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/s/

Sara Shepherd
9/11/02 12:49:04 PM
CSO

MEMORANDUM

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

DATE: September 4, 2002

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

VIA: Sara E. Shepherd, Regulatory Health Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Suboxone®
(buprenorphine HCL/naloxone HCL dihydrate) sublingual tablet
and Subutex® (buprenorphine HCL) sublingual tablet

The patient labeling which follows represents the revised risk communication materials for Suboxone® (buprenorphine HCL/naloxone HCL dihydrate) sublingual tablets and Subutex® (buprenorphine HCL) sublingual tablets and has been reviewed by our office and by DDMAC. The revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments are bolded, italicized, and underlined.

6 Draft Labeling Page(s) Withheld

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/s/

Jeanine Best
9/9/02 02:39:31 PM
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Anne, This is due today to the review division.
I just made a few corrections and re-entered
it into DFS for sign-off.

Anne Trontell
9/10/02 03:20:21 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: August 28, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, Neil Hyde, Graham Cairns, Chris Chapleo, Lisa Withers, and Andrea Knowles
Phone: USA Toll Free Number
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Ali Al Hakima, Pat Maturu, Tom Permutt, Celia Winchell, and Dale Koble, Division of Anesthetic, Critical Care, and Addiction Drug Products,
HFD-170

SUBJECT: Weekly TC

August 28, 2002

The Sponsor stated that the *in vivo* dissolution data will be completed by the end of September.

The Division stated that approval will not be delayed based on the deficiencies with the DMFs for the _____ If necessary the Sponsor will withdraw the _____ and the approval will be based on the bottles.

The Division stated that _____ submitted a partial response to the _____ /DMF issues. The Sponsor noted that the recent naloxone batches had less than _____ of the _____ present, thus, _____ must be dealing with the impurity.

The Division stated that _____ (or _____) was still a concern. Since this information is relatively new, it might be possible to use the _____ initially and to have a commitment with a specified timeframe for obtaining impurity and mutagenicity testing. The Sponsor stated that they will contact _____ and later submit a proposal to the Division.

Post Meeting Note: An alternate method of qualifying the safety of the _____ would be demonstration that it is a significant animal and/or human metabolite.

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/s/

Sara Shepherd
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**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: July 30 and 31, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, Neil Hyde, Graham Cairns, Chris Chapleo, Lisa, Withers, and Andrea Knowles
Phone: USA Toll Free Number
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Ali Al Hakima, Celia Winchell, Pat Maturu, Dan Mellon, and Dale Koble, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Weekly TC

July 30, 2002

The Division informed the Sponsor that the specifications for naloxone did not follow ICH criteria. The Sponsor stated that the naloxone complies with the USP and European Pharmacopei (EP) but not with ICH Q3A. The Division suggested that the Sponsor communicate with _____ and have the specifications tightened. The Sponsor agreed.

The Division also informed the Sponsor that there is a structural alert for mutagenicity for one of the impurities in naloxone _____. The Sponsor stated that the EP lists _____ impurities for naloxone. The Division requested that the Sponsor fax the naloxone section of the EP and the Sponsor agreed.

The Sponsor agreed to review their qualification studies and analyze the impurities to determine if this impurity is present and at what concentrations. The Sponsor will fax this information to the Division.

The Division stated that more internal discussions are needed to determine the appropriate specifications for this impurity. It was suggested that this impurity is a _____ versus a _____ and may be present in other narcotic drugs.

Post TC note:

The Division called _____ with regard to DMF _____ and informed them of the structural alert for mutagenicity for the _____. _____ agreed to provide a flow chart of the synthesis beginning with the natural product, and a stability update on naloxone.

The Division advised _____ to develop a sensitive method to detect the naloxone impurity. _____ is familiar with the EP but stated that the EP does not provide retention times for the _____ impurities.

The Division stated that ICH Q3A requires identification of anything at or above 0.1% and qualification of anything at or above 0.15%. Since this impurity is a possible mutagen, it is unclear what specifications are appropriate and the Division stated that internal discussions will be needed before a decision can be reached.

July 31, 2002

The Division and the Sponsor agreed that the data provided by the Sponsor demonstrates that the naloxone impurity is present in the naloxone. The Division questioned if this material was available for testing in a pure form. The Sponsor stated that they attempted to contact _____ to discuss the situation but were unsuccessful. Since the Division had talked to _____ on July 30, 2002, the contact name and phone number were provided to the Sponsor to help expedite the communication with _____

The Sponsor stated they plan to perform _____ studies for the potentially mutagenic impurity.

The Division advised the Sponsor to collect data on the incidence and level of impurities. The Sponsor should reexamine what lots were used with the mutagenicity and genotox studies and clarify if this impurity was present. Additional mutagenicity studies may be needed on this chemical entity. The Division also advised the Sponsor to perform a literature search on this and similar impurities. In the meantime, the Division will initiate internal discussions to determine the best approach.

