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HFD-170/Division Files

File Name: 21260/labelconsult.doc

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**REQUEST FOR CONSULTATION**

TO (Division/Office):  
OPDRA, HFD-400, (15B-03) 33  
Peter Honig, M.D.

FROM:  
HFD-170 (Division of Anesthetic, Critical Care, and  
Addiction Drug Products), Dr. Cynthia McCormick

	IND NO.	NDA NO. 21-260	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT May 25, 2000
NAME OF DRUG morphine sulfate)	PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE November 15, 2000	
NAME OF FIRM: Elan Pharmaceuticals				

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS/SPECIAL INSTRUCTIONS:**

Please review the trademark name for this drug. They have incorporated the company name Elan into the drug name.

If you have any questions, please contact Sara Shepherd, Regulatory Project Manager, at 301-827-7430. Thank you for your assistance.

SIGNATURE OF REQUESTER [ /S/ ]	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER [ /S/ ]

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March 20, 2002



Cynthia McCormick, M.D.  
Director  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Food and Drug Administration  
HFD-170 Room 9B-23  
ATTN: Document Control Room  
5600 Fishers Lane  
Rockville, MD 20857

**Re: NDA 21-260 Morphine Sulfate Extended Release Capsules  
Risk Management / Phase IV Commitment Plan**

Dear Dr. McCormick:

Reference is made to our pending new drug application for Morphine Sulfate Extended Release Capsules. Reference is also made to your telefax of March 18 with comments on our Risk Management Plan and your request for a Phase IV Commitment Plan. Please find enclosed within Attachment 1 the specific comments from your March 18 telefax on the Risk Management Plan, followed by our responses. In addition to the specific remarks contained within Attachment 1, we commit to revise the Risk Management Plan, to incorporate the comments and responses, for submission to the Division within 30 days post approval of this application.

Please find enclosed within Attachment 2 our proposal for a Phase IV Commitment Plan, which incorporates the items specifically discussed in our previous telephone conference call. Should you have any questions regarding the enclosed submission, please feel free to contact me. Thank you.

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Sincerely yours,

---

Sharon Hamm, Pharm. D., R. Ph.  
Sr. Vice President  
R&D Technical Services

SH/sp

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# ATTACHMENT 1

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## Response to Risk-Management Comments

### 1. Provide definitions of abuse and misuse.

RESPONSE: Abuse and addiction have been defined and redefined by several organizations over the past 25 years. Abuse and addiction are behavioral syndromes that exist along a continuum from minimal use to abuse to addictive use<sup>1</sup>. The most influential system of diagnosis for mental disorders is published by the American Psychiatric Association (APA), DSM IV (1994)<sup>2</sup>. The APA describes a cognitive, behavioral, and physiological cluster of symptoms indicating that the individual continues the compulsive use of the substance despite significant substance-related problems. **Addiction** ("substance dependence" in APA nomenclature) is defined as dependence on the regular use of opioids to satisfy emotional and psychological needs rather than medical needs like chronic pain. Addiction is characterized by compulsive use and should be considered if patients no longer have control over drug use and continue to use the opioid despite harm. Pain relief is a medical reason for taking opioids. **Abuse/Substance abuse** is a pattern of adverse consequences from repeated drug use, but the pattern does not meet the criteria for *addiction* (APA 1994). Other definitions of *substance abuse* include the concept of excessive use or of a flagrant misuse of the substance. Examples of substance abuse include repeated absences or poor work performance related to substance use, neglect of children or household, etc. **Misuse** refers to use of the opioid in ways other than those for which the drug was originally prescribed.

### 2. Additional data sources will need to be added to have a comprehensive program. Sales, distribution, and prescription patterns should be monitored in order to detect abnormal clusters. Include methods to estimate the number of person exposed. Monitor media reports and Internet activity.

RESPONSE: IMS audits will be utilized to monitor sales, distribution and prescription patterns for the product. At the end of each month DDD (Drug Distribution Data) and Xponent Prescriber Data will be analyzed for unusual levels of purchasing and the Xponent data will be analyzed to determine prescribing patterns that are significantly above the national average. With few exceptions, each prescription will be a new prescription because of the Schedule II status of this product. Epidemiology data for the utilization of opioids for malignant pain and for nonmalignant pain document the following for these patient groups. This information will be periodically reported to FDA.

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<sup>1</sup> Goodman and Gilman The Pharmacological Basis of Therapeutics, 9<sup>th</sup> Edition, Hardman, Joel G., Limbird, L.E. *et al.* pp 557-560.

<sup>2</sup> Diagnostic and Statistical Manual of Mental Disorders, DSM IV (4<sup>th</sup> Edition) Frances, Allen *et al* 1994.

Cancer patients are usually 90% compliant with a prescription for 30 days, take these medications for approximately 180 days, and chronic pain patients are usually only 60% compliant, and take these medications for only 90 days. Data derived from sales, distribution, and prescription patterns will be utilized to estimate the number of patients using this product.

Routine monitoring of the Internet will be conducted to screen chat rooms for reports of misuse and abuse of Avinza™. We will also monitor media reports, and utilize major search engines for any reports relating to abuse or misuse of this product

**3. Provide a protocol for the proposed Phase IV study and explain its scope and timeline for completion.**

RESPONSE: We commit to supplying a protocol to FDA to assess the misuse and abuse potential of AVINZA. This protocol will propose to use the "Aberrant Drug-Related Behavior Checklist" developed by Doctors Passik and Portenoy as part of making this assessment. The protocol will study patients meeting the label criteria for appropriate use of AVINZA and will follow the patients for 4 months on study.

We commit to supplying the protocol to FDA within 5 months of drug approval. Upon FDA feedback of protocol acceptance, a further 3 months will be required to initiate the study. Accrual is expected to require 3 years. Follow-up and data recovery will be complete 6 months thereafter with a study report submitted to the FDA, approximately 6 months after completion of follow-up.

**4. Report overdose and death due to Avinza abuse and treatment for Avinza addiction to the Agency as 15-day reports.**

RESPONSE: Spontaneous reports received by Elan/Ligand concerning overdose and deaths due to Avinza abuse and treatment for Avinza addiction will be reported to the Agency as 15-day reports.

**5. Delineate specific intervention procedures in response to signals of abuse and misuse.**

RESPONSE: As part of our Risk Management Plan, Ligand Pharmaceuticals will be conducting educational programs for health care professionals on potential abuse, misuse or diversion of Avinza. If Ligand Pharmaceuticals becomes aware of any signs of potential abuse or misuse of Avinza the following will be implemented:

- 1) The Appropriate Use Committee will review Ligand practices to assess what improvements can be made

- 2) Educational programs for health professionals will be increased locally, regionally and nationally
- 3) A Ligand Appropriate Use Committee will review the information provided and implement appropriate measures
- 4) Appropriate measures to educate and prevent abuse and misuse will be reviewed with the entire sales force

Reports will be submitted to the Agency annually and when an intervention is necessary. Involve the Agency when necessary, to assist with intervention.

**6. Clarify the data collection, analysis plan, risk management evaluation plan, frequency of independent advisory committee meeting and frequency of summary reports.**

RESPONSE: A baseline analysis will be completed to determine the current risks, adverse events and the potential for misuse and abuse for Avinza. Subsequent data will be reviewed in comparison to this baseline to determine warranted changes to the Risk Management Program. Data collection will include a review of the reported cases of adverse events or misuse/abuse of the product, periodic reviews of literature reports in MEDLINE and Excerpta Medica that focus on adverse events or reports of misuse or abuse, monitoring of the DAWN reports specific for morphine, and MedWatch reports will be reviewed for adverse events for this product. The independent Advisory Committee will meet annually and summary reports will be provided following the end of the first calendar year the product has been marketed, and every twelve months following this report.

