Wheelous, Teresa A

om	Kapcala, Leonard P
nt	Tuesday, May 27, 2003 11 05 PM
To	'Andrea Miller@mylanlabs com', 'Frank Sisto@mylanlabs com'
Cc	Kapcala, Leonard P, Wheelous, Teresa A
Subject	? About Outpatient Diary CRFs and Specific Analyses of Diary Data for APO202 and Other questions about treating "Off"
Importance	High

Hi Andrea and Frank,

I have some questions about treating "off" episodes

1 I was looking at vol 6 (of 111) for study 202 I was unable to find the CRFs for the outpatient diary data collection Are these CRFs somewhere in the NDA? If not would you please FAX me a copy of them on Wednesday?

2 Neither was I able to find the specific analysis plan for these data Pages 61 and 62 of vol 6 (8-5-61,62) briefly summarized an approach for analyzing these data and also noted that some revisions were made in the analytical approach to these data Is there a more detailed description of how outpatient diary data were analyzed in study 202? If so, please tell me where I can find it

3 Based upon the protocol for 202, it did not appear that information was captured in the diary to distinguish specifically whether the patient experienced an "end of dose wearing off" or an unpredictable "on/off" Is this correct? If not please tell me where I can find this information

4 In all 4 controlled studies (202 30 30 302) it did not appear that specific information was captured as to whether a
)tient
experienced an "end of dose wearing off" or an unpredictable "on/off" that was to be treated during the controlled phase Is this correct? If this is not correct, please specify where I can find information characterizing whether an "off" episode that was treated was an "end of dose wearing off" or an unpredictable "on/off "

5 In studies 301, 303, and 302, I understand that patients were to receive injection of study medication for their first "off" episode that occurred at least 1 hour after the usual morning therapy Is there information contained within the NDA that specifies whether these "off" episodes that were treated had occurred within each patient's dosing interval for levodopa or whether their next scheduled levodopa dose had to be held because an "off" episode (that was to be treated) had not yet occurred and regular medications were to be held until "off' was treated?

Would you please call me tomorrow to try to give me an update tomorrow about which issues/questions can be answered quickly and when answers can be expected for the remaining questions that were not yet able to be answered ?

Thanx

Len

301-594-5521

Wheelous, Teresa A

ɔm	Kapcala, Leonard P
⁼ent	Friday, May 23, 2003 12 00 PM
To	'Frank Sisto@mylanlabs com', 'Andrea Miller@mylanlabs com'
Cc	Kapcala, Leonard P, Wheelous, Teresa A
Subject	Very Important Please call today
Importance	High

Hi Frank and Andrea,

If either of you are in the office today, would you please call me at 410-531-3927? It's important that I talk to one of you today If we don't talk today, would you please call me Tuesday

As a separate, different issue, would you please tell me where I can find some specific information in the application or if you would have to assemble the desired information about repeat injections for no response or inadequate response **If the desired information is not available in the application in a format toward which you can direct my attention, please submit the answers to my questions**

I understand that patients were told that they could repeat an injection of apomorphine (APM) if they did not experience a response by 20 minutes after the injection If this understanding it incorrect, please provide clarification on this issue Where can I look to find answers to these following specific questions?

1 How many different patients (in all studes) took a repeat injection of APM a "short" time later if they did not experience a response within a "short time after their injection ?

Do you know the total number of times that a repeat injection was administered (in all studies) because of no response an inadequate response "shortly" after the injection of APM?

3 Do you know the average number of times this occurred on a per patient basis for each patient who ever did this?

4 Do you know the average time interval between the original injection and the repeat inejction?

5 Do you know the range (minimum and maximum times) for the time interval between the original injection and the repeat injection?

6 Do you know the frequency distribution of repeat inejctions relative to the time interval between the original injection and the repeat inejction? For example, you might show that 20 patients administered repeat injections between 20 to 30 minutes, 50 patients administered repeat injections between 31 to 60 minutes, and 30 patients administered repeat injections between 61 to 120 minutes after the "failed"injection

7 Do you have any information on the efficacy and safety of repeat injections such as how frequently a repeat injection was successful for reversing "Off" and the frequency of developing adverse reactions (if so, what were they by type and number?) associated with the repeat injections?