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/s/

Sara Shepherd
8/5/02 02:40:20 PM
CSO

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MEMORANDUM OF TELECON

DATE: July 24, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, Neil Hyde, Graham Cairns, Chris Chapleo, Lisa Withers, and Andrea Knowles
Phone: USA Toll Free Number
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Ali Al Hakima, Celia Winchell, and Dale Koble, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Weekly TC

July 24, 2002

Prior to the teleconference, the Sponsor sent information on the propose storage statement.

Store at

The Sponsor noted that this represents a change to that proposed by the Division but is similar to what the Sponsor proposed on the carton and bottle artwork submitted previously. The Sponsor stated that similar wording is used in the US and the use of _____ is recommended in the USP in the General Notices section.

The _____ was recommended by the Division for Suboxone and the Sponsor agreed. In addition, the Sponsor proposed to have the same precaution on the Subutex label to maintain the similarity of the two products. However, the Division questioned if both drug products are _____ he Sponsor said that both buprenorphine and naloxone were _____ 'reviously the Subutex was in _____ and the Suboxone was in _____

The Division referred the Sponsor to the draft stability guidance on the internet that has the appropriate storage statement. The Sponsor stated they will review this document. In the meantime the Division will send the Sponsor an appropriate storage statement.

Follow-up: An e-mail was sent on July 25, 2002, that stated that the following is the general storage statement usually recommend by the Division:

NDA 20-732, NDA 20-733

July 24 TC

Page 2

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP
Controlled Room Temperature]

The Sponsor agreed to incorporate this into the labeling.

DMFs

The Division stated that they have not received an adequate response from the holder of DMF
_____. Another letter will be sent to the DMF holder.

The Division advised the Sponsor that there are issues with DMF _____ and _____. Both of these
DMFs are for _____ Letters will be sent to both DMF holders. The
Division stated that there does not appear to be any issues with the DMFs for the _____

Risk Management Plan

The Division stated that they are in the process of reviewing the revised patient package insert
(PPI) and Question/Answer (QA) brochure from the risk management plan. The PPI needs to be
formatted into a standard MedGuide format which the Division is undertaking. The material has
been sent to DDMAC and ODS for comment.

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/s/

Sara Shepherd
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NDA 20-732, NDA 20-733
July 18 TC
Page 1

MEMORANDUM OF TELECON

DATE: July 18, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, and Neil Hyde
Phone: USA Toll Free Number
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Ali Al Hakima, Celia Winchell, and Tom Permutt,
Division of Anesthetic, Critical Care, and Addiction Drug Products,
HFD-170

SUBJECT: Weekly TC

July 18, 2002

Prior to the teleconference, the Sponsor sent a summary of the statistical analysis of the Subutex and Suboxone tablet stability data. The full reports will be sent once finalized.

The Sponsor stated that they would prefer the bottles and not the [redacted] Based on the data sent for the bottles, the Sponsor proposed a shelf-life of [redacted] for Subutex and [redacted] for the Suboxone tablet. The Division stated that from their analysis of the data, Subutex would have a [redacted] shelf-life and the Suboxone would be [redacted]. However the Division noted that the Suboxone data is driven by only [redacted] batch.

The Sponsor will provide a list of changes of sections/pages that have been modified since the March 13, 2002 CMC submission. The Division agreed to this approach.

The [redacted] information has been adapted to match the DMF and will be submitted with the update. The DMF has the information already and no changes will be needed to it.

The Sponsor confirmed that [redacted] was a secondary site for manufacturing buprenorphine. However this site is no longer used and the buprenorphine is being manufactured by Reckitt Benckiser.

The Division also requested the location of the full study report on the [redacted] study within the NDA. The Sponsor will follow up and send in a desk copy.

Risk Management Plan

The Division questioned if the Sponsor had read the latest revised information (Physician Information, Patient Package Insert) sent to the Division. The Sponsor stated that they had not

NDA 20-732, NDA 20-733

July 18 TC

Page 2

reviewed the document from Schering Plough prior to sending it to the Division. The Division provided examples of the problems (i.e., _____ n) with the revised version and the Sponsor stated they will follow up with Schering. The Division suggested a teleconference call with Schering to discuss the issue and the Sponsor agreed.

Follow-up: The Sponsor called later and stated that the document sent to the Division was not the correct version. The Sponsor stated that this information was _____ The Sponsor will send in the correct version. A teleconference was arranged for later in the day and this information was relayed to Schering Plough. The Division also requested WORD versions to help in the review process.

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/s/

Sara Shepherd
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MEMORANDUM OF TELECON

DATE: July 8, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, and Neil Hyde
Phone: USA Toll Free Number
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Dale Koble, Ali Al Hakima, Celia Winchell, and Tom Permutt, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: CMC issues/weekly TC

July 8, 2002

Prior to the teleconference, the Sponsor sent a draft report of the latest F1 and F2 data on the hexagonal tablets. During the teleconference the Sponsor noted that [redacted] lot did not meet the specifications for F1 and F2 (i.e., it had a quicker dissolution time). Of the [redacted] lots, the lot that had faster dissolution was the lot shipped for use in the dissolution study. The Sponsor asked for feedback on the fact that the [redacted] lot not meeting the F1/F2 criteria would be used in the *in vivo* dissolution study. In addition, the Sponsor had no explanation on why this particular lot acted differently than the other [redacted] lots.

