

NDA 20-732, NDA 20-733

Page 4

- c. The Sponsor stated that no CRFs are available from the new data generated by NIDA grantees. The Sponsor only has access to the study reports from these studies.
- d. The literature included in the PSU supports hepatic, pregnancy and allergic adverse events. The Division questioned if the literature was also examined for other adverse events. A teleconference call will be arranged to further discuss this issue (teleconference occurred on March 12, 2002).
- e. Based on a fax received from the Division on March 6, 2002, the Sponsor stated that the patient identification numbers in the dataset were not differentiated as needed in order to determine the number of patients who received each treatment. They will resubmit the data.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

*{See appended electronic signature page}*

Sara E. Shepherd  
Regulatory Project Manager  
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/

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Sara Shepherd  
3/13/02 07:37:21 AM  
CSO

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## MEMORANDUM OF TELECON

DATE: March 12, 2002

APPLICATION NUMBER: NDA 20-732 (Subutex), NDA 20-733 (St. boxone)

**BETWEEN:**

Name: Don Walter, Buprenorphine Developmental Manager  
Phone: (fax 011-44-1482-88-6021)  
Representing: Reckitt Benckiser Pharmaceuticals, Inc. (UK)

**AND**

Name: Gerald DalPan, M.D., Medical Reviewer  
Sara E. Shepherd, Regulatory Project Manager  
Division of Anesthetic, Critical Care, and Addiction Drug Products

SUBJECT: To discuss the Safety Update submitted December 31, 2001.

This teleconference was a follow-up to the telecon with Mr. Charles O’Keeffe on March 11, 2002 and focused on the Periodic Safety Update.

The Division requested that the following (Items 1-6 below) should be performed for ALL data (ie, previously submitted data integrated with current data).

- 1) Line listings for all deaths in ALL studies (both old and new), sorted by treatment (primary sort based on active ingredient or placebo), study (secondary sort), and patient ID (tertiary sort).

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Adverse Event Leading to Death													
New/ Old	Study	Patient ID	Treatm ent	Dose	Study Day	Body	Preferred	Verbatim	Serious	Severity	Relationship	Action	Study Day - Death
					- Onset	System	Term	Term				Indicated	

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Death

In the above table “New/Old” refers to whether or not the death was previously reported.

- 2) Narratives for all (both old and new) deaths in one place, sorted in the same order in which they appear in the listing.

- 3) Line listings all serious adverse events in ALL studies (both old and new), sorted by body system (primary sort), preferred term (secondary sort), treatment (tertiary sort based on active ingredient or placebo), study (quarternary sort), and patient ID (fifth level).

New/ Old	Study	Patient ID	Treatment	Dose	Study Day - Onset	Study Day - Resolution	Body System	Preferred Term	Verbatim Term	Serious	Severity	Relationship	Action Indicated	Outcome
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- 4) Narratives for all SAEs (both old and new) in one place, sorted in the same order in which they appear in the listing.
- 5) Line listings for all adverse events resulting in discontinuations, dose reductions, or temporary study drug interruptions in ALL studies (both old and new), sorted by body system (primary sort), preferred term (secondary sort), treatment (tertiary sort based on active ingredient or placebo), study (quarternary sort), and patient ID (fifth level).

New/ Old	Study	Patient ID	Treatment	Dose	Study Day - Onset	Study Day - Resolution	Body System	Preferred Term	Verbatim Term	Serious	Severity	Relationship	Action Indicated	Outcome
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- 6) Narratives for all adverse events resulting in discontinuations, dose reductions, or temporary study drug interruptions (both old and new) sorted in the same order in which they appear in the listing.
- 7) It appears that the Hepatic Report (Report RC010262, Attachment 4 of the Periodic Safety Update Report) reports narratives for subjects who had at least one LFT that was 'clinically abnormal' either at baseline (and also had follow-up data) or post-baseline (at a time when study medication was being administered). However, the text describing the data reports that that these patients had AST and/or ALT that was above the upper limit of normal.' Data from Study CR90/066 will be used as an example. The text of the Hepatic Report (Section 3.3.1.2) notes that "Of the 164 cases in the study, 20 of the 84 buprenorphine patients and 20 of the 80 methadone patients had AST and/or ALT levels that were above the upper limit of normal either at

baseline or during treatment.” However, it appears that many subjects whose most abnormal AST and/or ALT was ‘High’, but not ‘Clinically Abnormal’ were actually not included in this tally. For example, Subject 0005, 0006, 0007, 0009, 0010, 0011, 0012, 0014, 0018, 0023, 0024, and 0026 all had at least one AST and/or ALT value that was above the upper limit of normal but are not included in the tally or in the narratives (see table on next page). Furthermore, it appears that some subject with post-baseline clinically abnormal AST and/or ALT values were excluded if the post-baseline clinically abnormal value was recorded at a time when no study medication was being taken (for example, subject B9019\_0004, who had clinically abnormal LFTs on Day 145, was not included in this tally at a time when no study medication – methadone in this case – was recorded on this day). In view of these issues, explain the precise methodologies used to determine the number of hepatic cases in each study.

\*\*\*\*\*

Study CR90/066 – Examples of Subject With AST and/or ALT Values That Are ‘High’ But Not ‘Clinically Abnormal’ and Who Are Not Listed Among the ‘Hepatic Cases’									
Study	Subject	Treatment	Day	AST			ALT		
				Value	Flag	Upper Limit	Value	Flag	Upper Limit
CR90/066	B9019_0005	BUP_LIQ	-8	54	H	45	34		50
CR90/066	B9019_0005	BUP_LIQ	33	55	H	45	26		50
CR90/066	B9019_0006	METH	-11	54	H	45	64	H	50
CR90/066	B9019_0006	METH	29	44		45	59	H	50
CR90/066	B9019_0006	METH	63	67	H	45	100	H	50
CR90/066	B9019_0006	METH	86	64	H	45	95	H	50
CR90/066	B9019_0006	METH	125	102	H	45	97	H	50
CR90/066	B9019_0006	METH	149	59	H	45	72	H	50
CR90/066	B9019_0007	METH	-25	24		45	37		50
CR90/066	B9019_0007	METH	57	34		45	51	H	50
CR90/066	B9019_0007	METH	90	31		45	44		50
CR90/066	B9019_0007	METH	121	82	H	45	45		50
CR90/066	B9019_0009	METH	-12	22		45	11		50
CR90/066	B9019_0009	METH	30	33		45	22		50
CR90/066	B9019_0009	METH	57	39		45	27		50
CR90/066	B9019_0009	METH	84	56	H	45	53	H	50
CR90/066	B9019_0009	METH	121	49	H	45	37		50
CR90/066	B9019_0009	METH	149	31		45	18		50
CR90/066	B9019_0010	BUP_LIQ	-12	23		45	16		50
CR90/066	B9019_0010	BUP_LIQ	30	31		45	31		50
CR90/066	B9019_0010	BUP_LIQ	57	45		45	70	H	50
CR90/066	B9019_0010	BUP_LIQ	84	28		45	47		50
CR90/066	B9019_0010	BUP_LIQ	121	31		45	77	H	50
CR90/066	B9019_0010	BUP_LIQ	149	28		45	34		50
CR90/066	B9019_0010	BUP_LIQ	177	20		45	24		50
CR90/066	B9019_0011	METH	-10	42		45	64	H	50
CR90/066	B9019_0011	METH	35	36		45	65	H	50
CR90/066	B9019_0011	METH	60	34		45	65	H	50
CR90/066	B9019_0011	METH	89	50	H	45	80	H	50
CR90/066	B9019_0012	METH	-9	36		45	48		50
CR90/066	B9019_0012	METH	34	49	H	45	70	H	50
CR90/066	B9019_0012	METH	54	56	H	45	54	H	50
CR90/066	B9019_0012	METH	89	53	H	45	85	H	50
CR90/066	B9019_0012	METH	120	64	H	45	92	H	50

CR90/066	B9019_0012	METH	148	64	H	45	84	H	50
CR90/066	B9019_0014	BUP_LIQ	-9	98	H	45	94	H	50
CR90/066	B9019_0014	BUP_LIQ	29	127	H	45	111	H	50
CR90/066	B9019_0014	BUP_LIQ	64	101	H	45	112	H	50
CR90/066	B9019_0014	BUP_LIQ	93	97	H	45	102	H	50
CR90/066	B9019_0018	BUP_LIQ	-5	41		45	72	H	50
CR90/066	B9019_0018	BUP_LIQ	0	31		45	23		50
CR90/066	B9019_0023	BUP_LIQ	-11	45		45	32		50
CR90/066	B9019_0023	BUP_LIQ	29	54	H	45	26		50
CR90/066	B9019_0023	BUP_LIQ	58	45		45	23		50
CR90/066	B9019_0023	BUP_LIQ	90	57	H	45	30		50
CR90/066	B9019_0023	BUP_LIQ	125	59	H	45	32		50
CR90/066	B9019_0023	BUP_LIQ	149	70	H	45	36		50
CR90/066	B9019_0024	BUP_LIQ	-2	51	H	45	111	H	50
CR90/066	B9019_0024	BUP_LIQ	29	65	H	45	120	H	50
CR90/066	B9019_0024	BUP_LIQ	57	47	H	45	69	H	50
CR90/066	B9019_0024	BUP_LIQ	86	46	H	45	101	H	50
CR90/066	B9019_0024	BUP_LIQ	120	46	H	45	80	H	50
CR90/066	B9019_0024	BUP_LIQ	149	39		45	63	H	50
CR90/066	B9019_0026	BUP_LIQ	-11	34		45	39		50
CR90/066	B9019_0026	BUP_LIQ	31	46	H	45	48		50

