING:

1. Other- Clarification of comments from Pre-NDA logistics meeting

2. **Proposed Indication:** Colorectal cancer

FDA PARTICIPANTS:
Dr. Richard Pazdur, Division Director
Dr. John Johnson, Medical Team Leader
Dr. Amna Ibrahim, Medical Reviewer
Dr. Gang Chen, Statistics Team Leader
Dr. Mark Rothmann, Statistics Reviewer
Joann Minor, Associate Director, Cancer Liaison Program, OSHI
Christy Wilson, Consumer Safety Officer

SPONSOR PARTICIPANTS:
Remi Castan, Clinical Research
Nassir Habboubi, Clinical Research
Carlos Garay, Clinical Research
Sunil Gupta, Clinical Research
Brent Berger, Biostatistics
Bob Bigelow, Biostatistics
Tom Guinter, Clinical Information Systems
Mark Mariani, Drug Regulatory Affairs
Mark Moyer, Drug Regulatory Affairs

MEETING OBJECTIVES:

To provide clarification on specific comments made during the Pre-NDA logistics teleconference held on December 18, 2001.

BACKGROUND INFORMATION:

The sponsor sent the following information to the Division by e-mail on January 11, 2002 in preparation for this teleconference.

Databases - We did not make a specific proposal; therefore, we are not certain how to interpret your statement that the proposal is fine. Our proposal would be to include: EFC4584 study database as one dataset and the ISS database (as originally formatted) from the previously withdrawn NDA as another dataset. This would provide the safety data requested. The ISS database has datafield names that sometimes are not exactly the same names as in the EFC4584 database, but maintaining the database in the current format ensures that the programs utilized by both Sanofi-Synthelabo and FDA previously will still run properly. There are also some other differences that make it seem more appropriate to maintain the current ISS database as it currently exist, and separate from the EFC4584 database. Details of these differences can be discussed during the teleconference.

Time Related Efficacy Parameters - Please clarify if the request for analysis of these parameters if 50% of the patients have an event is for the 450 patients in the response rate analysis, or the overall study population of around 786 patients. Please also clarify which parameters that FDA would like included. It would be helpful to specifically discuss FDA's expectations during a teleconference, since Sanofi-Synthelabo is willing to provide what is requested.

DISCUSSION:

Regarding the Databases: The Division stated that the format used in the previous NDA submission was acceptable and preferred. The Division asked whether the sponsor was planning to submit a pooled analysis as well. The sponsor said that it would be difficult to match the different grading systems, but that they plan to provide a representation of all studies. They further explained that the study report databases would include more information, and would be comprehensive by study. The Division requested that all information be submitted with the NDA.

Regarding the Time-Related Efficacy Parameters: The Division explained that the 50% is out of the number of patients that are relative to the particular endpoint. The Division reminded the sponsor that they are to submit to the FDA the same data that is sent to the Data Safety Monitoring Board. The Division further clarified that if the sponsor has 50% of the patients, they should do an analysis. If they have less than 50% of the patients, they should not do an analysis, but the Division still wants to see the information.

The sponsor informed the Division that they anticipate submitting the NDA in June 2002.

There were no action items or unresolved issues. The meeting concluded at 12:45 pm.

/S/

Christy Wilson
Consumer Safety Officer

Concurrence Chair:

/S/

Amna Ibrahim, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
2/19/02 11:50:00 AM
Draft minutes signed by AIbrahim on 2-12-02 and by MRothmann on 2-13-02

Amna Ibrahim
2/20/02 04:16:40 PM

INTERNAL MEETING MINUTES

MEETING DATE: December 11, 2001 **TIME:** 12:30 pm **LOCATION:** B

IND/NDA: IND —— **Meeting Request Submission Date:** 10-24-01
Briefing Document Submission Date: 11-19-01
Additional Submission Dates: 12-17-01 (fax)

DRUG: Oxaliplatin

SPONSOR/APPLICANT: Sanofi-Synthelabo

TYPE OF MEETING:

1. Pre-NDA logistics meeting

2. **Indication:** Colorectal cancer

FDA PARTICIPANTS: Dr. Richard Pazdur, Division Director
Dr. John Johnson, Clinical Team Leader
Dr. Amna Ibrahim, Clinical Reviewer
Dr. Chengyi Liang, Chemistry Reviewer
Dr. Gang Chen, Statistics Team Leader
Dr. Mark Rothmann, Statistics Reviewer
Dr. Brian Booth, Biopharmaceutics Reviewer
Dr. Lilia Talarico, Detail, Special Assistant to the Director
Christy Wilson, Consumer Safety Officer