NOTE: The Division reviewed the data and advised the Sponsor that it should be acceptable to use the faster dissolving tablets in the *in vivo* dissolution study on the hexagonal shaped tablets.

The Sponsor stated that [redacted] batches of the hexagonal tablets have been manufactured and packed. The stability study was initiated on July 4, 2002. The [redacted] data will be available for the Division's review by the third week in August.

The Sponsor stated that a report is in preparation that describes the hardness and physical characterization of the hexagonal tablet.

The Division advised the Sponsor that there is an issue with DMF [redacted] and that the DMF holder has been contacted. The DMF is for the [redacted]

The Sponsor is still working on updated the graphic from the [redacted] in the DMF to match that listed in the NDA.

The Sponsor stated that the stability data is being tabulated and formal reports will be generated. The statistical analysis has been completed for Subutex but not for Suboxone. The Sponsor stated that from their interpretation of the data, the shelf-life may be

Risk Management Plan

The Sponsor is still waiting for final comments from Dr. Schuster and Schering Plough. The Sponsor will send the revised Education Materials for comment.

Labeling

The Sponsor is still reviewing the revised labeling sent to them. The Division stated that the dose modification in hepatic failure is still under review.

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/s/

Sara Shepherd
7/19/02 11:13:34 AM
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MEMORANDUM OF TELECON

DATE: June 26, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, and Neil Hyde
Phone: USA Toll Free Number
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Dale Koble, Ali Al Hakim, Tom Permutt, Celia Winchell, Pat Maturu, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Outstanding CMC issues

June 26, 2002 Teleconference

The Division and the Sponsor reviewed the current status of the applications.

The Sponsor just sent in stability data for Subutex (12-month, 12-month bottles) and Suboxone (12-month, 12-month bottles). For Subutex, the Sponsor stated that all parameters have been tested at 25⁰ C and 30⁰ C but not 40⁰ C. For Suboxone, there is missing data on the bottles because the analysis is still on going. The formal reports will be submitted soon. The Sponsor only sent the raw data and no statistical analysis has been done yet (waiting for Suboxone data).

The 8 mg hexagonal tablet has been packed and the 2 mg hexagonal tablet is being packed and the stability study will be started soon.

The Sponsor also sent in statements or

The Sponsor noted that

is used for both tablet strengths. This information is noted in the manufacturing section of the NDA.

The Division reminded the Sponsor that the batches on stability should not be from a

The Sponsor stated that the batches are from

The Sponsor will submit the revised pages of the March 2002, CMC submission in the next two weeks. Included in this submission will be justification of the new specification. The specifications will be updated for the versus the hexagonal tablets and the in-process controls.

The Sponsor is still resolving the issue about the description of how to remove the cap; different in the NDA as compared to the graphic printing on the bottle cap which was provided as a sample to the Division. The Division noted that there are two descriptions in the DMF and the Sponsor should reference the one that will be used on the bottle. The Division requested that this should be updated in the NDA.

The Sponsor questioned how to write the distribution plan in the Risk Management Plan when the expiration date has not yet been determined. The Division stated that based on the data submitted, the Sponsor should be able to draw a conclusion about the expiration date. The data is still under review by the Division. The Division reminded the Sponsor that it cannot extrapolate 6 months past real time. The data on the hexagonal Suboxone tablet will be ready by August. The shelf-life will be based on the tablet data and the hexagonal tablet data will also be taken into consideration. It is expected that the hexagonal tablet data will be comparable to the tablet stability data and there will be a trend. The Division suggested taking additional points during the first month of the stability study but the Sponsor stated they would not have time to do an analysis.

The Division questioned which parameter was limiting the expiration dating period for the drug product and the Sponsor stated that the determining parameter was the naloxone impurities. There was a discussion about revising the specifications of naloxone impurities but it was decided that the current specifications were sufficient.

The Sponsor is still awaiting comments from Dr. Schuster and Schering Plough before sending in a revised risk management plan.

The Sponsor will also be sending in a revised label based on the comments the Division sent.

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/s/

Sara Shepherd
7/9/02 09:16:49 AM
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MEMORANDUM OF TELECONS

DATE: June 5 and June 18, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, Graham Cairns, Lisa Withers, Neil Hyde
Phone: USA Toll Free Number
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Dale Koble, Ali Al Hakim, Tom Permutt, Celia Winchell, Pat Maturu, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Outstanding CMC issues

June 5 and June 18, 2002 Teleconferences

The Division and the Sponsor reviewed the current status of the applications.

The Division questioned if there had been any issues with the currently marketed lots of Subutex. The Sponsor stated that no problems have been reported. The problems appear to be the same for Subutex and Suboxone.

The Division asked for clarification on the flavor agents added to Suboxone. The Sponsor stated that there are no flavor agents in Subutex. It is present in the Suboxone due to

The Sponsor asked for information on the timing of the inspection of the packaging site. The Division stated that this site has been found acceptable due to previous inspections over the past two years.

The Division asked for clarification on the to-be-marketed tablet shape. The Sponsor stated that Subutex will be oval and Suboxone will be hexagonal.