The Sponsor agreed to provide the requested information.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

*{See appended electronic signature page}*

Sara E. Shepherd  
 Regulatory Project Manager  
 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/

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Sara Shepherd  
3/12/02 03:08:52 PM  
CSO

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<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>		<b>Clinical Pharmacology &amp; Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults</b>		
From: Tien-Mien Chen, Ph.D. (HFD-870)		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission		
DATE: 02/20/02	IND No.: Serial No.:	NDA No. 20-732 & 20-733	DATE OF DOCUMENT 02/04/02	
NAME OF DRUG [Subutex and Suboxone Sublingual Tablets]		PRIORITY CONSIDERATION	Date of informal/Formal Consult: 02/05/02	
NAME OF THE SPONSOR: [Reckitt and Benckiser]				
<b>TYPE OF SUBMISSION</b>				
<b>CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE</b>				
<input type="checkbox"/> PRE-IND	<input checked="" type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> ANIMAL to HUMAN SCALING	<input type="checkbox"/> BIOAVAILABILITY STUDIES	<input type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> IN-VITRO METABOLISM	<input type="checkbox"/> IN-VIVO WAIVER REQUEST	<input type="checkbox"/> CORRESPONDENCE		
<input type="checkbox"/> PROTOCOL	<input type="checkbox"/> SUPAC RELATED	<input type="checkbox"/> DRUG ADVERTISING		
<input type="checkbox"/> PHASE II PROTOCOL	<input type="checkbox"/> CMC RELATED	<input type="checkbox"/> ADVERSE REACTION REPORT		
<input type="checkbox"/> PHASE III PROTOCOL	<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> ANNUAL REPORTS		
<input type="checkbox"/> DOSING REGIMEN CONSULT	<input type="checkbox"/> SCIENTIFIC INVESTIGATIONS	<input type="checkbox"/> FAX SUBMISSION		
<input type="checkbox"/> PK/PD- POPPK ISSUES	<input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> PHASE IV RELATED		[     ]		
<b>REVIEW ACTION</b>				
<input type="checkbox"/> NAI (No action indicated)	<input type="checkbox"/> Oral communication with	<input type="checkbox"/> Formal Review/Memo (attached)		
<input type="checkbox"/> E-mail comments to:	Name: [     ]	<input checked="" type="checkbox"/> See comments below		
<input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox	<input type="checkbox"/> Comments communicated in	<input type="checkbox"/> See submission cover letter		
<input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others	meeting/Telecon. see meeting minutes	<input type="checkbox"/> OTHER (SPECIFY BELOW):		
(Check as appropriate and attach e-mail)	dated: [     ]	[     ]		
<b>REVIEW COMMENT(S)</b>				
<input checked="" type="checkbox"/> NEED NOT BE COMMUNICATED TO THE SPONSOR		<input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>				
[X] As agreed upon in the 11/29/01 meeting, the sponsor promised to generate the dissolution data/profiles for the Suboxone 2 and 8 mg biobatches used in the above PK study in order to finalize the new dissolution specifications proposed by the sponsor in the above meeting. Please see the 11/29/01 meeting minutes for details.				
This is a review of the dissolution data/profiles submitted in the 02/04/02 amendment (S.N. BB) to both NDAs 20-732 (Subutex 2 and 8 mg sublingual tablets) and 20-733 (Suboxone 2 and 8 mg sublingual tablets). Reviewed also were the previous dissolution data for stability batches that were submitted on 01/11/02 and 02/01/02.				
<u>Reviewer's Comment:</u>				

The additional dissolution data/profiles submitted on 02/04/02 for suboxone 2 and 8 mg biobatches used in the requested PK study No. 01-1 Plus dissolution data obtained from 01/11/02 and 02/01/02 submissions (only 2 and 8 mg \_\_\_\_\_ HDPE bottle at 25°C and 60% relative humidity up to \_\_\_\_\_, are summarized in Attachment 1 of this review. This reviewer concluded that the dissolution data obtained from the 2 and 8 mg Suboxone tablet biobatches are consistent with the previous dissolution data obtained from the 2 and 8 mg Subutex and Suboxone stability tablet batches (up to \_\_\_\_\_ using water as a medium and basket method at \_\_\_\_\_ pm.

As agreed upon between the OCPB and Chemist reviewers in an internal meeting on 02/05/02, the following comment and dissolution specifications proposed by the Agency were conveyed to the sponsor;

USP Apparatus I (Basket). \_\_\_\_\_ rpm

Water at 37°C

Specifications: Q= \_\_\_\_\_ at 7.5 min for buprenorphine and

Q= \_\_\_\_\_ at 7.5 min for naloxone

SIGNATURE OF REVIEWER: Tien-Mien Chen, Ph.D.

Date 02/25/02

SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.

Date 03/07/02

CC.: HFD # [170]; TL: [SD]

Project Manager: S. Shepherd Date 03/07/02



NDA 20-732  
NDA 20-733

Reckitt & Benckiser  
1909 Huguenot Road  
Suite 300  
Richmond, VA 23235

Attention: Alan Young  
Director of Regulatory Affairs

Dear Mr. Young:

Please refer to the meeting between representatives of your firm and FDA on November 29, 2001. The purpose of the Pre-NDA meeting was to discuss all remaining open issues from the approvable letters dated January 26, 2001, for Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

*{See ~~attached~~ electronic signature page}*

Sara E. Shepherd  
Regulatory Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY  
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**Meeting Objective:** The primary objective of this meeting was to discuss the open issues from the January 26, 2001, approvable letters for Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone). The first part of the meeting (1:00-3:00 PM) focused on the outstanding pre-clinical, clinical, and chemistry issues. The risk management plan was discussed during the second half of the meeting (3:15-5:15 PM). Schering Plough only attended the discussion about the risk management plan.

**General Discussion:** Following introductions, the discussion focused on the outstanding issues from the information provided in the May 18, 2001, meeting package and July 5, 2001, supplemental information package for the September 17, 2001, chemistry meeting. The Sponsor also sent new dissolution and stability data via e-mail on November 27, 2001 (formally submitted December 7, 2001, as a correspondence). In addition, a discussion ensued about unresolved pre-clinical, and clinical issues from the approvable letters. A meeting package containing a risk management plan was submitted on November 6, 2001, which was discussed in the latter half of the meeting.

It should be noted that the Division stated that a rolling review would be done for the NDAs. Discipline review letters will be sent during the rolling review. However, the Sponsor must submit complete CMC sections with no on-going developmental work included in the submissions. Each section should be complete and not refer to previously submitted material. The review clock will not start until the final submission is received.

#### Chemistry Issues

*We (Reckitt & Benckiser) would like to confirm the following:*

1. *That the validation of the three methods are acceptable.*

The Division stated that the validation protocol was acceptable. However, \_\_\_\_\_ (one of the buprenorphine impurities) should be included in the validation process. The Sponsor was concerned that the amount of material available for testing \_\_\_\_\_ would not be enough. However, the Division replied that \_\_\_\_\_ should be sufficient for the 5 parameters to be tested (e.g., linearity of response, precision, sensitivity etc.) and suggested that the Sponsor prioritize the testing.

2. *That the validation demonstrates that we can comply with the FDA requirement to report impurities at the \_\_\_\_\_*

The Division stated this was acceptable.

3. *That the threshold for reporting impurities is implicit and does not need to appear in the specifications. Future stability reports will quote the LOD/LOQ of the impurity methods used.*

The Division replied that the reporting threshold in Q3AR and Q3B are recommended, and that arithmetic values should be reported. The Division clarified that the impurities

reporting thresholds may be listed in the methods and were not needed in the specification sheet (tests and acceptance criteria).

4. *That the reports detailing the identification and characterization are acceptable.*

The Division stated this was acceptable.

5. *That the \_\_\_\_\_ impurities can be present in Subutex and Suboxone at levels above the ICH threshold of \_\_\_\_\_.*

The Division stated that the specifications and observed levels should be set no higher than those levels which were qualified. Continued efforts to identify the \_\_\_\_\_ impurity (impurity \_\_\_\_\_ in naloxone) should be submitted. The Division requested a brief summary on efforts to identify this \_\_\_\_\_ and the Sponsor agreed.