Wheelous, Teresa A

rom Kapcala, Leonard P
ent Wednesday, May 14, 2003 7 42 PM
To 'Andrea Miller@mylanlabs com'
Cc 'Frank Sisto@mylanlabs com', Kapcala, Leonard P, Wheelous, Teresa A
Subject Unable to find specific separate listing of clinically significant laboratory abnormalities

Importance High

Hi Andrea and Frank,

Would you please tell me where I can find a separate listing of the definitions/criteria of "clinically significant laboratory abnormalities?" I see in the ISS tables 100-104 there are data about laboratory abnormalities and that table 104 shows the criteria for clinically significant abnormal labs for individual patients in a listing over many pages However, I'm unable to find a separate listing of the definitions/criteria for clinically significant low and high lab abnormalities where they are all defined in a single location irrespective of individual patient results that deal with isolated abnormalities

If this is not available, would you please provide me (by fax initially and then formal submission) with a listing of the normal range for each test along with the definitions/criteria of clinically significant abnormal for each test?

Thanx

en
301-594-5521

-----Original Message-----
From Andrea Miller@mylanlabs com [mailto Andrea Miller@mylanlabs com]
Sent Thursday, May 08, 2003 3 17 PM
To Kapcala, Leonard P
Cc 'Frank Sisto@mylanlabs com', Kapcala, Leonard P, Wheelous, Teresa A
Subject Re Missing Information from 4/17/03 submission for NDA 21264

Good afternoon Dr Kapcala,

Just a quick e-mail to let you know that we received your attached e-mail
Your e-mail has been circulated to the appropriate individuals Responses
to your comments will be provided as quickly as possible I will contact
you with the proposed response date once your comments have been reviewed
and discussed Should there be any need for further discussion on these points, I will contact Teresa to arrange a telephone conference if needed

Warmest regards,

Andrea

"Kapcala, Leonard

P" To
"'Frank Sisto@mylanlabs com'" <Frank Sisto@mylanlabs com>

<KAPCALAL@cder fd cc "Kapcala,
eonard P" <KAPCALAL@cder fda gov>, "Wheelous, Teresa A"
a gov>
<WHEELOUST@cder fda gov>, "'Andrea Miller@mylanlabs com'"

<Andrea Miller@mylanlabs com>

05/08/2003 02 56 Subject Missing
Information from 4/17/03 submission for NDA 21264
PM

Hi Frank,

I was reviewing your 4/17/03 submission and noted that several tables appeared to be missing from Attachment 2 containing revised tables for the correction of the sign of the various orthostatic VS calculations

1 For Study 303, the last Table included is 14 3 8 1 Thus Tables
'4 3 8 2
hrough 14 3 8 6 appear to be missing In addition there are no
corrected
Tables 14 3 8 7 through 14 3 8 9 nor Tables 14 3 9 1 through 14 3 9 5

2 What is the definition of "penultimate dose" used in table 14 3 8 9?

3 In table 14 3 8 7 for the 10 mg apomorphine dose (volume 19 of the Safety
Update submission, p C-1-202), I have questions about the accuracy of the
magnitude of the change calculations I recognize that the sign needs to be
changed in all calculations for changing from sitting to standing However,
the magnitude of most of the changes if you calculate the difference between
mean sitting and mean standing data seems to be quite different than the
change calculations shown in the table I know that the change column only
assess the change in paired data whereas the mean figure may included
non-paired data However, in this table in particular the differences seem
much larger than expected and observed in other tables For example the
magnitude of the difference of mean sitting and mean standing pulse at 90
minutes is + 3 2 but the change is noted as - 5 8 (I know the sign needs to
be changed to + 5 8 if correct) Thus, the arithmetic difference I
alculate
s only about 1/2 what is presented At 40 minutes, the mean pulse is
identical for sitting and standing at 72 7 but a change is noted as -
3 5
Again, the magnitude of the apparent discrepancy is

Would you please have these data checked? If these data presentations for change are incorrect numerical values, please re-assess other numerical change calculations to see what other data are incorrect so that we don't have to wait for me to identify errors and ask for corrections

Please let me know if you have any questions

Would you please try to get the corrected tables (with the sign change) that appear to have been omitted as soon as possible?

Would you also please confirm as soon as you receive this e-mail that you did receive it and these issues are in the process of being addressed?