MEETING OBJECTIVES:

As identified by the sponsor in the background package dated November 19, 2001, the meeting objectives are:

- Review previous written agreements to ensure clarity
- Gain concurrence on data to support the response rate analysis, including safety and efficacy, to support proposed regimen
- Gain concurrence on NDA content and a proposal to limit the number of overlapping summary documents, since this NDA will be based on one study, EFC4584
- Review of a mock Item 11 electronic submission, including data for 3 representative EFC4584 patients
- Review patient profile content for ease of review
- Electronic archival submission: timing, content, format
- Review of overall NDA timing

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

The questions were divided into sections. The section titles precede the questions.

PREVIOUS WRITTEN AGREEMENTS

1. **Does the Division have any further clarifications that should be made to ensure agreement?**

   FDA RESPONSE:

   - You are referred to the correspondence exchanged since the submission of the initial protocol.

   - Regarding Sanofi's submission 343 dated March 9, 2001, which addressed the comment in Item #3, we would like to clarify that the statistician had found your proposal acceptable and had no additional comments.

NDA CONTENT

1. **Does the Division agree with the proposed studies for submission in Item 8 of this NDA as outlined in the NDA Content Proposal document (Appendix 1)?**

   FDA RESPONSE:

   - Inclusion of scientific rationale and purpose will be required. The omissions suggested are otherwise acceptable. Safety datasets and study reports for EFC2961, 2964 and 2962 should be submitted.

2. **Does the Division agree that individual patient data listings do not need to be included in the EFC4584 study report since the electronic database and patient profiles will be provided in Item 11 of the NDA?**

   FDA RESPONSE:

   - Yes.

3. **Does the Division agree with the proposal to omit or substitute the overlapping summaries contained in NDA Items 3 and 8 as outlined in the NDA Content Proposal document (Appendix 1)?**

   FDA RESPONSE:

   - No. Item 3.2: Scientific rationale and purpose will be required.

4. **Does the Division agree with the proposed approach for presenting safety and efficacy in the package insert?**

   FDA RESPONSE:

   - Yes. The safety databases from EFC 2961, 2962 and 2964 should be submitted.

5. **Does the Division agree with the proposal for the Integrated Safety Summary (ISS) to support this NDA?**

   FDA RESPONSE:

   - Yes. Please confirm that the cut off date for safety in the NDA will be 12-18-01.

DATA TO SUPPORT NDA

1. **Does the Division agree with Sanofi-Synthelabo's proposed data cut-off and the plan for handling late-occurring responses (CR and PR) to support an NDA based on the response rate analysis?**

   FDA RESPONSE:

   - Yes. Also, individual tumor measurements must be submitted to verify the investigator evaluations.

2. **Does the Division anticipate additional requests for updated data during the review?**

   FDA RESPONSE:

   - No further requests are anticipated at this time for updated data.

3. **If yes, is there any particular data parameter the Division would like to see?**

   FDA RESPONSE:

   - N/A.

4. **Does the Division want the survival and other secondary time-related parameters summarized in the EFC4584 response rate report?**

   FDA RESPONSE:

   - If the sponsor has looked at the survival data, the significance level for the final analysis needs to be adjusted appropriately. Any analyses performed either on survival or on any secondary endpoint need to be submitted with the NDA.

ITEM 11 ELECTRONIC SUBMISSION

1. **Are the content and format of the efficacy/safety datasets intended for submission adequate to support the Division's review of EFC4584?**

   FDA RESPONSE:

   - Yes.
   - We should receive all raw datasets for each individual patient.
   - Please provide definitions for rows, columns, and table content.

2. **Does FDA find that the documentation provided for the EFC4584 database is adequate?**

   FDA RESPONSE:

   - Yes.

3. **Does the Division have any comments on the patient profiles intended for submission in the NDA?**

   FDA RESPONSE:

   - These appear helpful. However, please provide a decode for various headings (at the time of submission of the NDA) in order to clarify certain points:
     - For example, why is the 'End date of Saltz to randomization' a number and not a date?
     - Do 'Days from last dose to off-study' pertain to the prior Saltz regimen or the current study drugs?
     - Do the numbers in the AE columns pertain to the grade of AE?

ITEM 11 ELECTRONIC SUBMISSION- HUMAN PK DATA

1. **Is the content and format of the PK database intended for submission adequate to support the Division's review of human pharmacokinetics?**

   FDA RESPONSE:

   No. Please make the following additions/corrections/inclusions:

   - Include the creatinine clearances for each patient in the electronic databases.