6. *That the correlation of impurities found in Subutex and Suboxone addresses the specific request.*

The Division stated this was acceptable.

7. *That the impurities named in the specifications for both products are appropriate.*

The Division requested the Sponsor to revise "individual unknown impurity..." to read "individual unidentified impurity..."

8. *That the information provided addresses the Division's concern regarding "different degradation products in Subutex and Suboxone."*

The Division stated this was acceptable.

9. *That based on toxicology qualified levels and levels observed in ICH stability studies, the degradant specifications for both Subutex and Suboxone are appropriate and acceptable.*

The Division stated that the stability data needs to be reviewed. The November 27, 2001, submission contained \_\_\_\_\_ stability for Suboxone. Dissolution data should be available by the end of December 2001.

The Division stated they are encouraged by the HDPE bottle stability data. The Division requested child-resistant testing, \_\_\_\_\_ data on the tablets in the bottle. The Division will provide any guidance for the development of a study. The Division stated that child-resistant caps should be used on the bottles and expressed concern about the \_\_\_\_\_. All DMF letters of authorization (page number, section, date submitted, volume number, etc.) that relate to the HDPE bottle packaging should be provided to the NDA \_\_\_\_\_

The Division requested clarification of the DMF numbers (either \_\_\_\_\_, for the \_\_\_\_\_). The Sponsor stated they will review all DMFs and update the DMF files accordingly.

The Division requested that all child-resistant testing be done on the to-be-marketed packaging only. Providing information on all the packaging tested would not be helpful to the reviewers. The Sponsor clarified that the \_\_\_\_\_

The Sponsor stated that the \_\_\_\_\_ was done by a contract manufacturer. The Division requested a complete list of manufacturers as soon as possible so that inspections can be arranged. The Sponsor did supply a list of sites in the November 27, 2001, submission and the Division advised them to select a specific site for this review cycle and change the \_\_\_\_\_ site, if needed, post approval. The Sponsor will provide information on one site whose product was used in the current stability studies.

The Sponsor stated they have \_\_\_\_\_ batches of each drug on stability, under ICH conditions. \_\_\_\_\_ stability samples for Suboxone will be ready in December 2001. The Subutex data will be available in mid-February 2002. The Sponsor stated that supportive data will be available from lots generated at a different contract manufacturer.

10. *That the buprenorphine and naloxone content in the release and shelf-life specifications are appropriate and acceptable*

The Division stated that the USP method and acceptance criteria should be used for the content uniformity test or the Sponsor should show that the EU and USP methods and acceptance criteria are comparable.

11. *That the dissolution methods and limits are appropriate and acceptable. If these are not acceptable, we would like to discuss either the option of replacing the dissolution test with the disintegration test alone or moving to a dissolution medium buffered to a pH at which all the buprenorphine and naloxone are utilized.*

See clinical pharmacology discussion below.

12. *That the overall specifications for Subutex and Suboxone are acceptable*

The Division stated that the following are still open issues: dissolution, content uniformity, weight uniformity, unspecified impurity, and development of a \_\_\_\_\_ test to be established in the specification and to be added to the stability test protocol. The \_\_\_\_\_ test will be added to the ongoing stability program.

13. *That based on currently available data, the Division can agree to an expiration date for Subutex and Suboxone and that this agreement can be reached during the meeting. If the proposed specifications are not acceptable to the Division, it is imperative that we establish exactly what amendments have to be made to make the specifications acceptable so that we can agree upon revised specifications during this meeting.*

The Division still needs to review the stability data, which should be available in December 2001 for Suboxone and in February 2002 for Subutex. The Division advised that the approach to setting specifications should be based upon review of the batch data, stability data, and pharm/tox safety qualification data.

#### Pre-Clinical Issues

14. *Is it accepted that norbuprenorphine is the metabolite of buprenorphine and is therefore qualified?*

The Division stated this was acceptable. Rats have been shown to produce the same metabolite in submitted publications.

15. *We would like to confirm that these toxicology studies are acceptable.*

The Division stated that the design of the studies appears to be suitable. However, the adequacy of the data will be a review issue.

16. *We would like to confirm that they qualify the individual buprenorphine and naloxone degradants up to the level of exposure in these studies (see #15).*

The Division stated this is a review issue. The 28-day toxicity in rats and three genotoxicity studies have been received and are under review.

17. *We would like to confirm that the calculations described are correct and acceptable.*

The Division stated the calculations appear acceptable.

18. *We would like to confirm that the degradant levels shown in column 5 of table 1 are qualified from a toxicological safety viewpoint.*

The Division stated the degradants appear to be qualified based on a safety factor of 10, but the data needs to be formally reviewed.

The Division noted that no carcinogenicity studies have been done for Suboxone. The Executive CAC have reviewed the rat study protocol and provided comments. The Sponsor stated that the rat study is in progress and will be done in 1.5 years. The Division notes that this study is not needed prior to approval.

#### Clinical Pharmacology

19. *We would ask the Agency to accept the change in dissolution method to take the measurement of dissolution after 7.5 minutes at  $\omega$  rpm rather than the originally intended 5 minutes at  $\omega$  rpm. (page 3, November 27, 2001, submission)*

The Division stated that the proposal is acceptable. In addition, the Division advised the Sponsor to take measurements at 1, 3, 5, 7.5, and 10 minutes to cover a broad range. It was noted that the stability data for Suboxone will not have all of these time points.

20. *As requested by the Agency the dissolution specification has also been changed from the original NDA by the introduction of the statistical approach to interpreting the data described in the USP. This is based on individual tablet dissolution and a value  $Q$  rather than the arithmetic mean of six results originally proposed. The difference in interpretation of results requires the value of  $Q$  to be set below the specified limit as the arithmetic mean. Therefore the original specification limit of a mean of  $Q$  for buprenorphine must be adjusted to a  $Q$  value of  $Q$*

The Division stated that available dissolution data does not support  $Q =$  at 7.5 min. Dissolution data (using water as a medium and basket method at rpm) should be obtained at 7.5 min. in addition to 5 min. from the batches used in the on-going stability program. The Sponsor should provide dissolution profiles including 7.5 min. as well for the batches used in the currently on-going PK study. The Division stated that the dissolution specifications will be finalized after reviewing the above data.

#### Safety Update

The Sponsor stated that the safety update should arrive in 2 weeks for review by the Division. The one piece that is holding it back is the hepatotoxicity data. The Sponsor presented a list of items to be included in the safety update, which, on its surface, appeared acceptable to the Division. Any acute allergic reactions to buprenorphine will be included in the safety update. The safety data collection cutoff was July, 2001.

#### Hepatotoxicity Data

The Sponsor stated the final report should be available the week of December 3, 2001. It will include data from published literature and clinical trials. Approximately 70,000 patients were included in this data. The Sponsor stated no overall conclusion could be reached from the post marketing hepatic data.

#### PK Study

The Sponsor stated that the clinical portion of the study will be complete on December 8, 2001. Raw data may be available on December 21, 2001, but the Division requested that the Sponsor wait for the complete analysis (due January/February 2002) before submitting it to the Division. The Sponsor will provide a preliminary report submitted prior to the final report.

#### Scheduling

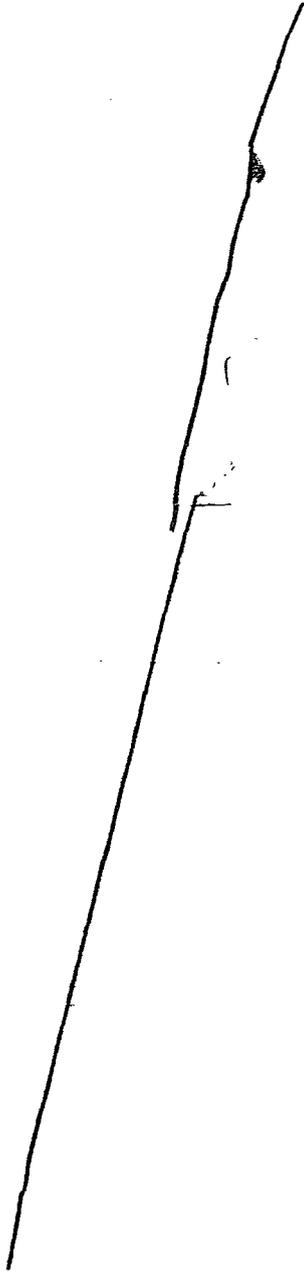
The Division noted that adjustments may be necessary for control/distribution of the product if the scheduling changes.

#### Common Labeling

The Division received a paper copy of the proposed common label for Subutex/Suboxone. The Division requested an electronic version in WORD. The Division advised the Sponsor that the labeling may change once the final data for the PK study is reviewed, in addition to other

sections of the label not supported by the current data. The Division stated that teleconferences to discuss the labeling would be needed in the future.