The Division received the information on the developmental tablet. The Sponsor stated that the recent F1/F2 (comparative dissolution) data was generated from orange tablets with different . The Sponsor was setting in-process controls for ..

The Sponsor stated that the [redacted] batch of hexagonal-shaped tablet is being [redacted]. The stability studies should start by July 1, 2002. The [redacted] stability data should be sent to the Division by August 15 or the week of August 19, 2002.

The Division reminded the Sponsor to link the recently [redacted] batches with the commercial lots.

The Division had no comments on the *in vivo* dissolution protocol and the Sponsor is sending it to the IRB no later than June 19, 2002. By the time the IRB review is complete the hexagonal tablets will have been prepared for the study.

The Division reminded the Sponsor to submit the dissolution data with the additional time point (i.e., a 7.5min point). The Sponsor stated they will have 1-year stability on the [redacted] tablet in the [redacted] bottle for Suboxone. There is [redacted] on the Subutex in [redacted]. The [redacted] hexagonal Suboxone tablet will be ready in August.

There was a discussion about the [redacted] versus the bottle packaging. Although the bottle appears to have a data for a longer shelf life, it was agreed to continue pursuing both packaging processes in the NDAs.

The Sponsor asked if the child-resistant packaging was acceptable. The Division replied that it appeared adequate. However, the Division noted that the description about how to remove the cap was different in the NDA as compared to the graphic printing on the bottle cap. The Sponsor stated they will correct this.

The Division stated they received the information on the [redacted] and it is under review.

The Division stated that there still may be an issue with the DMF holder for the [redacted]. The Sponsor stated they were aware of this issue (may not be an issue if they use the bottle packaging).

Risk Management Plan

The Sponsor questioned the [redacted] expiration date listed in the plan. The Division stated this was to address the reality of the situation with regards to the previous data. The expiration date will be determined during this review cycle.

Package Insert

The Division stated that they would send a DRAFT label to the Sponsor today. The bottle label will need to be updated with the appropriate storage conditions. The Division reminded the Sponsor to send in an official response about the nomenclature comments from DMETS.

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/s/

Sara Shepherd
7/9/02 09:10:15 AM
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MEMORANDUM OF TELECON

DATE: May 28, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe; Alan Young, Graham Cairns, Alf Davis,
Lisa Withers, Neil Hyde
Phone: USA Toll Free Number: 1-888-459-7564/passcode
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Dale Koble, Ali Al Hakim, Tom Permutt,
Division of Anesthetic, Critical Care, and Addiction Drug Products,
HFD-170

SUBJECT: → the 2 mg Suboxone tablet and other outstanding CMC issues

May 28, 2002 Teleconference

The Division and the Sponsor reviewed the outstanding action items:

- The tabulated statistical analysis of the stability data was received by the Division (*complete*)
- Provide comparison of USP versus European Pharmacopiea specifications/methods (excipients) (*complete*)
- Provide information on DMF _____ (*complete*)
- Provide → data of the hexagonal tablet with detailed explanations (*by May 31*)
- Provide F2 comparison of dissolution data (*initial data sent May 28*)
- Provide details on any — issues at U.S. clinical trials site (*by May 31*)
- Provide — data from _____
- Provide information on the holding time between release of drug product and packaging as there was no description found in the resubmission (*to be submitted*)
- Update storage statement in label (*to be submitted*)
- Add a 7.5min point on the 1 year stability data (*by June*)
- Provide statement that there is — of drug product (*to be submitted*)
- Provide stability/ — data on developmental batch — stability) and explain the new formulation (*to be submitted*)
- Provide a comparison of the drug substance specification in the DMF being consistent with the specifications in the application. (*to be submitted week of June 3*)
- Provide samples of the 2mg hexagonal shaped tablet (*complete*)
- Provide samples of the 8mg hexagonal shaped tablet (*by May 31*)
- SUPAC F1 and F2 on 2 mg hexagonal tablet (*complete*)

- SUPAC F1 and F2 on 8 mg tablet *(to be submitted)*
- Dissolution data on 2 mg and 8 mg hexagon tablet as discussed in May 23 telecon *(to be submitted)*
- Initiate stability studies on _____ batches of the 2 mg and 8 mg hexagon tablet. Sample at _____ *(to be submitted)*
- Provide information on the new manufacturing process and compare stability data with _____ tablet *(to be submitted)*
- Provide *in vivo* dissolution data as discussed in the May 23, 2002, teleconference *(to be initiated/submitted)*
- DMF/EVC _____ issues as stated in May 22, 2002 fax *(may not be an issue if Sponsor uses bottle and not _____)*

NOTE: As a follow-up to a questioned posed by Dr. AlHakim, the _____ test has been completed _____ and the tablets are not _____

/S/

Sara E. Shepherd
Regulatory Project Manager

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Sara Shepherd
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MEMORANDUM OF TELECON

DATE: May 23, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe,

Phone: 1-804-379-1090

Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Dale Koble, Ali Al Hakima, Tom Permutt, Celia Winchell, Suresh Doddapanenis, Parinda Jani, Bob Rappaport, Eric Duffy, Cynthia McCormick, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: CMC issues. — tablet

May 23, 2002 Teleconference

Scheduling Issues

The Division stated that preliminary comments from the DEA suggest no requests for a hearing, yet.