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**~~7. Inclusion of a coupon for free samples in the patient started kit is strongly discouraged as this practice generates a misconceived idea of safety and undermines the potential for abuse of the drug.~~**

RESPONSE: The patient starter materials will not include a coupon for a free sample of the product.

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- 8. Submit educational material to the Agency for evaluation prior to distribution.**
- The pharmacist component of the educational program should include verification of the size of the prescription.
  - Include a family and caregiver educational component.

RESPONSE: Educational materials for the Risk Management Program will be submitted to the Agency for evaluation prior to distribution. Included in these materials will be a pharmacist component that will include verification of the size of

the prescription (quantity and strength) with the physician and information for the pharmacist regarding signs of tampering and abuse with the prescription that should mandate a call to the prescribing physician. In patient materials, there will be a component for the family member(s) and the caregiver.

- 9. The message that the product contains a potent drug that should be kept out of the reach of children, pets and those to whom the drug has not been prescribed should be conveyed to the patient in every possible way.**

RESPONSE: All patient materials will include information that the product contains a potent drug that should be kept out of reach of both children and pets. In addition, patients will be advised that this medication that has been prescribed for them, should only be taken by the patient to whom the product was prescribed, and that the product should never be given to or sold to another person.

- 10. Provide to the Agency a copy of the letter submitted to DAWN expressing interest in participating in DAWN's sentinel event reporting system and a copy of DAWN's acceptance.**

RESPONSE: A letter is attached outlining the chronology of the interaction between Ligand and DAWN.

- 11. Although we recognize the limitations of name brand reporting in DAWN, these data are viewed as an important marker of abuse and should be collected and reported periodically to the Agency.**

RESPONSE: DAWN data will be collected and periodically reported to the Agency.

- 12. Report Abuse, misuse and diversion cases to the DEA as well as the Agency.**

RESPONSE: Publicly reported illegal activities involving abuse, misuse and diversion that come to our attention will be reported to the DEA as well as the Agency.

- 13. Clarification is needed for statements in Section 1, Analysis of Misuse/Abuse Risk referring to use of a baseline of the "current" risks associated with the use of morphine for future reference. Provide a more detailed clarification of what is mean by baseline. Specifically, does this refer to establishing a baseline rate of morphine abuse and misuse risk prior to launching Avinza for later comparison with Avinza, or will a baseline Avinza risk assessment be established over a specified period of time after launch?**

RESPONSE: The intent in Section 1 is to establish a baseline risk assessment for Avinza over a 12 month period following launch. Assessments after this initial period will be measured against this baseline assessment.

**14. Clarify what is meant by references to individuals with a “vested” interest in Section 1 c., and how such individuals will provide an objective assessment of benefit/risk assessment.**

RESPONSE: “Vested” was intended to refer to individuals who have expertise in the safe and effective use of opioids, including Avinza. (“Vested” does not refer to individuals who have financial interest in Avinza.) Based on this criteria, they would be expected to provide an expert, objective assessment.

**15. Clarify how becoming a corporate member in related medical professional societies will serve as a means of obtaining information concerning the monitoring or risk or misuse/abuse.**

RESPONSE: Corporate membership with pain-related medical professional societies will provide immediate links to press releases from these organizations and provide an opportunity for information sharing on risk, abuse and misuse of opioids. A corporate membership will also provide an opportunity to address key issues regarding opioids with executive officers of the society, and provide an opportunity to participate on any special committees or task forces that these societies might organize.

# **ATTACHMENT 2**

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In support of approval of NDA 21-260 Avinza™ (morphine sulfate extended release capsules), Elan and Ligand are prepared to commit to the following Phase IV Plan.

1) Fumaric Acid Toxicology Study

Despite the well-established history of fumaric acid as a food additive, FDA has asked that we develop further support for the administration of Avinza in high doses. As a result, the following GLP toxicology studies will be conducted to further characterize the pre-clinical safety profile of fumaric acid:

a) Dose Range studies in rats and dogs

These studies will be preceded by dietary study assessments as needed, to determine feed tolerability, stability in animal feed, etc.

b) Six / nine months repeat dose feeding studies in rats and dogs to include histopathological examinations.

The earlier acute and dose-ranging studies will be completed as needed in advance of final protocol development. As a result, the following timeline is proposed:

- Protocol for the definitive repeat dose studies in rats/dogs for submission to the agency within 6 months of completion of the dose finding studies.
- Definitive toxicology study initiation within 3 months of the FDA protocol approval.
- Final report completion for submission to the agency within 18 months following study initiation.

2) Long Term Safety Study

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To further support the administration of Avinza and the safety profile of fumaric acid in high dose patients, we commit to conducting a Phase IV safety study in approximately 100 patients receiving Avinza doses in excess of 500 mg per day including an adequate representation in doses has high as 3-5 gm per day for the treatment of pain. Patients will be followed for 6 months.

---

The timelines for this activity could vary depending upon the length of patient accrual and response time for FDA protocol review. Accrual is anticipated to be lengthy as this represents a small percentage of the overall target pain population. Based on this outline, we propose the following timeline:

- a) Protocol for the FDA review and agreement to be submitted within 5 months of FDA approval.
- b) Study initiation within 3 months of receiving comments approval from FDA on the study protocol.

## Phase IV Commitment Plan

- c) Study conduct and final report for submission to FDA within 33 months of study initiation.

### 3) Morphine Carcinogenicity Study

Despite the well-established history of morphine sulfate usage, FDA has asked for the conduct of a GLP carcinogenicity study on morphine. In an effort not to delay approval of this application, we will commit to conduct a carcinogenicity study in two rodent species using the lifetime (two year) bioassay. In the event that the agency subsequently determines it is not their policy to require this study, we reserve the right not to complete it.

In advance of the definitive two-year study (if required), we will commit to conduct dose-ranging studies in an attempt to determine the MTD (if needed). In addition, we will seek FDA review of the carcinogenicity protocols in advance of the definitive two-year carcinogenicity study (if required).

Recognizing these requirements, we anticipate a timeline that would enable:

- a) Definitive carcinogenicity study protocol submitted within 22 months following FDA approval.
- b) Study initiation within 3 months of receiving FDA comments on the protocol.
- c) Final report completion for submission to FDA within 32 months of study initiation.

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** March 12, 2002  
**TO:** File  
**FROM:** Kim Compton, R.Ph., Regulatory Project Manager, HFD-170  
**SUBJECT:** **Telecons prior to Action**  
NDA 21-260, Avinza (Morphine sulfate extended-release) capsules

3/8/02-Call to sponsor to discuss possible resolutions of concerns surrounding fumaric acid issue. Also discussed impurity issues to be resolved.

3/12/02-Call to sponsor to discuss labeling and requested sponsor create a patient package insert (PPI).

3/13/02-Call to sponsor to discuss clarification of issues conveyed to sponsor by in Discipline Review letter of March 12, 2002. Sponsor notified that responses to CMC issues would be required to be received from sponsor by Friday, March 15, 2002.

3/18/02-Call to sponsor to discuss additional CMC issues and information needed to finish CMC review. It was agreed that the sponsor would be granted— months expiration dating on the Bottle configurations and— months expiration dating on the blister configurations with a PA supplement to extend these.

~~3/18/02- Call to sponsor to discuss labeling, post-marketing commitments, pediatric plans, and PPI.~~

3/19/02- Call to sponsor to discuss edits on labeling.

3/20/02- Calls to sponsor to discuss labeling, RMP, and post-marketing commitments.