Risk Management Plan Critique (submitted in November 6, 2001, meeting package)



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NDA 20-732  
NDA 20-733

Reckitt & Benckiser  
1909 Huguenot Road  
Richmond, Virginia 23235

Attention: Alan Young  
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the meeting between representatives of your firm and FDA on September 17, 2001. The purpose of the meeting was to discuss the chemistry issues from the January 26, 2001, approvable letters for Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

*{See appended electronic signature page}*

Sara E. Shepherd  
Regulatory Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Date:** September 17, 2001

**Location:** Parklawn Building, Chesapeake Conference Room (12:30-2:00)

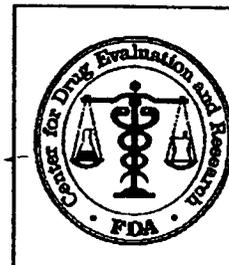
**NDA:** 20-732 (Subutex) and 20-733 (Suboxone)

**Sponsor:** Reckitt & Benckiser

**Type of Meeting:** Discuss chemistry issues from the AE letters

**Meeting Chair:** Dale Koble, Ph.D., Chemistry Team Leader  
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

**Minutes Recorder:** Sara E. Shepherd, Regulatory Project Manager, HFD-170



<b>Reckitt &amp; Colman</b>	<b>Title</b>
Alan Young	Regulatory Director
Neil Hyde	Buprenorphine Project Manager
<b>NIDA</b>	<b>Title</b>
Robert Walsh	Chief Regulatory Affairs Branch, DTRD
Moo Park, Ph.D.	Project Officer, Chemistry & Pharmaceuticals Branch
<b>FDA HFD-170</b>	<b>Title</b>
Cynthia G. McCormick M.D.	Division Director
Albert Chen, Ph.D.	Pharmacokinetics Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Ali-Al-Hakim, Ph.D.	Chemistry Reviewer
Pat Maturu, Ph.D.	Chemistry Reviewer
Tom Papoian, Ph.D.	Supervisory Pharmacologist
Daniel Mellon, Ph.D.	Pharmacologist
Sara Shepherd, M.S.	Regulatory Project Manager

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**Meeting Objective:** The primary objective of this meeting was to discuss the chemistry issues from the January 26, 2001, approvable letters for Subutex and Suboxone. Reckitt & Benckiser provided a meeting package dated May 18, 2001. The meeting on June 13, 2001, was cancelled due to an inadequate meeting package. Additional information was submitted in a July 5, 2001, supplemental meeting package and the meeting was scheduled for September 17, 2001.

**General Discussion:** Following brief introductions, the Division noted that several questions posed by Reckitt & Benckiser were review issues and the data were not reviewed for this meeting.

1. *We (Reckitt & Benckiser) would like to confirm the following.*

a. *That the validation of the three methods is acceptable.*

The Division stated that this was a review issue.

b. *That the validation demonstrates that we can comply with the FDA requirement to report impurities at the ' \_\_\_\_\_*

The Division stated \_\_\_\_\_

\_\_\_\_\_ Reckitt & Benckiser replied that nalxone will not meet these requirements. The Division stated it would take unique circumstances for the Division to accept noncompliance with ICH. Reckitt & Benckiser was concerned how this might impact the current stability studies, if the methodology was changed. The Division referred the Sponsor to the ICH Q3A guidelines.

c. *That the threshold for reporting impurities is implicit and does not need to appear in the specification. Future stability reports will quote the LOD/LOQ of the impurity methods used.*

The Division requested clarification of this statement. The proposed specifications should include a number that corresponds for each amount of each impurity as per the ICH reporting threshold (Q3A and Q3B). Therefore, Reckitt & Benckiser must provide acceptance criteria of not more than \_\_\_\_\_ for any individual unspecified degradation product and provide identification of each individual degradation product which occurs at \_\_\_\_\_ or greater.

2. *We (Reckitt & Benckiser) would like to confirm the following.*

a. *That the reports detailing the identification and characterization are acceptable.*

The Division stated that this was a review issue.

- b. *That the \_\_\_\_\_ impurities can be present in Subutex and Suboxone at levels above the \_\_\_\_\_*

This was discussed in Items 1 and 3.

3. *Pharmacology/Toxicology Issues*

- a. *Is it accepted that norbuprenorphine is the metabolite of buprenorphine and is therefore qualified?*

The Division concurred but stated that animals must be shown to produce the same metabolite. The Division requested additional publications be submitted as supporting data at resubmission of the application.

- b. *We would like to confirm that these toxicology studies are acceptable.*

The Division stated that the design of the studies appears to be suitable. However the adequacy of the data will be a review issue.

- c. *We would like to confirm that they [the tox studies] qualify the individual buprenorphine and naloxone degradants up to the level of exposure in these studies.*

The Division stated that this was a review issue. However, the Division recalculated the data based on a safety factor of 10 (see Table 1 below) and it appears that the data are acceptable.

- d. *We would like to confirm that the calculations described are correct and acceptable.*

The Division stated that the calculations appeared to be correct.

- e. *We would like to confirm that the degradant levels shown in column 5 of table 1 are qualified from a toxicological safety viewpoint.*

The Division stated this was a review issue, pending submission of the final study reports.

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4. *Impurities/Dissolution*

- a. *We would like to confirm that the correlation of impurities found in Subutex and Suboxone address the specific request.*

The Division stated that it appeared that inadequate method validation was provided to demonstrate that method \_\_\_\_\_ is capable of separating all of the decomposition products (e.g. \_\_\_\_\_). Reckitt & Benckiser stated in the July 5, 2001, revised meeting package that the impurities were now separated by method \_\_\_\_\_ for Subutex as well as Suboxone (specifications were amended accordingly). The Division stated that it was satisfied with this response.

- b. *We would like to confirm that the impurities named in the specification for both products are appropriate.*

The specification test for drug substance related impurities should be included in the release testing as well as the shelf-life testing for the drug products. Reckitt & Benckiser stated that the release specifications have been amended. The Division stated that this is satisfactory and that \_\_\_\_\_ method be included in the release specifications.

- c. *We would like to confirm that the information provided addresses the Division's concerns regarding "different degradation products in Subutex and Suboxone."*

Refer to the responses above.

- d. *We would like to confirm that based on toxicology qualified levels and levels observed in ICH stability studies, the degradant specifications for both Subutex and Suboxone are appropriate and acceptable.*

The Division stated that this is a review issue. There appears to be confusion concerning the impurities named in the methods. The synthesis of impurities versus degradation products must be reviewed.

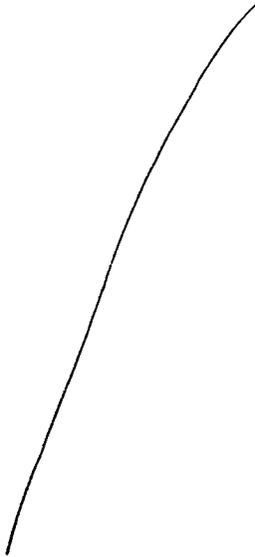
For Suboxone degradation products, the Division asked Reckitt & Benckiser to provide a linkage between the designation for the degradation products in the safety qualification and the code numbers in the methods validation report. Reckitt & Benckiser stated that this information can be found in Appendix 20 of May 18, 2001, package meeting. The Division stated that this was satisfactory.

- e. *We would like to confirm that the buprenorphine and naloxone content in the release and shelf-life specifications are appropriate and acceptable.*

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The Division stated that this was a review issue. The Division cannot determine the shelf-life until the newest data have been submitted for review. The standard specification for release testing and shelf-life testing must be \_\_\_\_\_ The buprenorphine was within the standard specification. However, the naloxone ( \_\_\_\_\_ ) fell outside of this standard. Reckitt & Benckiser should provide justification for the lower level noted with naloxone based upon the level needed to avoid inducing withdrawal.

POST MEETING NOTE: Reckitt & Benckiser provided a fax on October 12, 2001 with summarized information on the amount of naloxone required to precipitate withdrawal. The Division requested a copy of the complete final study report for study CR94/003 which was received on October 31, 2001. After review of this study, the Division agreed that the proposed specification for the naloxone content \_\_\_\_\_ of the Suboxone tablet was acceptable.



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- g. *We would like to confirm that the overall specifications for Subutex and Suboxone are acceptable.*

The Division stated that this is a review issue. New stability data are still being collected and have not been submitted for review. The Division advised Reckitt & Benckiser to submit only the new data at resubmission.

- h. *We would like to confirm that based on currently available data the Division can agree to an expiration dating period for Subutex and Suboxone and that this agreement can be reached during the meeting. If the proposed specifications are not acceptable to the Division, it is imperative that we establish exactly what amendments have to be made to make the specifications acceptable so that we can agree upon revised specifications during this meeting.*

The Division stated this was a review issue and depended on qualifying the impurities under ICH, decreased dissolution a  $\mu\text{m}/\text{water}$ , and submission of new stability data. The Division noted that the request for stability data at ICH conditions for additional batches of each strength (letter dated January 26, 2001) was not addressed. Reckitt & Benckiser stated that batches of each batch tablet strength) are being used in the stability study program which started on June 26, 2001. The Division stated that batches released should be tested using method and real-time stability data submitted.