- Include the plasma concentration of 5-FU and demographic data for the patients/subjects in studies INT 3681 and INT 3682 in the electronic database.

- Include the in vivo biotransformation data for study PKM2983, part 1 in the electronic database.

2. **Does FDA find that the documentation adequately describes the database?**

   FDA RESPONSE:

   - Yes.

ELECTRONIC ARCHIVAL PROPOSAL

1. **Does the Division agree that the electronic archival copy can also serve as the review copy, i.e., no paper documents will be submitted except those requiring an original signature?**

   FDA RESPONSE:

   - No. See #2 below.

2. **If FDA requires a paper review copy, Sanofi-Synthelabo will submit a paper review copy of the portions of the technical sections, as required in the 1999 electronic submission guidance, for Items 4, 5, 6, and 8. If Sanofi-Synthelabo opts to make a pre-submission, does the Division agree that the paper review copy of the pre-submission does not need to be provided again at the time of the complete NDA submission?**

   FDA RESPONSE:

   - In addition to Items 1, 2, and 3, and the technical sections of the NDA identified above, the reviewers have identified the following items that they request be submitted in paper form:

     Clinical – Items 11, 12, and all study reports. (Only CRF's for SAE's and deaths need to be submitted)

     Clinical Pharmacology – All study reports.

     Statistics – Reports of all analyses.

   - You will not be required to resubmit these if submitted prior to the complete NDA submission.

3. **For FDA's convenience, Sanofi-Synthelabo will provide paper desk copies of the Item 3 NDA Summary and CDs containing the line-numbered proposed labeling document in Microsoft Word.**

   a. **How many paper desk copies of the Item 3 NDA Summary does the Division require?**

      FDA RESPONSE:

      - Please submit 15 desk copies of the NDA Summary volume.

   b. **Which version of Microsoft Word is currently being used in the Division?**

      FDA RESPONSE:

      - Word 95 and 97.

   c. **How many CDs containing the line-numbered proposed labeling does the Division require?**

      FDA RESPONSE:

      - One- submitted to the Project Manager.

4. **Does the Division require the 3 review copies of the CMC analytical methods validation, and 4 review copies of the draft labels and labeling?**

   FDA RESPONSE:

   - The CMC section should include the information of analytical method validation. However, the finalized method validation package is submitted just after the approval of an NDA (one copy is for the review Division and the other two copies are for FDA laboratories).

NDA TIMING

1. **Will the Division accept the 4-month safety update as the safety submission required at approval?**

   FDA RESPONSE:

   - Complete safety data will be required at the time of NDA submission. 4- month safety update will be acceptable as part of the safety submission for accelerated approval. For an accelerated approval, we need the safety update at 3 months.

OTHER COMMENTS

NDA/sNDA Presentations to CDER's Division of Oncology

- The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

  These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

  Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

Financial Disclosure Final Rule

- We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety.

  Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

Pediatric Final Rule

- Please note that you will need to address the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA unless your product/indication has been designated an Orphan Drug. You may be eligible for a waiver under 21 CFR 314.55(c). Please refer to http://www.fda.gov/ohrms/dockets/98fr/120298c.txt.

Pediatric Exclusivity

- Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if Oxaliplatin is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Request (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "*Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act*" at Drug Information Branch (301) 827-4573 or http://www.fda.gov/cder/guidance/index.htm. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at http://www.fda.gov/cder/guidance/3756dft.htm.

The Division faxed responses to the sponsor on December 11, 2001. The sponsor then sent "Requests for Clarification" back to the Division on December 17, 2001. However, the Division determined that more time would be needed to review some of the clarification questions. The Division agreed to answer the clarification requests as soon as possible and fax the responses to the sponsor. The "Requests for Clarification" are listed below.

CLARIFICATIONS

1. **Sanofi-Synthelabo has safety databases for individual studies EFC2961, 2964 and 2962, as well as an Integrated Summary of Safety (ISS) database containing safety data for all three studies. In the integrated database some adverse events and pre-listed toxicities have been recoded to ensure consistency for pooling of data. The primary study EFC4584 safety database is in a different format, which is more in agreement with FDA's ESUB guidance. Can the FDA provide further details on what datasets the Agency would like to receive in the NDA submission?**

   FDA RESPONSE:

   [DEFERRED]