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**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** March 18, 2002

**TO:** File

**THROUGH :** Sharon Hertz, M.D., Medical Officer Bob Rappaport, M.D., Deputy  
Division Director, Cynthia McCormick, M.D., Division Director, HFD-170,  
Silvia Calderon, Ph.D., Chemist, HFD-009

**FROM:** Kim Compton, R.Ph., Regulatory Project Manager, HFD-170

**SUBJECT:** **Risk Management Plan-comments for sponsor**  
NDA 21-260, Avinza (Morphine sulfate extended-release) capsules

The following comments on the Risk Management Plan, will be provided to the sponsor via fax transmission today. These comments were generated from a meeting with the review team and from a prior review and discussions with the Controlled Substances Staff.

1. Provide definitions of abuse and misuse.
2. Additional data sources will need to be added to have a comprehensive program. Sales, distribution, and prescription patterns should be monitored in order to detect abnormal clusters. Include methods to estimate the number of persons exposed. Monitor media reports and Internet activity.

---

3. Provide a protocol for the proposed Phase IV study and explain its scope and timeline for completion.
4. Report overdose and death due to Avinza abuse and treatment for Avinza addiction to the Agency as 15-day reports.

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5. Delineate specific intervention procedures in response to signals of abuse and misuse.
6. Clarify the data collection, analysis plan, risk management evaluation plan, frequency of independent advisory committee meeting and frequency of summary reports.
7. Inclusion of a coupon for free samples in the patient starter kit is strongly discouraged as this practice generates a misconceived idea of safety and undermines the potential for abuse of the drug.

8. Submit educational material to the Agency for evaluation prior to distribution.
    - The pharmacist component of the educational program should include verification of the size of the prescription.
    - Include a family and caregiver educational component.
  9. The message that the product contains a potent drug that should be kept out of reach of children, pets and those to whom the drug has not been prescribed should be conveyed to the patient in every possible way.
  10. Provide to the Agency a copy of the letter submitted to DAWN expressing interest in participating in DAWN's sentinel event reporting system and a copy of DAWN's acceptance.
  11. Although we recognize the limitations of name brand reporting in DAWN, these data are viewed as an important marker of abuse and should be collected and reported periodically to the Agency.
  12. Report Abuse, misuse and diversion cases to the DEA as well as the Agency.
  13. Clarification is needed for statements in Section 1, Analysis of Misuse\Abuse Risk referring to use of a baseline of the "current" risks associated with the use of morphine for future reference. Provide a more detailed clarification of what is meant by baseline. Specifically, does this refer to establishing a baseline rate of morphine abuse and misuse risk prior to launching Avinza for later comparison with Avinza, or will a baseline Avinza risk assessment be established over a specified period of time after launch?
  14. Clarify what is meant by references to individuals with a "vested" interest in Section 1 c., and how such individuals will provide an objective assessment of benefit/risk assessment.
  15. Clarify how becoming a corporate member in related medical professional societies will serve as a means of obtaining information concerning the monitoring of risk or misuse/abuse.
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# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** March 15, 2002

**TO:** File

**THROUGH :** Dale Koble, Ph.D., Chemistry Team Leader, HFD-170  
Alina Mahmud, R.Ph., Safety Evaluator, Office of Drug Safety, HFD-400  
Cynthia McCormick, M.D., Division Director, HFD-170

**FROM:** Kim Compton, R.Ph., Regulatory Project Manager, HFD-170

**SUBJECT:** Revised Carton and container labels-comments for sponsor  
NDA 21-260, Avinza (Morphine sulfate extended-release) capsules

The following comments on the revised carton and container labels submitted March 12, 2002, will be provided to the sponsor via fax transmission today. These comments were generated from a meeting with the review team that included the clinical staff, chemistry team and a safety evaluator from the Office of Drug Safety.

1. Provide samples of empty capsules of each strength.
2. Pursuant to 21 CFR 201.10 (g)(2), increase the prominence and legibility of the established name relative to the proprietary name, e.g. using a different font style, boldfacing, etc.
3. With reference to question 2(a)(4) in the Agency letter dated January 17, 2001, provide improved differentiation between the various strengths by boxing, using more dissimilar colors, etc. and also provide consistency between the capsule colors and label colors on the packages, e.g.

- 
- Better color separation between the 60-mg and 120-mg labels
  - 30-mg strength: The label color should be \_\_\_\_\_

4. Increase the prominence of "30-mg" and "60-mg" strengths on the 30 count bottles.
5. Revise the established name by bringing the word "capsules" inside the parenthesis so that it reads "(morphine sulfate extended-release capsules)".

6. Provide a revised proprietary name with a style consisting of one uniform color, e.g. black, one font style, and without a red extension line on the letter "v" as is currently depicted.
7. Revise the blister carton labels to read "USUAL DOSAGE: ONE CAPSULE DAILY. SEE PACKAGE INSERT."
8. Increase the prominence of the "Rx Only" statement on all container labels.
9. Increase the prominence of the established name and strength on the lidding of each blister strength.

The following comments pertain to the overall chemistry portion of the submission and were generated by the chemistry review team.

1. Provide revised drug substance and drug product specification sheets with the following corrections:

Drug substance:

"Individual unspecified drug-related impurity: \_\_\_\_\_ in place of \_\_\_\_\_"

Drug Product:

"Individual unspecified drug-related degradation product: \_\_\_\_\_ in place of \_\_\_\_\_"

2. Per question number 12 of our Discipline Review letter of March 12, 2002, provide revised stability protocols including a revised set of specifications and the statistical protocol to be used for statistical analysis for extension of expiration in the future. The response received with your submission of March 15, 2002 is inadequate.

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# MEMORANDUM OF TELECON

DATE: July 6, 2000

JUL 09 2000

APPLICATION NUMBER: NDA 21-260, Morphelan (morphine sulfate)

## BETWEEN:

Name: Sharon Hamm, Jeff Lazar  
Phone: 770-538-6343  
Representing: Elan Pharmaceuticals

COPY

## AND

Name: Pat Hartwell, Bob Rappaport, Sara Shepherd  
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: The first telecon was requested to discuss the clinical database. The second telecon was to clarify the clinical information needed by the Agency. The third telecon was to request information needed by the chemistry reviewer.

## PHONE CALL #1

The following items were requested by the Agency:

- a. The location of tables containing the extent of exposure for all patients.

Ms. Hamm responded that all of the data were not integrated into the same table.

Dr. Hartwell replied that we need both pooled and unpooled data, including that on-healthy-volunteers.

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Dr. Rappaport replied that we need the compiled information to make a filing determination.

---

Ms Hamm stated that she will compile the requested information and get back to the Agency later in the day.

---

## PHONE CALL #2 (Dr. Rappaport was not present at this telecon)

Ms. Hamm called to clarify the summary tables in the NDA submission. Dr. Hartwell replied that she already reviewed the tables and at issue was the drop-off in exposure after 6 months. Ms. Hamm stated that they were aware of the lack of patients at the later time points. Ms. Hamm stated that they are in the process of analyzing the 4-month data and this information will increase the number of patients at the 6-month and later time point.

Dr. Hartwell replied that this issue will be discussed with the Division Director next week.

Ms. Hamm stated that there is no data tables for the exposures on healthy volunteers. It was stated in the NDA that there were 141 normal healthy volunteers. Dr. Hartwell requested a table with the normal healthy volunteer information.

PHONE CALL #3 (between Ms. Shepherd and Ms. Hamm)

The Agency requested the following information:

- a. Verification that the sites are ready for inspection.
- b. A copy of the patent 6,066,339.

Ms. Hamm replied that she would obtain the information and send it to the Agency via fax and hard copy to the document room. The copy of the patent will not be faxed.