The Division noted that dissolution is now the primary concern. No data have been submitted from the new stability studies that would enable the Division to make a preliminary decision on the expiration dating period of the products. The data will be reviewed following resubmission.

5. *The Division stated that some of the most important deficiencies (comments 3,4, and 5) in the FDA letter dated January 26, 2001, were not addressed in the May 18, 2001, meeting package. These deficiencies concerned identification of the package materials and packaging sites to be used for commercial production of the drug products.*

Reckitt & Benckiser provided the packaging site and primary package information for Subutex and Suboxone in the July 5, 2001, meeting package. The DMF references were also provided. The Division stated the DMFs will be reviewed and requested that real time stability data should be submitted for review at the resubmission.

6. *The Division requested a complete updated description of the packaging process to be used for commercial drug product (child resistant packaging) including the in-process controls (e.g. , and a description of the in-process controls and tests used for the relevant stability batches.*

Reckitt & Benckiser stated that the sole packaging site now proposed for the production of the Suboxone and Subutex Reckitt is Benckiser Healthcare (UK) Limited, Dansom

Lane, HU8 7DS, in the UK. The Division stated that the response will be reviewed following resubmission.

The Division noted that \_\_\_\_\_ should be supported by stability studies. Optimization of \_\_\_\_\_ based upon \_\_\_\_\_ testing alone will not be acceptable without extensive justifications.

7. *Other issues raised by the Division:*

- a. The Division requested clarification of the proposed dissolution specification for naloxone where Q=—, on page 19 of the July 5, 2001, meeting package and Q=—, on page 18. Reckitt & Benckiser clarified that Q=— was release testing and Q=— was shelf-life testing. However the Division stated that the specification should be the same.
- b. The Division reminded Reckitt & Benckiser to submit data to show that the European Pharmacopoeia basket method is comparable with the USP dissolution method. The Division stated that the mesh size should be the same as used in the USP method. Reckitt & Benckiser replied they will review the procedure to ensure it meets USP guidelines.
- c. The Division stated that the content uniformity test should be performed as per USP <905>. Reckitt & Benckiser will confirm that the test follows USP.

The Division stated that it cannot guarantee approval of the applications until all of the material has been reviewed. The purpose of this meeting was to discuss the Division's requirements for resubmission. All items should be corrected prior to submission and problems addressed early and not during the review cycle. Final methodologies should be decided upon and no on-going developmental work should be submitted. Due to the poor quality of the previous submission, a fully revised CMC dossier, for each NDA, must be submitted for the next review cycle. The Division referred Reckitt & Benckiser to guidance documents posted on the internet (<http://www.fda.gov/cder/guidance/index.htm>).

The Division also suggested an additional meeting be held to discuss the risk management plan and to ensure that there are no outstanding issues remaining prior to resubmission.

The meeting ended at 1:45PM  
Meeting minutes recorded by Sara E. Shepherd

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Sara Shepherd  
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NDA 20-732  
NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.  
1909 Huguenot Road  
Richmond, VA 23235

Attention: Alan Young  
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the teleconference between representatives of your firm and FDA on May 15, 2001. The purpose of the meeting was to discuss the appropriate data format to examine the potential for buprenorphine-induced hepatotoxicity as stated in the January 26, 2001, approvable letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

*{See appended electronic signature page}*

Sara E. Shepherd  
Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation, II  
Center for Drug Evaluation and Research

Enclosure

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## SPONSOR MEETING ATTENDEES

**Meeting Date:** May 15, 2001

**Location:** Teleconference 1:30-2:30 PM

**NDA:** 20-732 (Subutex) and 20-733 (Suboxone)

**Sponsor:** Reckitt & Colman

**Type of Meeting:** Discuss data format

**Meeting Chair:** Celia Winchell, M.D.

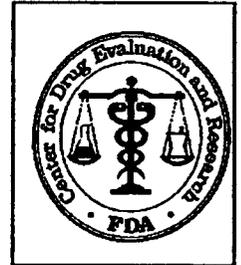
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

**Minutes Recorder:** Sara E. Shepherd, Regulatory Project Manager, HFD-170

**Attendees: Reckitt & Colman:** Charles O'Keefe, Paul Bevan, Don Walter, Tim Baxter

**NIDA:** Frank Vocci, Bob Walsh

**HFD-170:** Cynthia G. McCormick, Celia Winchell, Ana Szarfman,  
Randy Levin, Sara Shepherd



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## MEETING OBJECTIVE

The primary objective of this meeting was to discuss the appropriate format for data in order to examine the potential for buprenorphine-induced hepatotoxicity and the role of viral hepatitis in increasing vulnerability to hepatotoxicity as requested in the January 26, 2001, approvable letters.

## GENERAL DISCUSSION

The Division stated that the two datasets (Zhepdb.zip and Zhepsaf.zip) submitted on November 22, 2000, were not sufficient to draw conclusions about the role of buprenorphine in the fluctuation of hepatic enzymes observed in hepatitis-positive patients. Only four weeks of controlled data were available in these datasets, which were insufficient to draw conclusions. Conversely, the longer-term data lacked any comparator group. The Division requested that ALL data available for evaluating this issue be assembled and examined. A full compilation and integrated assessment is requested rather than a table indicating various places where previously submitted information can be found. Where no comparator groups are available, the Sponsor should provide information on the natural history of hepatic enzyme fluctuation in hepatitis-positive subjects not treated with buprenorphine.

The Division stated that the datasets presented a number of barriers to review. They did not have a single field containing a unique patient identifier and were formatted as character fields rather than numeric fields. The datasets had to be manipulated a great deal before review. Therefore, the Division requested that the data from the previously-submitted studies be re-formatted according to the suggestions provided below and that any new studies identified containing suitable data be submitted in the appropriate format. The Sponsor stated that many of the current studies are not requiring blood chemistry, thereby limiting the amount of new data available for the data analysis. However, the Sponsor agreed to integrate all the data from the previous studies.

The Division stated that the analyses reported in the material submitted with the datasets focused on measures of central tendency such as changes in group mean values. These analyses were less relevant in circumstances where events were expected to be seen in a relatively small number of subjects. The Division requested analyses focused on outliers and extreme changes from baseline. Shifts from "normal" to "abnormal" in this population could be less revealing than typically seen because of the high prevalence of baseline abnormality. Identification of subjects with simultaneous changes from baseline in two or more measures of hepatic function would be valuable, and any accompanying symptoms in these subjects should be reported.

#### **DATA FORMAT SPECIFICATIONS**

To accelerate the review of the data, the Sponsor should:

1. Provide the demographic, clinical adverse events, concomitant medications, laboratory values, normal ranges, deaths, and dosage information as SAS transport files (if there is a preference for text files, the hard returns in the headers of each column should be removed).
2. Provide the narratives of each serious/dropout/death as a long field of a text file. Hard returns within a narrative should be removed.
3. Provide identically structured data from multiple datasets to simplify combining data from multiple studies for the ISS. Provide data from files from different data domains for which the data structures will differ to simplify combining these datasets at the patient level (i.e., demographics data, lab data, AE data, concomitant medications data, narratives, etc).

To simplify combining these datasets, the Sponsor should use the same unique subject numbers scheme (patient key) across all datasets, including the dataset containing the narratives (i.e., combining Study, investigator, and patient ID).

4. Use the same date format across all the datasets to simplify the analysis of time oriented data.

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## THE IDEAL DATA STRUCTURE

### The Basics

There should be at least one one-record-per-patient dataset, normally the demographic dataset.

One of the datasets (ideally one of the one-record-per-patient datasets) should contain the study entry date (time) so that "days since" can be calculated for events with date (time) stamps.

Some of the data should ideally already be in a "tall skinny" format. These are usually the adverse events, concomitant medications, and the lab values datasets. "Tall skinny" means that there should be a column with the name of the event, a column with the date (time) at which the event occurred, and a column for AE severity, a column for AE relationship, a column for lab test result. It is common practice when there are only a few standard times at which the measurements occur (for example "pre" and "post") to have separate columns for the "pre" date, the "pre" value, the "post" date, the "post" value.

### Combining Multiple Studies or Multiple Sites

To perform graphical analyses that mix together the data from multiple studies or multiple sites in the SAME PICTURE, or to start from the big picture and then go to the fine details, it will be necessary to combine the data from multiple sources. Ideally, the data from multiple studies or multiple sites should already be combined into common datasets. For example, there would already be a single dataset containing the adverse events, and in that dataset there would be a column indicating the protocol or site. The studies do not necessarily need to have the same set of datasets, but the presence or absence of a dataset should not indicate anything more than that that kind of data wasn't collected for that study.

Matching datasets should have the same set of columns. In detail, this means the same number of columns. Each column by position should mean the same thing (name does not actually matter, although it would make it easier if these matched too). For example, the second column might be the costart code in an Adverse Events dataset. The matching column should be of the same type (i.e., numeric versus character).