Hepatic Data

The Clinical review on the safety update has been completed. A post marketing surveillance study will be included in the action letter. This study will provide information on the hepatotoxicity issue.

Risk Management Plan

The Division will provide additional comments to the Sponsor. The Sponsor has been making changes to the plan based on the 10 issues that were sent to them from the Division (comments from the Office of Drug Safety). It was agreed that the Sponsor will submit a revised plan after receiving the additional comments from the Division.

CMC Issues

It was proposed that the Sponsor manufacture 8mg hexagonal tablets as well as the 2 mg tablets to keep the shape consistent for the drug product. The Sponsor stated they have — production batches and dissolution data available and will provide this data to the Division.

The Division advised the Sponsor to initiate stability studies with the hexagonal tablet as soon as possible. The Sponsor agreed. The Division stated that this would allow at least ~~_____~~ stability data to be available for review prior to the action date (October 8, 2002). The Division also requested F1 and F2 tests on all ~~_____~~ batches. The Sponsor clarified that not changes will be made in the packaging prior to the action date but maybe done as a post approval supplement ~~_____~~. The Sponsor noted that the stability data for the new manufacturing process will be provided as supportive data to the applications.

The Division stated that the new tablet shape will require *in vivo* dissolution data. No plasma levels will be needed. The study should be similar to the Sponsor's recent pharmacokinetic study (01-1). The study should be a randomized, three way cross-over with at least ten subjects (healthy subjects administered naltrexone to block opioid agonist effects or opiate dependent subjects). The study should include the ~~_____~~ tablet as a control and be a 20 mg dose (2 x 8 mg + 2 x 2 mg tablets) given simultaneously or sequentially. A letter will be sent to the Sponsor with details about the study. The evaluations should include (a) an examination of the subject's mouth periodically and time taken for dissolution of the tablets and (b) any discomfort that the subjects may experience with the use of hexagon tablets. If needed, it was agreed that a teleconference will be arranged between the Division, the Sponsor, and NIDA.

The Sponsor noted that the hexagon tablet manufactured by the new process will soon be submitted for approval in the European market.

Nomenclature

The Division advised the Sponsor that the proprietary names Subutex and Suboxone are not acceptable to the Division of Medications Errors and Technical Support (DMETS). A letter will be sent to the Sponsor with specific details. The Division advised the Sponsor to provide a rationale for keeping the names Subutex and Suboxone. The Sponsor agreed.

/s/

Sara E. Shepherd
Regulatory Project Manager

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/s/

Sara Shepherd
6/10/02 02:19:47 PM
CSO

**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: May 20, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, Alan Young, Graham Cairns, Alf Davis,
Lisa Withers, Neil Hyde
Phone: USA Toll Free Number: 888-603-8923/passcode
Representing: Reckitt Benckiser

AND

Name: Sara E. Shepherd, Dale Koble, Ali Al Hakima, Tom Permutt, Celia
Winchell, Division of Anesthetic, Critical Care, and Addiction Drug
Products, HFD-170

SUBJECT: CMC issues

May 20, 2002 Teleconference

The Division requested that the Sponsor provide a comparison of the information in the resubmission with the data recently submitted to the Division with regards to the new tablet shape. The Sponsor agreed to provide this information.

The Sponsor stated that they faxed the F2 dissolution data (today) as requested during the May 14, 2002 teleconference. The data was generated in the developmental batch of the 2mg hexagonal tablet (new manufacturing process).

The Division requested that the Sponsor initiate stability studies on batches of the to be commercialized hexagonal tablets. The Sponsor agreed to initiate this study.

The Division questioned if the Sponsor will keep the 8mg Suboxone tablet or change to hexagonal. The Sponsor replied they would prefer to change the 8mg to make it consistent with the 2 mg tablet. The Sponsor questioned if they could go to market with just the 8mg tablet. However, the Division stated that the 2mg and the 8mg would be needed at launch.

The Division requested samples of the 8mg hexagonal and tablets (placebo). The Sponsor agreed to provide the samples.

It was decided that the teleconferences would continue on a weekly basis.

Sara E. Shepherd
Regulatory Project Manager

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/s/

Sara Shepherd
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**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: May 13 and May 14, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex) and NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe, Alan Young, Graham Cairns, Alf Davis,
Lisa Withers, Neil Hyde
Phone: USA Toll Free Number: 888-603-8923/passcode
Representing: Reckitt Benckiser

AND

Name: Cynthia McCormick, Sara E. Shepherd, Dale Koole, Ali Al Hakima,
Division of Anesthetic, Critical Care, and Addiction Drug Products,
HFD-170

SUBJECT: — the 2 mg Suboxone tablet and other CMC issues

May 13, 2002, Teleconference

Charles O'Keeffe called on May 10, 2002, requesting that a teleconference be arranged with Dr. McCormick to discuss a quality assurance problem with Suboxone. The participants for the teleconference on May 13, 2002, were Charles O'Keeffe, Cynthia McCormick, and Sara Shepherd. Mr. O'Keeffe informed the Division about the — the 2 mg Suboxone tablets in the bottles. Their plan was to change the shape of the — 2 mg tablet to a hexagonal shaped tablet with no change in the current formulation. The Division expressed concern about a possible change in bioavailability with the new shape. Since the May 13, 2002, teleconference was just to inform Dr. McCormick of this new development, the — issue was discussed in more detail at the May 14, 2002, teleconference which had been previously arranged to discuss outstanding CMC issues.