[ *IS!* ] 7-7-00

Sara E. Shepherd  
Regulatory Project Manager

cc: Original NDA 21-260

HFD-170/Div. File

HFD-170/Sara Shepherd

HFD-170/C. Schumaker 7/7/00

HFD-170/P. Hartwell 7/7/00

HFD-170/B. Rappaport 7/7/00

Drafted: Sara Shepherd, July 7, 2000

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TELECON



May 30, 2000



elan pharmaceutical research corp.

1300 Gclid Drive  
Gainesville, Georgia 30504, USA  
Telephone (770) 534-8239  
Fax (770) 534-8247

Dr. Cynthia McCormick  
Food and Drug Administration  
Division of Anesthetic, Critical Care and Addiction Drug Products  
Attn: Central Document Room, Room 9B-23  
5600 Fishers Lane  
Rockville, MD. 20857

**Deliver To: Ms. Cathie Schumaker**

Re: NDA 21,260: \_\_\_\_\_<sup>™</sup> (morphine sulphate) \_\_\_\_\_ ; Extended Release  
\_\_\_\_\_ Capsules 30mg, 60mg, 90mg and 120mg

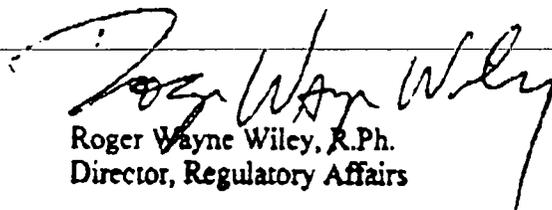
Dear Dr. McCormick

Reference is made to the \_\_\_\_\_ NDA 21-260 received at FDA's Central Document Room located at 12229 Wilkins Ave. on May 30, 2000. In addition, reference is made to the telephone call to Ms Cathie Schumaker explaining that the electronic SAS data sets on CD-ROM for the clinical program were being delivered directly to her by courier.

Enclosed is the CD-ROM.

If you have any questions regarding this submission, please contact myself or Sharon Hamm at 770-534-8239.

Sincerely yours,

  
Roger Wayne Wiley, R.Ph.  
Director, Regulatory Affairs

Enclosure

APPEARS THIS WAY  
ON ORIGINAL

COPY FROM  
DFS  
6-5-00

Record of Telecon

Date: May 10, 2000

NDA: 21-260

IND: \_\_\_\_\_

Product: Morphine sulfate sustained-release capsules

Firm: Elan

Name and Title of Contac: Wayne Wiley/Regulatory Affaris

Telephone Number: 770-538-6360

---

I informed Mr. Wiley of the following with regard to the the \_\_\_\_\_ batch record request.

1. Provide one representative executed batch record per strength.

Mr. Wiley responded that they have identified a lot that was used for clinical studies and stability testing. They will provide the representative executed batch record for this lot. Other records will be available if needed during the review.

2. Provide linkage between drug substance lots, drug product lots and stability studies, and preclinical and clinical trials in a tabular form.

Mr. Wiley stated that they have not conducted any preclinical studies, so those data are not applicable. They have provided such a chart that contains the link between the drug stubstance lots, drug product lots and clinical studies. They will provide the additional information as requested.

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3. Provide lot analysis of drug substance lots used and drug product lots used in any of the above studies.

Mr. Wiley asked for clarification as to which data should be included. Dr. Koepke's e-mail of May 11, 2000, clarifies that basically everything that was analyzed that may become a regulatory specification for the drug product should be included.

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In addition, I asked Mr. Wiley to provide evidence that \_\_\_\_\_ is not formed in the drug product and a summary of the product development report and the product scale up report. }

Mr. Wiley replied that Elan submitted an evidence document on April 3, 2000 (serial #069). The document includes a report of the investigation using thermal analysis and x-ray diffraction. He asked that we let him know if the report was not adequate.

He also stated that they have now TWICE provided the summary of the product development report and the product scale-up report. They provided it once in reference to the executed batch record request and again with the CMC presubmission.

Attachments: May 10, 2000, D'Sa e-mail  
May 11, 2000, Koepke e-mail

Cc:  
Orig NDA 21-260  
Orig IND  
HFD-170/Div(2)

**APPEARS THIS WAY  
ON ORIGINAL**

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**Date:** June 26, 2001

**To:** Cynthia G. McCormick, M.D.  
Director, Division of Anesthetic, Critical Care  
and Addiction Drug Products, HFD-170

**Through:** Deborah B. Leiderman, M.D.  
Director, Controlled Substance Staff, HFD-009

**From:** Silvia N. Calderon, Ph.D.  
Controlled Substance Staff, HFD-009

**Subject:** NDA 21-260 (Morphine Sulfate Extended Release  
Capsules)  
Sponsor: Elan Pharmaceuticals, Inc

This memorandum responds to a consult from the Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170, with respect to the Sponsor's proposal to address one of the issues conveyed to them in the March 30, 2001 approvable letter for NDA 21-260.

In the approvable letter among other issues the Sponsor was asked to "provide results of an appropriate *in-vitro* test of the extraction of your Morphine Sulfate Extended-Release Capsule crushed in a manner intended to simulate intravenous abuse of the product."

In an attempt to address this issue the Sponsor responded that they would conduct a simple *in vitro* experiment by which the lowest (30 mg) and highest (120 mg) strength capsules would be ~~\_\_\_\_\_~~ and the ~~\_\_\_\_\_~~ taken in water to determine the amount of morphine extracted via an ~~\_\_\_\_\_~~ assay.

In general when trying to extract a drug substance from a mixture the use of various solvents is recommended and extractability of the drug substance at different pHs is explored. In this particular case the first solvent of choice is water, either tap or deionized, since it is expected that morphine sulfate would be solubilized in each. If this procedure does not afford a considerable amount of active component it is recommended that other organic solvents be explored. In addition it is recommended that the presence of ~~\_\_\_\_\_~~ in the extracted material be analyzed, since ~~\_\_\_\_\_~~ is one of the excipients in ~~\_\_\_\_\_~~ and can be a potential health risk if administered intravenously. If ~~\_\_\_\_\_~~ is extracted

the label should include information about the toxicity associated with parenteral injection of the capsule constituents.

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ON ORIGINAL

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

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/s/

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Silvia Calderon  
6/26/01 04:37:29 PM  
CHEMIST

Deborah Leiderman  
6/26/01 05:17:43 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

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## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** March 22, 2001

**To:** Dr. Cynthia G. McCormick.  
Director, Division of Anesthetic, Critical Care  
and Addiction Drug Products, HFD-170

**From:** Silvia N. Calderon, Ph.D. and *SLC*  
Ann-Kathryn Maust, M.D. *AKM*  
Controlled Substance Staff, HFD-009

**Through:** *Carinne P. Moody*  
Dr. Deborah B. Leiderman  
Director, Controlled Substance Staff, HFD-009

**Subject:** NDA 21-260, \_\_\_\_\_<sup>™</sup> (Morphine Sulfate Extended Release  
Capsules)  
Sponsor: Elan Pharmaceuticals, Inc