The coding of values should be the same. For example, if column 17 is coding the severity of an adverse event, "0", "1", "2", and "3" should mean the same thing in each dataset with no surprise "9" used only by one study. Consistently followed standards for missing or incomplete values such as choosing either "Not Done" or "N/D" would be helpful.

*Field names:* SAS field names are limited to 8 characters and thus difficult to make meaningful. However there is an optional associated LABEL that can be much longer. For example, the field "AETXYN\_" may have a LABEL "Treatment Required?". For example:

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pos=17 name=AETXYN\_ label="Treatment Required" type=s dist=d. This makes it easy for the reviewer to figure out what's what and even change the name of the variable.

*Date fields:* the dates in a SAS dataset should be stored using the SAS system conventions for representing dates and datetimes. These are stored in SAS as numbers. Then the SAS field should have an associated "format" that uses any one of the common SAS format names for datetime values. Examples are "DATE", "MMDDYY", "MMYY", "JULIAN", etc.....

*Field type:* SAS fields that should be interpreted numerically should have a SAS datatype of numeric. SAS fields that should be interpreted as character strings should have a SAS datatype of character. A common error seems to be to automatically label any field that looks numeric as numeric. In the case of such fields as {Investigator} or {Subject} this is not correct.

Reference values for the lab parameters should be provided, as well as scheduled and unscheduled clinical and laboratory adverse events data.

#### **ADDITIONAL GUIDANCE DOCUMENTS**

The guidance documents called Regulatory Submissions in Electronic Format General Considerations (January 1999) and Regulatory Submissions in Electronic Format—NDAs (January 1999) can be located at <http://www.fda.gov/cder/guidance/index.htm>. The Division advised the Sponsor to review these documents.

The Division also recommended the web page called Clinical Data Interchange Standards Consortium which can be located at <http://www.cdisc.org>.

#### **ACTION ITEM**

The Sponsor stated that they would send in a sample dataset to make sure the format is acceptable. The Division agreed.

The meeting adjourned at ~2:15 PM

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Sara Shepherd  
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NDA 20-732  
NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.  
1909 Huguenot Road  
Richmond, VA 23235

Attention: Alan Young  
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the teleconference between representatives of your firm and FDA on April 26, 2001. The purpose of the meeting was to discuss the pharmacokinetics study requested in the January 26, 2001, approvable letters for Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone) and discussed in the February 27, 2001, face-to-face meeting between your firm and the FDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

*{See appended electronic signature page}*

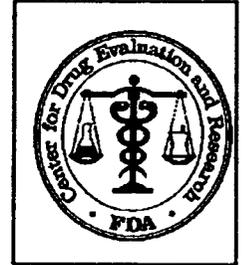
Sara E. Shepherd  
Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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**SPONSOR MEETING ATTENDEES****Meeting Date:** April 26, 2001**Location:** Teleconference 12:00-1:00 PM**NDA:** 20-732 (Subutex) and 20-733 (Suboxone)**Sponsor:** Reckitt & Colman**Type of Meeting:** Discuss PK study**Meeting Chair:** Suresh Doddapaneni, Ph.D.

Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

**Minutes Recorder:** Sara E. Shepherd, Regulatory Project Manager, HFD-170

<b>Reckitt &amp; Colman</b>	<b>Title</b>
Charles O'Keefe	President
Alan Young	Regulatory Director
Don Walter	Buprenorphine Developmental Manager
Neil Hyde	Buprenorphine Project Manager
<b>NIDA</b>	<b>Title</b>
Nora Chiang	Chief, Chemistry and Pharmaceutics Branch, DTRD
Robert Walsh	Chief Regulatory Affairs Branch, DTRD
<b>FDA HFD-170</b>	<b>Title</b>
Cynthia G. McCormick M.D.	Division Director
Celia Winchell, M.D.	Medical Team Leader
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader
Albert Chen, Ph.D.	Clinical Pharmacology Reviewer
Sara Shepherd, M.S.	Regulatory Project Manager

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**Meeting Objective:** The primary objective of this meeting was to discuss the pharmacokinetic study requested in the January 26, 2001, approvable letters for Suboxone and Subutex.

**Historical Information:** In the January 26, 2001, approvable letters, the Division requested that the Sponsor conduct a pharmacokinetic study to establish the proper method of administering doses requiring more than two tablets of buprenorphine, comparing simultaneous dosing vs. sequential dosing at various intervals, in order to provide specific dosing instructions to patients and physicians that will permit the accurate delivery of the desired dose. The Division believes that the PK data will provide meaningful information for clinicians regarding the administration of various intermediate doses of buprenorphine requiring multiple tablets. Data reviewed earlier by the Division suggested that the physical limitations of the sublingual space might prevent optimal dissolution of tablets when many (specifically three or more) tablets were placed under the tongue at one time. A loss of dose proportionality at high doses suggested that there were potential effects on bioavailability attributable to the presence of numerous tablets. This raised the possibility that variability in blood levels might occur if tablets were dosed in different ways at different times. Reliable dosing from day to day is important to patients who have been titrated to an individualized, effective dose. If there is a significant effect on bioavailability attributable to variations in dosing technique, this is important to clinicians in helping their patients obtain reliably effective blood levels.

**General Discussion:** Following introductions, the discussion focused on the PK protocols submitted in the meeting package.

The Sponsor proposed a crossover PK study in healthy volunteers, under naltrexone block, comparing 20 mg doses (two 8mg + two 2 mg tablets) in simultaneous and sequential fashion. The Division agreed that this approach was acceptable and one dose would be satisfactory. However, the data must be provided before approval, not after approval.

The Sponsor stated that the      study described in the briefing package provides the necessary data, but the Division disagreed. The Division stated that the      study is not sufficient. The tablets were given shortly after administration of the alcohol solution, resulting in a significant increase in bioavailability compared to the findings of previous studies in which tablets were dosed alone. The data generated in the      study are artificial, influenced by the presence of alcohol, and would not help in answering questions about specific dosing methods. In addition, the      study did not compare sequential and simultaneous dosing. The Sponsor conceded that the      study would not meet the Division's requirements.

The Sponsor asked if the Australian study would be adequate to answer the questions about specific dosing methods. The Division stated that this was not a pivotal study. The Australian study did not support efficacy, only safety. It actually demonstrated that buprenorphine was slightly less effective than methadone on its primary outcome measure.

The Division suggested folding the PK study into another on-going trial, but the Sponsor decided not to pursue this path.

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The Sponsor acknowledged that the PK study is a barrier to the approval of their drug. However, the Division reminded the Sponsor that the PK study has been requested in the previous approvable letters.

A discussion initiated about the length of time required to carry out the PK study. The Division stated that the actual study should only take 4-6 weeks. However the Sponsor noted that the protocol review, IRB approval, scheduling, and data analysis will increase the time frame to 4-6 months.

The Division stated that the 8 mg tablet could be approved based on historical data, but the intermediate doses would not be approved without the PK data. The Sponsor replied that approval of only the 8 mg tablet may be their best option.

The Sponsor will send in the PK protocol for review and the Division stated it would be reviewed promptly. The Division reiterated that the data from the PK study must be analyzed and submitted for review prior to approval.

The meeting adjourned at ~12:30 PM

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/s/

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Sara Shepherd  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-732  
NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.  
1909 Huguenot Road  
Richmond, VA 23235

Attention: Alan Young  
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the meeting between representatives of your firm and FDA on February 27, 2001. The purpose of the meeting was to discuss the January 26, 2001, approvable letters for Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

*{See appended electronic signature page}*

Sara E. Shepherd  
Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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**SPONSOR MEETING ATTENDEES**

**Meeting Date:** February 27, 2001

**Location:** Parklawn Building, Conference Room C (10:00-11:30)

**NDA:** 20-732 (Subutex) and 20-733 (Suboxone)

**Sponsor:** Reckitt & Colman

**Type of Meeting:** Discuss AE letters

**Meeting Chair:** Celia Winchell, M.D.  
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

**Minutes Recorder:** Sara E. Shepherd, Regulatory Project Manager, HFD-170



<b>Reckitt &amp; Colman</b>	<b>Title</b>
Charles O'Keefe	President
Alan Young	Regulatory Director
Don Walter	Buprenorphine Developmental Manager
Neil Hyde	Buprenorphine Project Manager
Paul Field	Team Leader Buprenorphine R&D
	Toxicology Expert
<b>NIDA</b>	<b>Title</b>
Frank Vocci	Director, Division of Treatment Research and Development
Nora Chiang	Chief, Chemistry and Pharmaceuticals Branch, DTRD
Robert Walsh	Chief Regulatory Affairs Branch, DTRD
<b>FDA HFD-170</b>	<b>Title</b>
Cynthia G. McCormick M.D.	Division Director
Celia Winchell, M.D.	Medical Team Leader
Steve Koepke, Ph.D.	Deputy Director, DNDCII
Suresh Doddapaneni, Ph.D.	Pharmacokinetics Team Leader
Albert Chen, Ph.D.	Pharmacokinetics Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Ali-Al-Hakim, Ph.D.	Chemistry Reviewer
Pat Maturu, Ph.D.	Chemistry Reviewer
Tom Papoian, Ph.D.	Supervisory Pharmacologist
Sara Shepherd, M.S.	Regulatory Project Manager

**APPEARS THIS WAY  
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**Meeting Objective:** The primary objective of this meeting was to discuss the issues in the approvable letters for Subutex and Suboxone.