May 14, 2002, Teleconference

— *Issue*

It was noted that during a December 2001 meeting with the Sponsor that the Division requested — data be performed on the tablets since the Sponsor was examining the packaging of the drug product in bottles versus — to improve the stability of the drug product. The Sponsor began the — studies by following the European Pharmacopeia method and not the USP. During the — testing it was noted that there was — the 2mg Suboxone tablets.

The Sponsor stated they have developmental batches of hexagonal shaped tablets — (stability) available. These batches are from the new formulation (—). The Division stated that this data could be used as supportive information for the change in tablet shape.

The Division stated that a bioavailability study may be needed to support the change in the tablet shape. The Division will discuss this internally and inform the Sponsor of what information will be needed. However, the Division requested that the Sponsor perform an F2 comparison of the dissolution data and send this information to the Division. The Sponsor stated they have some dissolution data with hexagonal shaped tablets from a new manufacturing process and could provide this to the Division.

The Division stated that the stability data for the — tablet is under review. There is concern that if problems are noted with the stability data from the — then there will be added doubt about the hexagonal tablet.

The Division questioned if the stability studies were done with product from the commercial packaging sites or is the Sponsor proposing a change in the site. The Sponsor stated that they will not change the site and confirmed the stability studies were done with product from the commercial site.

The Division questioned if table' — in the field was being reported to the Sponsor. The Sponsor will follow up with the distributor to determine if there has been a problem with —

Additional Issues

The Division asked the Sponsor to provide information on the holding time between release of drug product and packaging as there was no description found in the resubmission. The Sponsor agreed to provide this information.

The Division asked if any — was done. The Sponsor replied that no — was done and will follow up with a submission to the NDA.

The Division asked the Sponsor to modify the storage statement in their label. The Sponsor agreed to modify this statement.

The Division stated that there were only two points provided with the dissolution data. The Division requested that data should be taken at 7.5 min. and the Sponsor agreed. The Division also noted aberrant data points in the assay, which may shorten the expiry date. The Sponsor replied that these are lab errors. The Division stated that these data points should be explained as lab error or the data will be used in the analysis. (It should be noted that the Sponsor sent the statistical data in electronic format as requested by the statistician).

The Division inquired if the drug substance specification in the DMF were consistent with the specifications in the application. The Sponsor will provide this information.

Scheduling

The Sponsor stated that the scheduling will be changed on the label as required. The Division requested information on the time of launch relative to the approval action. The Sponsor stated that the product —

Sponsor to provide the following information

- The tabulated and statistical analysis of the stability data was received by the Division
- Provide comparison of USP versus European Pharmacopeia specifications/methods (excipients)
- Provide information on DMF _____
- Provide _____ data of the hexagonal tablet with detailed explanations
- Provide F2 comparison of dissolution data
- Provide details on any _____ issues at U.S. clinical trials site
- Provide _____ data from _____
- Provide information on the holding time between release of drug product and packaging as there was no description found in the resubmission
- Update storage statement in label
- Add a 7.5min dissolution point on the 1 year stability data
- Provide statement that there is _____ of drug product
- Provide stability _____ data on developmental batch _____ and explain the new manufacturing process
- Provide a comparison of the drug substance specification in the DMF being consistent with the specifications in the application.
- Provide samples of the 2mg hexagonal shaped tablet

The Sponsor agreed to provide this information. The Division also noted that the no action could be taken on the applications by June due to the extensive amount data needed because of the tablet shape change.

|S|

Sara E. Shepherd
Regulatory Project Manager

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Sara Shepherd
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NDA 20-733

INFORMATION REQUEST LETTER

Reckitt & Benckiser
1901 Huguenot Road
Richmond, VA 23235

Attention: Alan N. Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suboxone (buprenorphine HCL/naloxone).

We also refer to the teleconference on May 23, 2002, and your proposal to change the — shaped tablet to a hexagon shaped tablet due to —

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests related to the tablet shape change. We request a prompt written response in order to continue our evaluation of your NDA.

1. The dissolution of 20 mg dose (2 x 8 mg + 2 x 2 mg tablets) of — and hexagon shaped tablets should be investigated *in vivo*. In a randomized, three way cross-over fashion, at least ten subjects (healthy subjects administered naltrexone to block opioid agonist effects or opiate dependent subjects) should be administered with the following three treatments;

Treatment A: 20 mg dose (2 x 8 mg + 2 x 2 mg tablets) of — shaped tablet administered simultaneously

Treatment B: 20 mg dose (2 x 8 mg + 2 x 2 mg tablets) of hexagon shaped tablet administered simultaneously

Treatment C: 20 mg dose of hexagon shaped administered sequentially, i.e., 2 x 8 mg tablets followed by 2 x 2 mg tablets after the complete dissolution of 2 x 8 mg tablets.