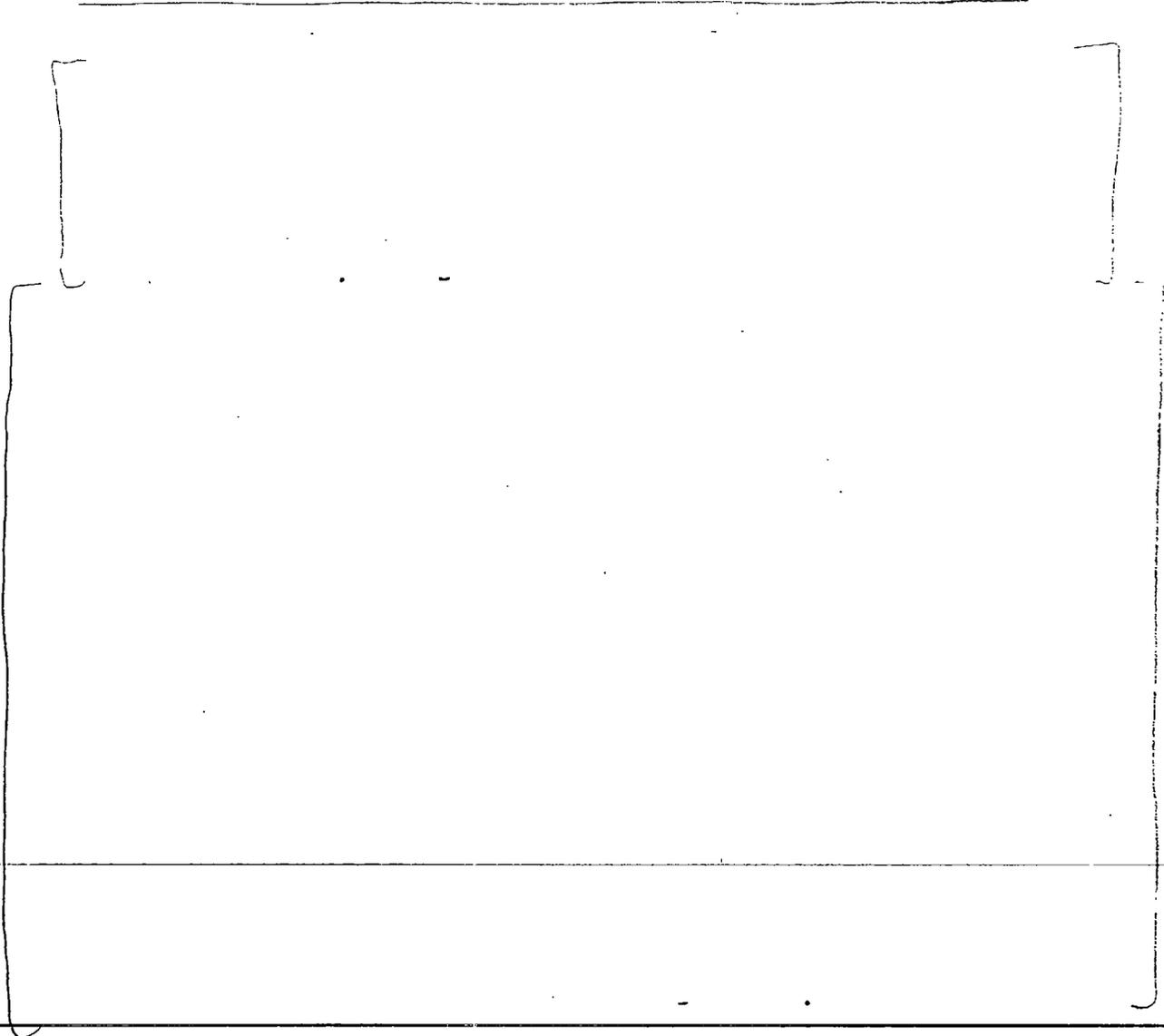
This memorandum responds to a consult from the Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170, with respect to the label of \_\_\_\_\_<sup>™</sup> from the controlled substances perspective. \_\_\_\_\_<sup>™</sup> is an extended release oral formulation of morphine sulfate that contains both immediate release and extended release encapsulated beads of morphine sulfate. This product is indicated for the relief of moderate to severe pain in patients who require repeated dosing with opioid analgesics over periods of more than a few days.

SUMMARY AND RECOMMENDATIONS

1. In the "Note to the Pharmacist" section of the Bottle label Text and after the ~~"DISPENSE IN A TIGHT, LIGHT-RESISTANT CONTAINER AS DEFINED IN USP"~~, the following warning should be included:

- \_\_\_\_\_
- \_\_\_\_\_
1. The product label describes a clinical study conducted in patients with moderate to severe \_\_\_\_\_ pain. This raises concerns from the drug abuse and diversion perspective because it could be interpreted that \_\_\_\_\_ has a role in the pain management associated with such condition.

NDA 21-260.  
Page 3 of 3



Tierney LM, McPhee SJ, Papadakis MA, eds. Current Medical Diagnosis and Treatment – 40<sup>th</sup> Ed. New York: McGraw Hill Companies, Inc., 2001.

7.



/s/

-----  
Corinne Moody  
3/27/01 04:10:40 PM  
CSO

Silvia Calderon  
3/27/01 04:22:09 PM  
CHEMIST

**APPEARS THIS WAY  
ON ORIGINAL**

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REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY  
DATA  
MEMO TO FILE

Reviewer: Kathleen Haberny, Ph.D.

Date: March 6, 2002

NDA: # 21-260

Submission: # BZ/July 26, 2001

Drug: (morphine sulfate) Extended-Release Capsules

Sponsor: Elan Pharmaceutical Research Corporation

Re: Impurities in drug product

According to information provided by the reviewing chemist, Dr. Ravi Harapanhalli, the proposed drug product specifications for the following impurities are at levels of and above:



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\*NMT: not more than

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Dr. Harapanhalli requested that the sponsor address these specifications and informed the sponsor that qualification would be needed for substances the threshold for qualification of degradation products in new drug products with a maximum total dose of according to ICHQ3B.

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The sponsor submitted limited preclinical and clinical safety information on the impurities listed above in the chemistry section of the NDA resubmission (July 26, 2001) as a rationale for the position that qualification of the above impurities should not be needed.

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The Clinical Pharmacologist, Dr. Suliman Alfayoumi, reviewed the published reports on morphine metabolites in humans submitted by the sponsor. According to Dr. Alfayoumi,

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(M3G) and morphine-6-glucuronide (M6G). Codeine and normorphine are known to be minor metabolites of morphine in humans. However, there is very limited information in literature on the remaining metabolites listed. Dr. Alfayoumi noted that 10-hydroxymorphine, a morphine impurity with identical pharmacological properties and HPLC retention time as a previously identified *in vivo* human metabolite was isolated and identified in 1990 (Farsam *et al.* 1990. *Pharmaceutical Res* 7(11):1205-7), and that oxidation at the C-10 position has been hypothesized to be related to hepatotoxicity by morphine (Correia *et al.*, 1986)<sup>1</sup>.

Pseudomorphine is a dimer of morphine that occurs naturally in aqueous solutions. The information presented in two published articles on the pharmacology of morphine-N-oxide, a human metabolite of morphine (Fennessy and Fearn. 1969. *J Pharm Pharmac* 2:668-673; Heimans *et al.*, 1971. *J Pharm Pharmac* 23:831-836) suggested that morphine-N-oxide does not pose major safety issues in mice or rats (Fennessy and Fearn, 1969) and dogs (Fennessy. 1969. *Eur J Pharmacol* 8: 261-268). Thus, the impurities identified as morphine metabolites in humans are codeine, 10-hydroxymorphine, and morphine-N-oxide.

In the submitted rationale the sponsor noted that pseudomorphine has been found in marketed morphine products (Vermeire and Remon. 1999. *Int J Pharm* 187:17-51), at levels as high as 1% in an intrathecal preparation (Caute *et al.* 1988. *Pharm Pharmacol* 40:644-645).

Pseudomorphine was reported to be a metabolite in animals (Roerig *et al.* 1976. *Biochem Pharm* 25:1075-1080), but has not been identified as a human metabolite. Pseudomorphine toxicity and pharmacological effects were studied in several animal species (mice, cats, rats, rabbits, route of administration not provided) in an early study by Eddy (1936. *Studies of morphine codeine and their derivatives. XII. The isomers of morphine and dihydromorphine.* 421-431). Pseudomorphine was found to be less acutely toxic than morphine in mice. This study is inadequate to support the safe use of pseudomorphine. The sponsor described 10-oxomorphine as a decomposition product of morphine (Proska. 1984. *Pharmazie* 39:687-688) that may be metabolized to 10-hydroxymorphine (Farsam *et al.*, 1990). No preclinical toxicology information was provided to support the safety of 10-oxomorphine.