**General Discussion:** Following introductions, the discussion focused on the following issues from the approvable letters dated January 26, 2001. The approvable letter issues were linked to the questions in the information package submitted by Reckitt & Colman.

The Division stated that future meetings will be needed to ensure that the Sponsor is on the right track to address all the issues in the approvable letter.

NOTE: The issues listed in italics are from the Suboxone approvable letter. These issues are similar to the Subutex approvable letter.

*1. Concerning the tests, test methods, and acceptance criteria for the drug product:*

- a. Provide an updated specification sheet, when the drug product specifications (tests, test methods, and acceptance criteria) have been agreed upon with the Agency.*

The Division stated that the specification sheet should be updated with each submission. The Sponsor agreed.

- b. Update the acceptance criteria for color if the tablet is changed from light orange. In addition, identify the effect of changing the color on the \_\_\_\_\_*

The Division asked for clarification on the tablet color. The Sponsor stated that the color will remain light orange for the Suboxone tablet in order to differentiate it from the white Subutex tablet.

- c. Provide safety qualification for individual degradation products of buprenorphine and naloxone that have acceptance criteria of \_\_\_\_\_, or higher.*

**Safety Qualification of the Degradation Products**

The Sponsor asked the Division to comment on the need for safety qualification in view of the fact that a portion of the tablets used in human studies were sufficiently aged to be expected to contain the degradation products in question. The Division does not agree that exposure in human studies obviates the need for safety qualification and thus preclinical safety qualifications cannot be waived.

The Division stated that the results from the 28-day dietary toxicity study (attachment 1 in meeting package) in rats fed degradation products from the Suboxone tablet extracts should demonstrate a sufficient safety margin

(based on surface area or  $\text{mg}/\text{m}^2$  when compared to the human therapeutic exposure) (see impurity levels of Suboxone Tablet Extraction).

The Division asked for clarification on the method of administering the extracts. The Sponsor stated that in earlier studies the animals received the degradation products by gavage and in more recent studies it was by dietary administration.

The Division stated that the degradation product \_\_\_\_\_ can be considered qualified, provided that it can be demonstrated that this \_\_\_\_\_ is produced in the specific species used in the *in vivo* toxicology studies.

#### Interpretation of the Qualification Studies for the Degradants

The Division stated it was difficult to interpret the multiples used by the Sponsor in the Suboxone Tablet Extraction table (attachment 1 in meeting package). A column comparing the dose in animals and the human equivalent dose ( $\text{mg}/\text{kg}/\text{day}$ ) would be helpful. Also, this would help determine specifications for the drug.

The Sponsor described, in detail, the method used to qualify the impurities. The Suboxone tablets were stressed to force degradation. The tablets \_\_\_\_\_ to increase the ratio of active ingredient and degradant to excipients (a 10-fold increase). The Suboxone was a 4.5:1 mixture of buprenorphine hydrochloride and naloxone and this was compared to the Suboxone tablet extracts in the Ames test and the 28-day dietary toxicity study. The results showed no mutagenic or clastogenic effects. The Sponsor reported no difference between the toxicity of Suboxone and Suboxone tablet extracts at \_\_\_\_\_ ppm. The Sponsor will submit the final study report in March 2001. The Division reminded the Sponsor to include all of the degraded products/impurities.

To calculate the level of impurities, the Sponsor used a mean human weight of 70 kg. The Division stated that it is more acceptable to use a weight of 50 or 60 kg since 70 kg represents only the male population. The Sponsor stated that they would take those numbers into consideration when they calculated the impurities to determine the equivalent to the daily human dose ( $\text{mg}/\text{day}$ ). The maximum dose of 32 mg buprenorphine and 8 mg naloxone is used to calculate impurity levels as a percentage of parent compound. The Sponsor also includes a safety margin of 10-fold reduction and 25-fold reduction. Based on the impurities, the Sponsor has identified \_\_\_\_\_ impurities for buprenorphine and \_\_\_\_\_ for naloxone. The impurities have been characterized and the information will be submitted to the Division.

**ACTION:** The Sponsor will submit the information about the characterization of the impurities to the Division.

The Division would also like a clarification of the certificate of analysis (COA) for Suboxone (tablet and tablet extract) used in these studies. The COA submitted with the meeting package was not clear. The Sponsor agreed to clarify the COA.

**ACTION:** The Sponsor will clarify the COA listed in the meeting package for the Suboxone extract used in the pre-clinical studies in impurities.

The Division also stated that the safety qualification for individual degradation products of Subutex (e.g., \_\_\_\_\_ after \_\_\_\_\_ storage at 25°C/60% RH) should be provided as stated in the Subutex approvable letter.

- d. *Provide acceptance criteria of not more than 0.1% for any individual unspecified degradation product of buprenorphine and of naloxone.*

**ACTION:** The Sponsor will provide the appropriate data.

- e. *Provide identification of individual degradation products occurring at \_\_\_\_\_ or greater (refer to ICH Q3B Guideline).*

**ACTION:** The Sponsor will provide the appropriate data.

- f. *Provide acceptance criteria for each individual degradation product based upon the levels observed in the stability studies.*

**ACTION:** The Sponsor will provide the appropriate data. The Sponsor has improved their identification and monitoring process.

- g. *Provide a test and acceptance criteria (through shelf life) for individual tablet dissolution.*

**ACTION:** The Sponsor will provide the appropriate data. In the submission, the data were reported as mean data but the individual tablet data are available.

2. *You must develop (e.g., through reformulation, more protective packaging, refrigeration storage) a more stable drug product, or alternatively provide data (see below) supporting a longer expiration dating period. The 12-month stability data provided under ICH*

conditions support less than c — expiration-dating period for the drug product. In order to support a longer expiration dating period:

- a. Provide a complete characterization of the degradation product profile and safety qualification of degradation products for naloxone occurring at —  
[NOTE: —

1. However, complete testing, tests, and acceptance criteria for individual degradation products have not been provided and the — indicates individual degradation products will occur above the qualification level of —. In addition, significant degradation products were noted in Subutex which have not been monitored in the stability studies for Suboxone.]

There appears to be different degradation products in the Subutex and Suboxone. The Sponsor is aware of this and believes it to be —

— The Sponsor will provide data on this issue.

ACTION: The Sponsor will provide data to cross correlate the different degradation products found in Subutex and Suboxone.

- b. Provide data for individual tablet dissolution and provide data demonstrating that the use of — rpm for dissolution in stability studies is as sensitive and discriminating as the use of — rpm. [NOTE: There is a significant decrease in dissolution of buprenorphine on stability (e.g., — dissolution for batch 141 after — at 25 °C/60% RH). Decreases in individual tablet dissolution may alter bioavailability.]

It was agreed that the Sponsor will use — rpm for the dissolution studies. The Sponsor stated that the dissolution basket is a USP apparatus. The Sponsor also proposed to adopt the USP method, which allows more emphasis on individual tablet dissolution. The specification will change from “mean —” to “Q=—” However the Division was unsure if — would be acceptable. The Sponsor stated that pH may play a role in the dissolution method.

It was unclear if the ICH stability batches were done at — rpm or — rpm. The Division stated this can be resolved at the next meeting.

3. Identify the packaging components (DMF number, submission date, page number, and item number) used in the stability studies. Each component of the package/ — must be supported by drug product stability data. The Agency has accepted the present ICH stability studies, which used the non-child-resistant packaging (a backing is being added to this packaging to make it child-resistant), for review. However, any additional

*stability studies should be performed with the to-be-commercialized child-resistant packaging.*

The Sponsor stated that several types of packaging have been examined and some have failed. The Sponsor is working with the Consumer Product Safety Commission but is concerned about the length of time to correlate the packaging to the stability studies. The Division stated that in the November teleconference, it was recommended that the Sponsor initiate stability studies as soon as possible. However the Sponsor stated that it took \_\_\_\_\_ to get all the \_\_\_\_\_ packaging material ordered. The material sold in \_\_\_\_\_ is not packaged in a child-resistant package, but the components are the same, minus the backing. Data may be available from \_\_\_\_\_ since they have a single batch rolling stability study on-going. The Division reiterated that any change in packaging, design, or manufacturing must be correlated to stability studies. The Sponsor will review the data and determine if anything can be salvaged.

4. *Provide identification for the site of packaging of the drug product batches used for the ICH stability studies and the proposed site(s) of commercial drug product packaging. Stability data must be provided for drug product batches packaged at each proposed packaging site.*

ACTION: The Sponsor will provide this information.