2. **Sanofi-Synthelabo has been asked by the EFC4584 independent data safety monitoring committee (DSMC) to provide statistical analysis of the primary survival endpoint and other time-related endpoints prior to the NDA submission. These analyses would be confidential and would be known only to an in-house statistician and the DSMC. Persons involved with the conduct of the study will not see these analyses. Sanofi-Synthelabo is of the opinion that providing these analyses to the DSMC does not inflate the type I error and will not require adjustment in the final analysis. Does the FDA concur? Does the FDA want any analyses of time-related parameters [(1) Time to Symptom Worsening (TTSW), (2) Time to Progression (TTP), (3) overall survival, etc] submitted in the NDA, or will response rate alone with safety and dosing information be sufficient? Does FDA want calculated time-related parameters to be included on the database for individual patients, even if no analysis is done?**

   FDA RESPONSE:

   [DEFERRED]

3. **Sanofi-Synthelabo proposes to fulfill FDA's request for in vivo biotransformation data for study PKM2983, part 1 by providing the percentage of platinum for each of the separated metabolites in plasma and urine on a per subject basis. Where available, the identity of the component will be provided. Also to be included will be the standard demographic information on these patients as given in the other ESUB data sets. Does FDA agree that this represents the data request?**

   FDA RESPONSE:

   - Yes.

4. **Regarding the NDA Esub, Sanofi-Synthelabo would like to clarify the intended format of the submission contents. We propose to submit the archival NDA copy as a fully electronic submission in accordance with the 1999 Guidance for Industry, "Providing Regulatory Submissions in Electronic Format - NDAs". In addition, we propose to provide a full paper review copy of all Items with the exception of Item 11 (CRTs) and Item 12 (CRFs). These items will be provided in full in the electronic submission. [Please note that per the Esub Guidance the paper review copy of Item 10 (Statistical) will be a duplicate of Item 8, but jacketed for the statistician.]**

   FDA RESPONSE:

   [DEFERRED]

5. **Additionally, per your request, 15 desk copies of the NDA Summary volume will be submitted along with a CD containing the line-numbered proposed labeling document.**

   Does the Division find the clarification above acceptable?

   - Yes.

Other than the "Requests for Clarification" listed above, the sponsor felt no further discussion was needed and cancelled the teleconference scheduled for December 18, 2001.

The internal meeting concluded at 1:15 pm.

/S/ /S/

Christy Wilson
Consumer Safety Officer

Concurrence Chair:

Amna Ibrahim, M.D.
Medical Officer

ADDENDUM TO MEETING MINUTES

In response to the "Requests for Clarification," the Division forwarded the following comments to the sponsor by facsimile transmission on December 21, 2001.

1. The safety databases as proposed are acceptable.

2. Regarding time to event endpoints, the FDA would like this information submitted for each individual patient. If more than 50% of the patients have had an event, a statistical analysis should be submitted. If patients, investigators and Sanofi are still blinded to this information, the FDA will make every effort not to disclose it publicly, e.g., in relation to a Public Advisory Committee meeting.

   If a statistical analysis is done for the DSMC, a statistical adjustment must be made for subsequent analyses.

3. The proposal regarding the e-submission is acceptable.

/S/ /S/

concurrence:

Christy Wilson
Consumer Safety Officer

Amna Ibrahim, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
1/11/02 11:04:33 AM

Amna Ibrahim
1/24/02 01:51:32 PM

INTERNAL MEETING MINUTES

MEETING DATE: July 29, 2002 **TIME:** 3:30 pm **LOCATION:** B

IND/NDA: NDA 21-492

Meeting Request Submission Date: N/A
Briefing Document Submission Date: N/A
Additional Submission Dates: N/A

DRUG: Eloxatin (oxaliplatin) for Injection

SPONSOR/APPLICANT: Sanofi-Synthelabo, Inc.

TYPE OF MEETING:

1. Pre-Approval Safety Conference

2. **Proposed Indication:**
   Eloxatin in combination with infusional 5-FU/LV is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan.

   The approval of Eloxatin is based on response rate and an interim analysis of time to radiographic progression. No results are available from controlled trials at this time that demonstrate a clinical benefit, such as improvement of disease-related symptoms or increased survival.

PARTICIPANTS:

Dr. Donna Griebel
Dr. Atik Rahman
Dr. Brian Booth
Dr. Anne Zajicek
Dr. Steven Hirschfeld
Dr. Julie Beitz
Dr. Susan Lu
Dr. Kate Phelan
Dr. Mark Avigan
Patrick Guinn
Christy Wilson

MEETING OBJECTIVES:

To identify potential expected adverse events that the Office of Drug Safety should be aware of for post-marketing surveillance.