2. The evaluations should include (a) an examination of the subject's mouth periodically and time taken for dissolution of the tablets and (b) any discomfort that the subjects may experience with the use of hexagon tablets.

3. The study design aspects from completed pharmacokinetic study 01-1 can be incorporated into this study.
4. Additional investigations may need to be carried out if there is a significant increase in *in vivo* dissolution time for the hexagon shaped tablets compared to the — tablets.
5. Submit your study protocol for comment by the Division. The *in vivo* study will need to be completed prior to the Division taking action on this application.

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/30/02 09:21:30 AM

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Memo

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

From: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

Through: Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Sara E. Shepard
Project Manager, HFD-170

Date: May 21, 2002

Re: OPDRA Consult 00-0143; NDA 20-732 Subutex (Buprenorphine Hydrochloride Sublingual Tablets) and NDA 20-733 Suboxone (Buprenorphine Hydrochloride and Naloxone Hydrochloride Sublingual Tablets)

This memorandum is written in response to an April 19, 2002, request from your Division for review of the proposed proprietary names, Subutex and Suboxone. The sponsor for both applications is Reckitt and Colman Pharmaceuticals, Inc.

I. INTRODUCTION

The Division submitted a review for the proprietary name Suboxone on August 5, 1999, which we found acceptable. Suboxone is a combination product containing the active ingredients buprenorphine hydrochloride and naloxone hydrochloride that will be indicated for opiate dependence.

However, at the time of the review DMETS was unaware of the proposal to submit a companion product namely, Subutex. Subutex contains the active ingredient buprenorphine hydrochloride. Subutex will also be indicated for opiate dependence and is presently marketed in Europe for the same indication of use.

Currently, the sponsor markets an injectable formulation of buprenorphine hydrochloride in the United States under the proprietary name Buprenex. Buprenex was approved prior to January 1, 1982 under NDA 18-401 for the treatment of moderate to severe pain. Given the existence of Buprenex, DMETS was concerned that the introduction of a different name for a new dosage form containing the same active ingredient would create confusion in the market place. DMETS recommended the best nomenclature approach to pursue was _____

7

According to e-mail from the Division, they are going to allow the use of Subutex and Suboxone despite our original recommendations. If approved there will effectively be three products on the market from the same manufacturer that contain the same active ingredient:

- Buprenex Injection (Buprenorphine Hydrochloride)
- Subutex Sublingual Tablets (Buprenorphine Hydrochloride)
- Suboxone Sublingual Tablets (Buprenorphine Hydrochloride and Naloxone Tablets)

II. RISK ASSESSMENT

DMETS disagrees with the proposal to market buprenorphine hydrochloride and buprenorphine hydrochloride/naloxone hydrochloride tablets under alternate proprietary names than the existing approved proprietary name Buprenex.

Pursuant to a December 1, 2000, CDER policy meeting with the Center Director, Janet Woodcock, M.D. and senior management, DMETS strongly discourages the use of different proprietary names by the same applicant and/or manufacturer for products that contain the same active ingredient. We have been consistent with this policy, as we have objected to several such proposals. A most recent example is that of Zoloft/Zoloft-PMDD. The Agency is concerned that the proliferation of proprietary names may be misleading and may also lead to product confusion resulting in medication errors and/or patient harm for the following reasons:

- Practitioners and patients may not realize that two drug products with different names might actually be the same drug product. This could lead to a potential overdose if a patient is seen by different practitioners for different reasons and is prescribed two prescriptions (with different names) for the same active ingredient.
- A patient who is allergic or intolerant of an active ingredient might unknowingly take the drug again under a different proprietary name.

- When two generic equivalents become available to the two branded proprietary name/products, selecting the correct generic product could be especially difficult for the pharmacist, since both generic products would likely not have proprietary names and would have the same established name. The package insert of these generic products would be the only reasonable way to discern the different products and their associated indications and uses.
- The use of an alternate proprietary name for the same active moiety and different indications of use is misleading to practitioners and patients. Certain well-established adverse events and risks are associated with the existing proprietary name and approved indications of use. However, patients and health care providers may be falsely assured that the medication does not carry significant risks because the FDA has approved its use for a new indication under a different name.

In summary, we believe the safe use of this product is best managed under one proprietary name. DMETS believes the most effective strategy will be in direct-to-consumer advertising and educational campaigns about this newly approved indication for opiate dependence

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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/s/

Carol Holquist
5/21/02 01:47:21 PM
PHARMACIST

Jerry Phillips
5/21/02 02:07:09 PM
DIRECTOR

Shepherd, Sara

From: Shepherd, Sara
Sent: Tuesday, May 14, 2002 3:13 PM
To: 'Hyde, Neil'; Shepherd, Sara; O'Keefe, Charles
Cc: Young, Alan
Subject: info request

Neil,
Dr. Al Hakim has asked me to forward the following request.