5. *Regarding the child-resistant packaging:*
  - a. *Provide updated labeling incorporating instructions for opening (i.e., \_\_\_\_\_ the child-resistant packaging.*
  - b. *Provide data supporting the patients' success in opening the \_\_\_\_\_ according to the proposed instructions for opening.*
  - c. *Provide confirmation that the child-resistant packaging meets the requirements of the Consumer Product Safety Commission under 16 CFR 1700.14 (a)(4) for controlled drugs.*
  - d. *Provide an updated reference (DMF number, submission date, page number, item number, composition, etc.) for the child-resistant packaging (e.g., \_\_\_\_\_ to be used for the commercial drug product.*

Several issues regarding the child-resistant packaging were discussed in item #3. A report provided in the meeting package indicated that the \_\_\_\_\_ packaging did not pass the test for child resistance.

6. *Conduct a pharmacokinetic study to establish the proper method of administering doses requiring more than two tablets of buprenorphine, comparing simultaneous dosing vs. sequential dosing at various intervals, in order to provide specific dosing instructions to patients and physicians that will permit the accurate delivery of the desired dose.*

The Division stated that this deficiency requests the Sponsor to generate data that provide meaningful information for clinicians regarding the administration of various intermediate doses of buprenorphine requiring multiple tablets. Data reviewed earlier by the Division suggested that the physical limitations of the sublingual space might prevent optimal dissolution of tablets when many (specifically three or more) tablets were placed under the tongue at one time. A loss of dose proportionality at high doses suggested that there were potential effects on bioavailability attributable to the presence of numerous tablets. This raised the possibility that variability in blood levels might occur if tablets were dosed in different ways at different times. Reliable dosing from day to day is important to patients who have been titrated to an individualized, effective dose. If there is a significant effect on bioavailability attributable to variations in dosing technique, this is important to clinicians in helping their patients obtain reliably effective blood levels.

The Division stated that the  $\sim$  study described in the briefing package will not suffice. The data submitted with the meeting package do not address the specific mode of administration of the tablets. Furthermore, because of the double-dummy technique, the tablets were coadministered with an alcohol solution, resulting in a significant increase in bioavailability compared to the findings of previous studies in which tablets were dosed alone. Therefore, the  $\sim$  study will not be helpful in answering questions about specific dosing methods. The Sponsor stated that the  $\sim$  study may provide the necessary data but the Division disagreed and stated that this study actually showed bioequivalence between the solution and the tablet when coadministered.

The Division suggested a crossover study in currently maintained patients at various doses using different dosing techniques. The question regarding the effect of different tablet administration techniques could be answered in a crossover study involving patients already stabilized on buprenorphine under various IND-sanctioned studies. Such subjects could take their medication by their "usual" method and subsequently be crossed over to taking their tablets in various ways: all at once or separated by various intervals. The different dosing conditions for this study should be generated by surveying the researchers who have used or are currently using buprenorphine tablets in their studies and learning how, specifically, doses of three or more tablets are administered in their studies. The most commonly reported methods should be tested. Ideally, doses requiring three or more tablets (including combinations of 8 mg and 2 mg tablets) throughout the range of 6 mg to 32 mg should be tested. Dose-

proportionality or lack thereof should be assessed so that clinicians can understand the effective blood level increase that is likely to result from a particular dose increase. A complete PK profile is needed (Cmax and AUC) to address the issue.

The Sponsor agreed that it was possible to interview clinicians and determine the method of administration but are concerned about the time constraints on performing an entire PK study. The Sponsor suggested that this should be a post-marketing commitment but the Division stated that this was a study that was requested in the past approvable letters for these drugs and it is important that it be done before approval.

The Division stated that it may be possible to approve the 8 mg dose based on historical data but the other doses would have to be dropped. However the stability and dissolution issues need to be resolved first.

**ACTION:** No agreement was reached on a study design and this issue will need to be resolved by telecon or another meeting.

- 7. Provide a safety update, including a complete review of all existing safety data, including data from ongoing and completed studies sponsored by Reckitt & Colman's CRADA partner, NIDA, and its grantees. This update should specifically examine the potential for buprenorphine-induced hepatotoxicity, the role of viral hepatitis in increasing vulnerability to hepatotoxicity, and the proper approach to prevention and management of hepatic adverse events. Analyses should focus on outliers and extreme values, rather than measures of central tendency, and should provide comparison groups wherever available. Data sets with unique patient identifiers should be submitted together with the reports of the analyses. The analyses of uncontrolled studies of buprenorphine should compare the course seen in treated patients to the natural history of hepatic enzyme fluctuation in viral hepatitis. In addition, the safety data should be examined for any cases of acute allergic reaction to buprenorphine.*

The data submitted previously were reviewed, but the Division is requesting additional analyses and requesting that an effort be made to identify and analyze any other available data on the interaction between serologic status and hepatic effects, and to identify any additional cases of acute allergic reaction. The data sent were analyzed prior to taking action on the application. However, the data were limited to lab values from a single study, in which only four weeks of controlled data were included. The remainder of the data is uncontrolled, making it difficult to tease out the role of buprenorphine in the fluctuation of hepatic data. The analyses submitted focused on measures of central tendency and on the numbers of patients shifting from normal to abnormal on various parameters. While shift tables are useful, group means in this circumstance are not. The data should be examined for certain patterns of simultaneous elevation on different measures of hepatic function in individual subjects, and an effort should be made

to locate ALL available data, not simply the data from this single trial. The Division is available to discuss specific approaches to the data, because there is not a standard approach to evaluation for signals of hepatotoxicity in datasets with a high prevalence of abnormality at baseline.

8. *Develop and submit a protocol for urine screening for buprenorphine that can be made available to emergency rooms and poison control centers in order to facilitate distinguishing buprenorphine-related adverse events from events attributable to other drug use.*

If there is a commercially available urine-screening test that is readily available for emergency room use, it is not necessary that the sponsor develop a new method. The Sponsor stated that a commercially available kit is available.

9. *Design and submit a risk management and active surveillance program to ensure the safe and effective use of buprenorphine, and to identify trends in inappropriate use that might have adverse effects on the public health. An acceptable program must be finalized prior to approval of this application or your application for single ingredient buprenorphine sublingual tablets.*

To be discussed at a separate meeting.

10. *Develop and submit a common package insert for both Subutex and Suboxone.*

The Division would like to see both products described on a single package insert. This approach was used for Nicorette and Nicorette DS. Because both products rely on an almost entirely overlapping set of safety and efficacy data, the few differences between the two products are best highlighted by including them on the same package insert, rather than expecting the clinician to read both labels and undergo a laborious mental "document compare" process. The Sponsor agreed.

The Sponsor stated that Suboxone has many issues to resolve and Subutex may be a better option to get to market in a timely manner. However the Division stated that Subutex has stability and dissolution problems that need to be resolved. The Sponsor stated that they thought the \_\_\_\_\_ data were sufficient for approval of Subutex. However the Division did not agree. The Sponsor stated that it will be impossible for them to do stability under ICH conditions with the child-resistant packaging in a reasonable time frame. The Division stated that the qualification of the impurities was a step in the right direction but it was unclear why the Sponsor stopped their ICH stability studies.

The Sponsor stated that a less than — shelf life would be acceptable. However the Division stated that approving the drug with a shelf life of only — would raise concerns about the possibility of a drug shortage.

The Division requested the Sponsor submit a summary of all to the stability studies with details about ICH conditions, lots etc. The Sponsor agreed.

**ACTION:** The Sponsor will submit a summary of all the stability studies.

The Sponsor stated that they would like to address several of the chemistry issues by March and get back on track. The Division agreed and again suggested sending in a request for another meeting.

In general, the Sponsor voiced concern over the length of time the Subutex and Suboxone applications have been under review. Subutex is approved in many countries and it is unclear to the Sponsor why it is still not approved in the United States.

It was developed as an orphan drug with the support of NIDA. The Sponsor stated that they may need to reconsider pursuing the development of the drugs due to the time consuming process involved in obtaining approval. The Sponsor felt they had enough stability with the \_\_\_\_\_ data but believes the Division has changed its criteria for approval by requiring stability data under ICH guidelines. A better tablet is under development but it will take time to accumulate the data and the Sponsor feels the Division needs to recognize the public health benefit and approve the drugs. The Sponsor stated that the degradation products present in the Suboxone and Subutex tablets will not affect the target population of drug addicts.

The Division stated that public health is our main responsibility and reiterated that the criteria for approval have not been altered over the past several review cycles. Criteria for approval are not different for this patient population. The Sponsor should review their data and submit a complete package and not rush into submitting too soon. The Division stated that the Sponsor has not understood the issues in the previous approvable letters. The Sponsor needs to give itself time to develop the drug appropriately. The Division sees this as a viable product but cannot rush the approval process.

The Division restated that another meeting should be scheduled prior to the next submission.

**ACTION:** The Sponsor agreed to send in a request for another meeting prior to the next submission.

**APPEARS THIS WAY  
ON ORIGINAL**