DISCUSSION:

Dr. Griebel listed neurotoxicity, thromboembolic events, neutropenia, ataxia, and isolated incidences of cranial nerve palsies as potential adverse events to watch for post-marketing. She also explained the results of DMETS' tradename review and the potential for medication errors between Eloxatin and Cefoxitin and Loxitane. Dr. Griebel also noted a medication error problem between oxaliplatin and carboplatin and described 4 cases of overdosage where patients received oxaliplatin instead of carboplatin. Dr. Beitz suggested that the Division contact Jerry Phillips to discuss potential proactive measures that can be taken to educate pharmacists about this potential medication error. It was mentioned that similar education techniques were utilized to lessen the potential for confusion between carboplatin and cisplatin. Ms. Wilson noted that the Division plans to ask for a Phase 4 commitment to follow up on and report any medication errors that occur due to the tradename (similar to the Phase 4 commitment for Faslodex). Ms. Wilson also noted that the Division of Medication Errors and Technical Support agreed with this proposal.

Dr. Beitz inquired about the renal impairment issue. Dr. Griebel explained that the Division decided to remove the dosing recommendations from the labeling and include a statement that there is inadequate data to determine dose adjustments for renal impairment. Dr. Griebel further explained that the sponsor has agreed to this wording. Dr. Rahman noted that in the European and Australian labels for Eloxatin, it is contraindicated in patients with severe renal impairment. Dr. Rahman noted that the Division plans to ask for a Phase 4 commitment for a study in renally impaired patients.

Dr. Hirschfeld mentioned that sensitivity to cold exposure may be an issue. Dr. Gavigan asked whether the cold sensitivity was distinct to this drug. Dr. Griebel responded that it is unique to Eloxatin. She further noted that exposure to cold could bring on paresthesia. She also explained that the neurotoxicities seen with Eloxatin are not always reversible.

Dr. Phelan asked whether the adverse reactions of deafness and visual disturbances were related to neuropathy. Dr. Griebel replied that they were effects related to all platinum drugs and could be permanent. Dr. Lu asked whether myelosuppression was commonly seen with Eloxatin. Dr. Griebel said that neutropenia was most common.

Dr. Phelan noted that the occurrence of paresthesia appeared to be higher in younger patients. Dr. Griebel replied that a predominance of paresthesia in younger patients could be related to higher exposure to the drug and if they received more cycles.

Dr. Beitz asked if the Patient Package Insert has been reviewed. Ms. Wilson replied that Jeannine Best from the Division of Surveillance, Research, and Communication Support had reviewed the PPI.

The meeting concluded at 4:00 pm.

/S/

Christy Wilson
Consumer Safety Officer

Concurrence Chair:

/S/

Donna Griebel, M.D.
Medical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
7/31/02 11:38:12 AM

Donna Griebel
7/31/02 11:42:12 AM

INTERNAL MEETING MINUTES

MEETING DATE: May 10, 2001 **TIME:** 10:30 am **LOCATION:** A

IND/NDA: IND — **Meeting Request Submission Date:** 04-23-01
Briefing Document Submission Date: 04-23-01
Additional Submission Dates: N/A

DRUG: Oxaliplatin

SPONSOR/APPLICANT: Sanofi-Synthelabo

TYPE OF MEETING:

1. Other- Guidance

2. **Proposed Indication:** Colorectal cancer

FDA PARTICIPANTS: Dr. Richard Pazdur, Division Director
Dr. Amna Ibrahim, Medical Officer
Dr. Mark Rothmann, Statistician
Christy Wilson, Consumer Safety Officer

MEETING OBJECTIVES:

Discuss sponsor's question in briefing document dated April 23, 2001.

QUESTION for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **Does the Division agree that patients who have progressed after first line Xeloda ® (capecitabine) should be eligible for EFC4585?**

   FDA RESPONSE:

   - Yes. Please ensure that there is an equal number of patients that have progressed after first line Xeloda on both arms.

   - We will conduct additional analyses comparing the two arms for the subgroup of patients who progressed on Xeloda and for the subgroup of patients who progressed on 5-FU/LV.

These comments were faxed to the sponsor on May 10, 2001. There were no action items or unresolved issues. The meeting concluded at 11:00 am.

/S/

Christy Wilson
Consumer Safety Officer

Concurrence Chair:

/S/

Amna Ibrahim, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Wilson
5/15/01 11:39:39 AM

Amna Ibrahim
5/15/01 01:07:00 PM