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Dr. Harapanhalli noted that these impurities are observed in other morphine products, with typical specifications of NMT 0.5% for some of them (not specified). Pseudomorphine is a major degradant in aqueous solutions of morphine.

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In summary, codeine, 10-hydroxymorphine, and morphine-N-oxide are human metabolites and, thus, do not require further non-clinical qualification. 10-oxomorphine is not identified as a human metabolite. No preclinical toxicology information is available to support the safety of 10-oxomorphine in clinical use at the specification of NMT 0.2%. Therefore, for an adequate safety evaluation, 10-oxomorphine requires nonclinical qualification according to ICH standards if the specification is not decreased to below 0.2%. Pseudomorphine has not been identified as a human metabolite, and the available nonclinical safety information is inadequate to support the proposed specification at the level of 1.0%. For an adequate safety evaluation, qualification is needed for pseudomorphine at levels of  $\geq 0.2\%$  according to ICH guidelines. It should be noted that these impurities are observed in previously approved morphine products at levels of 0.5% or higher.

<sup>1</sup>The publication referred to is Kroweetch G, Caldera-Munoz PS, Straub K, Castagnoli N Jr, Correia MA. 1986. Morphine metabolism revisited. III. Confirmation of a novel metabolic pathway. Chem Biol Interact 58(1):29-40. The authors suggest that oxidation at the benzylic C-10 position may form an electrophilic species that can react with nucleophilic thiols (e.g., N-acetylcysteine, glutathione). N-acetyl-cysteine is a precursor to the widely distributed endogenous enzyme glutathione that is involved in detoxification of reactive metabolites via redox reactions to prevent oxidative damage. Therefore, endogenous protection from toxicity by the electrophilic species hypothetically formed by C-10 oxidation is present.

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

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Kathy Haberny  
3/6/02 01:56:22 PM  
PHARMACOLOGIST

Timothy McGovern  
3/6/02 02:29:28 PM  
PHARMACOLOGIST  
I concur.

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ON ORIGINAL**

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Write (Dr letter)

DFS copy

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:**

February 5, 2001

**DUE DATE:**

March 1, 2001

**OPDRA CONSULT #:**

01-0029

**TO:**

Cynthia McCormick, MD  
Director, Division of Anesthetic, Critical Care and Addiction Drug Products  
HFD-170

**THROUGH:**

Kim Compton, Project Manager  
HFD-170

**PRODUCT NAME:**

**Avinza**  
(Morphine Sulfate Extended Release)  
Capsules  
30 mg, 60 mg, 90 mg and 120 mg

**MANUFACTURER:** Elan Pharmaceuticals

**NDA #: 21-260**

**SAFETY EVALUATOR:** Alina Mahmud, R.Ph.

**SUMMARY:** In response to a consult from the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170), OPDRA reviewed the proposed container labels, carton and blister package labeling, for possible interventions that may help minimize medication errors.

**OPDRA RECOMMENDATION:** OPDRA has made recommendations for labeling revisions to minimize potential errors with the use of this product.

\_\_\_\_\_  
Jerry Phillips, R.Ph.

Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
Fax: (301) 480-8173

\_\_\_\_\_  
Martin Himmel, M.D.

Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

**APPEARS THIS WAY  
ON ORIGINAL**

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

Cathie Schumaker, R.Ph.  
Chief, Project Management Staff  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Cc: Ligand Pharmaceuticals  
10275 Science Center Drive  
San Diego, CA 92121-1117  
Attention: Howard T. Holden, Ph.D.  
Vice President, Regulatory Affairs and Compliance

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ON ORIGINAL**

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/s/

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Cathie Schumaker

1/17/01 01:02:10 PM

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## Draft Labeling

The following includes a set of draft labeling which includes the bulk container label, market pack container labels, and the package insert.

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ON ORIGINAL**

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**000001**

/s/

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Cathie Schumaker

2/27/01 04:39:52 PM

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ON ORIGINAL**

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MINUTES OF MEETING WITH SPONSOR

IMTS: 5193

Meeting Date: January 18, 2000

Time: 1:00 - 2:30 p.m.

Location: Parklawn Building, Conference Room K

Type of Meeting: Pre-NDA

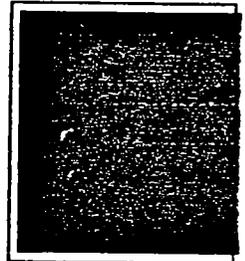
IND: \_\_\_\_\_

Sponsor: Elan

Drug: \_\_\_\_\_ (Morphine sulfate sustained release capsules) 30, 60, 90 and 120 mg

Meeting Chair: Bob Rappaport, M.D., Deputy Director

Minutes Recorder: Nancy Chamberlin



<u>FDA Attendees:</u>	<u>Titles:</u>	<u>Offices:</u>
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD 170
Monte Scheinbaum, M.D.	Medical Reviewer	HFD-170
Albinus D'Sa, Ph.D.	Chemistry Team Leader	HFD-170
Pat Maturu, Ph.D.	Chemistry Reviewer	HFD-170
Cathie Schumaker	Chief, Project Management Staff	HFD-170
Anwar Goheer, Ph.D.	Pharmacology/ Toxicology Reviewer	HFD-170
Ramana Uppoor, Ph.D.	Clin.Pharm. & Biopharmaceutics Team Leader	HFD-870
Shinja Kim, Ph.D.	Clin.Pharm. & Biopharmaceutics Reviewer	HFD-870
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170
John Gibbs, Ph.D.	Director, DNDCII	HFD-820
Steve Koepke, Ph.D.	Deputy Director, DNDCII	HFD-820
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170

<u>Elan</u>	<u>Participants</u>	<u>Titles:</u>
Sharon Hamm, Pharm.D., R.Ph.		Sr. V.P., Research and Development Technical Operations
Pia Lynch, M.D.		Director Clinical Research
Jackie Butler, Ph.D.		Director Pharmacokinetics
Wayne Wiley, R.Ph.		Director Regulatory Affairs
Carl Bauman, R.Ph.		Director of Medical Information
Darlene Conrad		Manager, R&D Quality Operations
Pat Kenny		Clinical Project Coordinator
Beth Vause		Consultant, Clinical Research
Jeff Lazar, M.D., Ph.D.		Consultant, Clinical Research
Shari Medendorp, M.Sci		Consultant, Exec.Dir. Statistics/SCIREX
Joe Gao, Ph.D.		Consultant/ Senior Statistician/SCIREX

**MEETING OBJECTIVE:** The primary objective of this meeting was to discuss the sponsor's proposed NDA as provided in the December 21, 1999, briefing package.

**DISCUSSION ISSUES:** Discussion was held on the questions provided in the sponsor's proposed NDA briefing package.

**BEST POSSIBLE COPY**

**FIRM'S QUESTIONS:**

**A. General NDA Format**

- 1. Are there any specific comments regarding the proposed NDA format or approach as outlined in the table of contents, or in the media formats identified?**

Division's Response:

Dr. Rappaport commented that whenever possible the Agency would like to receive electronic format following the Agency's guidelines. Review Aids for clinical in Word were requested.