The sampling plan for the analytical methods could not be located, please provide the following information regarding the sampling plan:
1) Specify the number of individual drug product samples, which will be analyzed in each test based on the proposed batch formula. This is different from general sampling procedures required under CGMPs.

2) Brief Overall description of the sampling plan(s) for production batches and selection of sub-samples for analysis.

3) Location for samples subjected for analysis (e.g., beginning, middle, end) and the number of samples per production batch.

If the answer is in the NDA, please give us the page volume and page number.

Thanks
Sara

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/s/

Sara Shepherd
5/14/02 03:26:56 PM
CSO

Shepherd, Sara

From: Shepherd, Sara
Sent: Monday, April 22, 2002 11:44 AM
To: Charles O'Keeffe (E-mail); 'alan.young@reckittbenckiser.com'
Subject: info request

Charles and Alan

Please address the issues listed below with a formal submission to the NDAs.--Thanks

- 1) In order to insure the that your response to Item 8 is complete, indicate where the response to each of the individual points in Item 8 (ie, Item 8(a), 8(b)(1), 8(b)(2), through 8(b)(9)) of the January 26, 2001 Approvable letter is located in the submission.
- 2) Indicate if all the deaths in the published reports are included in Attachment 3, Part 2 (Tables 1 and 2). If the deaths are not located in this section, indicate where in the resubmission they are summarized.
- 3) Indicate if all the adverse events and serious adverse events in the published reports are included in Attachment 3, Parts 3 and 4. If the adverse events and serious adverse events are not located in these sections, indicate where they are located.

Sara E. Shepherd
Regulatory Project Manager
FDA/CDER/Division of Anesthetic,
Critical Care, and Addiction Drug Products
301-827-7430

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Sara Shepherd
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MEMORANDUM OF TELECON

DATE: March 11, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex), NDA 20-733 (Suboxone)

BETWEEN:

Name: Charles O'Keeffe
Phone: 804-379-1090
Representing: Reckitt Benckiser Pharmaceuticals, Inc.

AND

Name: Celia Winchell, M.D., Medical Team Leader
Gerald DalPan, M.D., Medical Reviewer
Cynthia McCormick, M.D. Division Director
Sara E. Shepherd, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products

SUBJECT: To discuss the Risk Management Plan submitted February 19, 2002. There was also a brief discussion of the Safety Update submitted December 31, 2001.

1. There was a brief discussion on the recent submissions to the NDAs
 - a. The pharmacology/toxicology study has been reviewed.
 - b. The pharmacokinetics review is nearly complete. However, the Division noted that other PK studies were found in the Safety Update. There was information on a _____ formulation and a study using ketaconazole. The Sponsor stated that they are not asking for approval of the " _____ product. It was include in the Safety Update to make a complete package. The Sponsor stated that the ketaconazole study was probably submitted to the Schering IND as a final study report. The Division indicated that only items submitted to the NDA would be reviewed, and that the submission of the study report to the IND would not accomplish its inclusion in the NDA.
 - c. The Sponsor stated that the full CMC section should arrive the week of March 11, 2002. The Division stated that the Safety Update also included chemistry. The Sponsor clarified this was added for completeness of the Safety Update and the same chemistry would be in the full CMC section.

2. Risk Management Plan (RMP)

The Division stated that the RMP captured many of the issues discussed in the December 20, 2001, meeting. However, there are several issues that need to be resolved.

- a. The Division stated that the surveillance section is thorough. However, the reporting requirements need to include the stipulation that significant events including new addictions, death due to overdose, neonatal withdrawal, etc. should be reported as 15-day

safety reports. The Sponsor agreed to include this in the surveillance plan.

- b. The Division stated that the product distribution section needs more detail about the distribution channel.

- c. The Division reminded the Sponsor that the educational piece needs to focus only on topics pertaining to the specific drug and not general marketing issues. The focus should be on the use of the specific medication (Subutex and Suboxone) and not on general information about addiction. The patient education piece should be a detailed patient package insert, include such topics as how to take the medication safely, taking medication at home, proper administration, the importance of adhering to the dosing regimen, keeping the medication secure in the patient's home, important warnings and safety information, etc. The physician's education piece should focus on the "nuts and bolts" of using buprenorphine, such as how to obtain a supply for in-office use, how to secure in-office medications, how to keep records of medications dispensed, how to establish a relationship with a pharmacy or wholesaler to ensure patients can get their prescriptions filled, and other practical matters specific to the use of buprenorphine.

The Sponsor agreed to remove this section. It was agreed that this material, although included in the package, would not be a component of the RMP.

The Division reminded the Sponsor to remove all promotional statements. The Sponsor agreed to revise the educational piece.

3. Periodic Safety Update (PSU)

- a. The Division requested that the PSU include information from previous safety data and not only new data.

- b. The Division requested that the old and new data be integrated. The Sponsor should create a line listing of all deaths, serious adverse events, and adverse events leading to discontinuation of study drug, drug reduction, and temporary study drug interruption. New and old data should be included in this line listing. The old and new data should be indicated as such in the line listings. A narrative should immediately follow the line listing and be in the same order as the line listing.

Grouping should be done in order of adverse events and not study number.