- 2. Are there any requests for additional review or desk copies of any individual sections of the application, beyond those routinely required?**

Division's Response:

The Agency requested the sponsor to provide the following at the time of NDA submission:

- Statistics with their own set of clinical volumes
  - Statistics electronic version of data sets in SAS version 5
  - Dissolution data volumes to the biopharmaceutics sections in addition to the chemistry section
  - 2 additional volumes containing the ISS/ISE for Dr. McCormick & Dr. Rappaport
  - 10 Desk copies of the initial index volume and labeling volume for the CSO to distribute to the review team
- 
- Word version of labeling

**B. Clinical/Statistical Section**

- 1. Are there any specific Agency comments regarding the patient exposure numbers as summarized?**

Division's Response:

Dr. Rappaport commented that we were satisfied with the total numbers, however, they look short on the high dose number with time. The sponsor was asked to create a table with delineated dose exposure and duration.

Dr. McCormick noted that the Division prefers to receive the 4-month safety update at 4 months.

2. **Are there any specific comments regarding the individual statistical plan proposals?**

Division's Response:

Dr. Permutt noted that there appear to be a lot of potential comparisons. The data analysis plan should be specific to avoid later concerns about multiplicity.

3. **Are there any specific comments or discussion regarding the proposed ISE/ISS statistical analysis plans?**

Division's Response:

Dr. Rappaport noted that the Agency generally looks at individual studies for efficacy, and combined data for safety. Dr. Rappaport suggested that the sponsor provide safety data for the 2 controlled trials pooled and unpooled for the Agency to review.

4. **Are there any specific comments regarding the narrative summary population as described, the sample report formats, or their proposed locations within the NDA?**

Division's Response:

Dr. Rappaport noted that the sponsor had proposed to not provide the narratives for the non-morphine treated patients. He informed the sponsor that the Division requires submission of narratives on all subjects with serious adverse events, subjects who discontinue due to adverse events, and for all subjects who died.

5. **Has Elan's request for a pediatric study waiver been granted? If not, the sponsor would appreciate a discussion regarding the rationale.**

Division's Response:

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Dr. Rappaport noted that there has been discussion within the Agency. At present there is no information on the safe and effective use of morphine in pediatrics, and the Agency feels that this product would be useful in pediatrics if reformulated. Therefore, the Agency will not grant the waiver.

---

Dr. Rappaport suggested that the sponsor submit their Proposed Pediatric Study Request. In addition, provide the development plans for Pediatrics. As noted, the Agency feels that there is a younger age group that could use the product. Dr. McCormick noted that the sponsor would have to provide additional safety data and pharmacokinetic information.

6. **Are there any specific comments regarding the location of data listings or the media format as described?**

Division's Response:

No comment.

**C. Pharmacokinetics Section**

1. Are there any specific comments regarding the overall pharmacokinetic study data package as presented herein the briefing package?

Division's Response:

Based on study titles, the overall pharmacokinetic development plan, as presented in the briefing package, seems adequate for an NDA. However, the sponsor did not discuss the effect of "special populations", such as hepatic and renal impairment on the PK of morphine. Therefore, please submit literature reports (and summarize the reports) to evaluate the effects on 'special populations' and also analyze for gender effect based on PK studies in the NDA.

505(b)(2) issue: Please clarify which drug product will be referenced in your NDA, especially in regard to pharm/tox information. If it is ——— the sponsor must provide a comparative bioavailability study. The sponsor stated that they do not intend to use ——— as a reference. They only intended to use the label format of ——— to create the ——— label.

Ms. Schumaker reminded that sponsor that they would need to provide the patent certification for any product that they reference in the NDA.

2. Are the electronic data formats desired, in addition to the hard copy presentation? Are there any specific comments regarding the media formats?

Division's Response:

Yes, electronic data formats as proposed for PK data are desired, in addition to the hard copy presentation. Also, please submit pharmacodynamic data, if collected, especially from those studies that also have PK evaluation (including the data used to develop PK-PD model), in the same format proposed for PK data. Dr. Kim also requested that the sponsor provide the individual study reports in word 6.0 on a CD ROM.

3. Are there any specific comments regarding the IV/IVC analysis approach? Does the Agency require submission of the S-PLUS codes?

Division's Response:

Dr. Kim requested that the sponsor provide the following:

- S-PLUS codes (and the model)
- Dissolution data for all strengths (individual dissolution data from ——— units/lot). Also, provide dissolution data ——— on all strengths manufactured at both sites. These dissolution data for biobatches should be submitted to item 6 of the NDA, in, addition to the CMC section.

The sponsor asked whether data in \_\_\_\_\_ media are needed for all strengths even if dissolution is shown to be independent of pH of medium. Agency agreed that, **with appropriate justification to show that dissolution is pH-independent**, the sponsor can provide dissolution data in one medium.

- For dissolution specification setting, please refer to the FDA Guidance "Extended release oral dosage forms: Development, evaluation and applications of *in vitro/in vivo* correlations." Also, please note that the last time point of specification should be at a time when at least \_\_\_\_\_ of the drug is dissolved.
- Dissolution data as well as plasma concentration-time data, which were used to develop IV/IVC.
- The sponsor stated that external validation is not necessary, if the model can be internally validated. However, this statement is generally valid when the model is developed based on mean/population data. Since the IV/IVC model is developed by fitting it to each individual plasma concentration-time data, rather than using 'average/pooled data', (assuming that the internal validation uses individual parameters) the sponsor needs to submit the external validation as well. There may be additional comments when data are reviewed.

#### D. Pharmacology/Toxicology

1. As this application is intended for submission pursuant to Section 505(b)(2), does the Agency have any specific comments regarding the approach to this technical section?

##### Division's Response:

Dr. Rappaport noted that sponsor intends to reference other products; however, the Agency is reassessing ~~what we require for old opiates and what is available from the~~ literature. He noted that the Division would consider accepting a waiver for acute and chronic pharm/tox studies. However, the following studies would still be needed:

- A standard battery of studies, evaluating the mutagenic potential of morphine will be needed, preferably at the time of NDA submission, or as a Phase 4 commitment.
- Reproductive toxicology studies on embryo-fetal development (Segment II) in 2 species will be needed at the time of the NDA submission.
- Studies to evaluate the carcinogenic potential of this drug product will be needed as a Phase 4 commitment.

Dr. McCormick noted that the sponsor would not be able to complete these by the proposed March submission date and suggested that the sponsor look at the quality of

literature studies and if the material referenced is not adequate, they would have to do the studies as Phase 4 commitments.

Dr. McCormick noted that the sponsor may have to conduct additional pharm/tox studies on the salt (ie. morphine fumarate).

**E. CMC Section**

**Are there any specific comments or questions regarding the proposed data package for CMC submission or its format?**

Division's Response:

Dr. D'Sa stated that the proposed data package requires a revision by including the following CMC information:

- Section 4 A6. Drug substance: Provide chromatograms and certificates of analysis for all drug substance lots (C10520, C12599, C13471, etc) used in clinical testing with a linkage to protocol numbers/study numbers (TRG004-01, 02, 03, 04, 05 and 06; 1096003, 197006, 596009, 698002, 596008, 299001).

Impurities and degradation products have to be identified and quantified as per ICH

Because \_\_\_\_\_ is added at the drug product manufacturing stage, provide analytical evidence to show that your drug product is morphine sulfate and not morphine fumarate.

- Section 4B.2 Drug product: Provide quantitative composition, mg/tab and Kg/lot, for all \_\_\_\_\_ lots listed below (clinical test materials)

30 mg lots (n=3): —039918,  
—903 (— capsules lot mfg. at Atholone/Ireland/CFN# with date of  
mfg. 10.11.97)  
—933

60 mg lots (n=8) —904  
—039921  
—934

of  
mfg. —039920 (1 — capsules lot mfg. at Gainesville /USA/CFN# with date  
mfg. 2.99)  
—039922  
—959 (— capsules lot mfg. at Atholone/Ireland/CFN# with date of  
14.9.98)  
—4525 (— capsule lot ?)  
—14626

90mg lots (n=6) —905  
—039925

937  
39923  
039924  
9925

120 mg lots (n=5):

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

- Ranges for povidone talc, have to be justified. Target has to be specified and controlled.
- Ranges are not acceptable for blending beads and beads. Target has to be specified and controlled.
- Mean dissolution for capsules on certificate of analysis is not acceptable. Individual capsule data have to be reported (6hr, 12hrs, 22hrs in buffer pH 6.8). Also, report individual capsule data in the stability report.
- Hardening of beads upon storage has to be controlled from lot to lot and from capsule to capsule within lot.
- Provide executed batch records for all clinical lots/biolots/primary stability lots.
- Provide chromatograms at zero test point (release), at the end of clinical study duration, yearly retest points for all clinical lots.
- Impurities and degradation products have to be identified and quantified as per \_\_\_\_\_ and \_\_\_\_\_
- Development pharmaceuticals report.
- Technology transfer report from \_\_\_\_\_ to \_\_\_\_\_ summary.
- Scale-up reports summary: \_\_\_\_\_ capsules lot size to \_\_\_\_\_ capsules lot size).
- Process validation report with in-process blend test results for blend uniformity, and in-process blend uniformity for all clinical lots.
- Blister package has to be child resistant to comply with 21 CFR 1700.14 (a)(4). Child resistant test results have to be included for blisters and bottle closures.

Dr. Koepke asked the sponsor when they start the expiration dating. The sponsor responded that the start time for the expiration is \_\_\_\_\_

Dr. Koepke asked the sponsor how long they hold the beads before formulation. The firm answered \_\_\_\_\_ months and agreed to specify this fact in the NDA.

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Dr. D'Sa recommended that the sponsor follow the guidance for the Environmental Assessment.

**F. Labeling Section**

**Are there any specific comments/recommendations regarding labeling development that the sponsor should consider?**

Division's Response:

Dr. McCormick commented that the labeling will be a review issue based on their product. However, the labeling format (with respect to PK) of ——— seems adequate.

**CONCLUSIONS:**

Dr. Rappaport concluded the meeting with a reminder to the sponsor to provide the information on financial disclosure to the NDA.

**ACTION ITEMS:**

- The Division will provide the sponsor with a copy of the meeting minutes.
- Sponsor agreed to provide the CMC requests as soon as possible.

Minutes Prepared By: N. Chamberlin, Pharm.D. \_\_\_\_\_

Minutes Concurred By Chair: Bob Rappaport, M.D. \_\_\_\_\_

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cc: Original IND \_\_\_\_\_  
HFD-170/Div. Files  
HFD-170/CSO Chamberlin  
HFD-170/ C McCormick  
B Rappaport  
A D'Sa\ P Maturu  
A Goheer\ D Jean  
T Permutt  
C Schumaker  
M Scheinbaum

HFD-870/ S Kim/ R Uppoor  
HFD-820/John Gibbs/ Steve Koepke

Drafted by: N.Chamberlin 2-8-99  
Revised: 2-16-00 per Tom, Abi, Ramana, Jean , 2-17-00 per Bob & Cathie  
Initialed by: Monte, Shinja, Pat, Anwar on 2-16-00,  
Final:  
Filed under: # \_\_\_\_\_ .mtg.118.DOC  
MEETING MINUTES

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NDA 21-260

Ligand Pharmaceuticals Inc.  
10275 Science Center Drive  
San Diego, CA 92121

Attention: Howard Holden, Ph.D.  
Vice President, Regulatory Affairs and Compliance

Dear Dr. Holden:

We received your February 9, 2001 correspondence on February 12, 2001 requesting a meeting to discuss your appeal of our recommendation against the use of the tradename "Avinza." The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You requested a type A meeting. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B. The meeting is scheduled for:

Date: April 3, 2001

Time: 10:00 am

Location: 5600 Fishers Lane, Rockville, MD 20857, 3<sup>rd</sup> Floor Conference Center.

CDER participants: Cynthia McCormick, M.D. Division Director  
Bob Rappaport, M.D. Deputy Division Director  
Patricia Hartwell, M.D. Medical Officer  
Kathleen Haberny, Ph.D. Pharmacologist  
Thomas Papoian, Ph.D. Supervisory Pharmacologist  
Pat Maturu, Ph.D. Chemist  
Ravi Harapanhalli, Ph.D. Chemist

Dale Koble, Ph.D.	Acting Chemistry Team Leader
Shinja Kim, Ph.D.	Biopharmaceutics Reviewer
Suresh Doddapaneni, Ph.D.	Biopharmaceutics Team Leader
Kimberly Compton	Project Manager
Cathie Schumaker, R.Ph.	Chief Project Management Staff
Sammie Beam	Project Manager, OPDRA
Alina Mahmud, R.Ph.	Safety Evaluator, OPDRA
Judy Staffa, R.Ph., Ph.D.	Epidemiologist, OPDRA

Provide the background information for this meeting at least one month prior to the meeting. If we do not receive it by March 3, 2001, we may need to reschedule the meeting.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

*{See appended electronic signature page}*

Cathie Schumaker, R.Ph.,  
Chief, Project Management Staff  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Cc: Elan Pharmaceuticals  
1300 Gould Drive  
Gainesville, GA 30504

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Attention: Sharon Hamm, Pharm.D.  
Senior Vice President, R&D Technical Operations

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/s/

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Cathie Schumaker

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 21260/000 Priority: 3S Org Code: 170  
 Stamp: 30-MAY-2000 Regulatory Due: 20-MAR-2002 Action Goal: District Goal: 19-JAN-2002  
 Applicant: ELAN PHARM Brand Name: (MORPHINE  
 1300 GOULD DR SULFATE)30/60/90MG ER  
 GAINESVILLE, GA 30504 Established Name:  
 Generic Name: MORPHINE SULFATE  
 Dosage Form: CRC (CONTROLLED RELEASE CAPS  
 Strength: 30,60,90,120MG

FDA Contacts: S. SHEPHERD (HFD-170) 301-827-7430 , Project Manager  
 R. HARAPANHALLI (HFD-170) 301-827-7410 , Review Chemist  
 D. KOBLE (HFD-170) 301-827-7428 , Team Leader

Overall Recommendation:

**ACCEPTABLE on 04-MAR-2002 by J. D AMBROGIO (HFD-324) 301-827-0062**  
**WITHHOLD on 22-MAR-2001 by J. D AMBROGIO (HFD-324) 301-827-0062**  
**WITHHOLD on 19-OCT-2000 by P. LEFLER (HFD-324) 301-827-0062**

Establishment: 1035761 DMF No:  
 ELAN PHARMACEUTICAL RESEARC AADA No:  
 1300 GOULD DR  
 GAINESVILLE, GA 30504

Profile: CTR OAI Status: OAI ALERT Responsibilities: FINISHED DOSAGE  
 Last Milestone: OC RECOMMENDATION MANUFACTURER  
 Milestone Date: 04-MAR-2002  
 Decision: ACCEPTABLE  
 Reason: DISTRICT RECOMMENDATION

Establishment: [ ] DMF No:  
 AADA No:

Profile: CTL OAI Status: NONE Responsibilities: [ ]  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 01-FEB-2002  
 Decision: ACCEPTABLE  
 Reason: BASED ON PROFILE

Establishment: [ ] DMF No:  
 AADA No:

Profile: CSN OAI Status: NONE

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **01-FEB-2002**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

Responsibilities: [ ]

Establishment: [ ]

DMF No:  
AADA No:

Profile: **CTR**            OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **01-FEB-2002**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

Responsibilities: \_\_\_\_\_

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