Thank you very much

Len

APPEARS THIS WAY
ON ORIGINAL

Wheelous, Teresa A

From	Kapcala, Leonard P
Sent	Wednesday, May 14, 2003 4 00 PM
To	'Andrea Miller@mylanlabs com'
Cc	'Frank Sisto@mylanlabs com', Kapcala, Leonard P, Wheelous, Teresa A, Duan, John Z
Subject	Questions about Apparent Numerical Discrepancies between Orthostatic Change Data in Tables 14 3 6 1 and 14 3 8 1 through 7
Importance	High

Hi Andrea and Frank,

We (the Biopharm reviewer and myself) have some additional questions after reviewing some of the orthostatic VS tables For "change" data (based upon paired observations) shown in tables Tables 14 3 6 1 and 14 3 8 1 through 7, why are many of the numerical mean changes calculated and shown appear to differ in many instances when you compare these tables? We would expect them to show the same data in tables 14 3 8 1 through 14 3 8 7 for the different treatments that are summarized in table 14 3 6 1 because they should all be based upon paired changes of the same data

We are faxing an example of the differences shown for the 10 mg dose group at + 20 minute (table 14 3 8 7) compared to the same summarized data in table 14 3 6 1 and showing results for all treatment groups There are many values that are different but some mean and standard error values that are identical in both tables

Would you please let us know why there are these apparent discrepancies? ıese apparent numerical discrepancies were present in the Safety Update so they did not just recently appear with the edits of the tables for the sign changes

Would you please confirm that you received this and let us know approximately how long it might be to get an answer?

Thanx

Len
301-594-5521

-----Original Message-----
From Andrea Miller@mylanlabs com [mailto Andrea Miller@mylanlabs com]
Sent Thursday, May 08, 2003 3 17 PM
To Kapcala, Leonard P
Cc 'Frank Sisto@mylanlabs com', Kapcala, Leonard P, Wheelous, Teresa A
Subject Re Missing Information from 4/17/03 submission for NDA 21264

Good afternoon Dr Kapcala,

Just a quick e-mail to let you know that we received your attached e-mail
Your e-mail has been circulated to the appropriate individuals Responses
to your comments will be provided as quickly as possible I will ontact
ou with the proposed response date once your comments have been reviewed
and discussed Should there be any need for further discussion on these points, I will contact Teresa to arrange a telephone conference if needed

Warmest regards,

Andrea

"Kapcala, Leonard P" To "'Frank Sisto@mylanlabs com'" <Frank Sisto@mylanlabs com>
<KAPCALAL@cder fd a gov> cc "Kapcala, Leonard P" <KAPCALAL@cder fda gov>, "Wheelous, Teresa A" <WHEELOUST@cder fda gov>, "'Andrea Miller@mylanlabs com'" <Andrea Miller@mylanlabs com>
05/08/2003 02 56 PM Subject Missing Information from 4/17/03 submission for NDA 21264

1 Frank,

I was reviewing your 4/17/03 submission and noted that several tables appeared to be missing from Attachment 2 containing revised tables for the correction of the sign of the various orthostatic VS calculations

1 For Study 303, the last Table included is 14 3 8 1 Thus Tables 14 3 8 2 through 14 3 8 6 appear to be missing In addition there are no corrected Tables 14 3 8 7 through 14 3 8 9 nor Tables 14 3 9 1 through 14 3 9 5

2 What is the definition of "penultimate dose" used in table 14 3 8 9?

3 In table 14 3 8 7 for the 10 mg apomorphine dose (volume 19 of the Safety Update submission, p C-1-202), I have questions about the accuracy of the magnitude of the change calculations I recognize that the sign needs to be changed in all calculations for changing from sitting to standing However, the magnitude of most of the changes if you calculate the difference between mean sitting and mean standing data seems to be quite different than the change calculations shown in the table I know that the change column only assess the change in paired data whereas the mean figure may included on-paired data However, in this table in particular the differences seem much larger than expected and observed in other tables For example the magnitude of the difference of mean sitting and mean standing pulse at 90

minutes is + 3 2 but the change is noted as - 5 8 (I know the sign needs to
be changed to + 5 8 if correct) Thus, the arithmetic difference I calculate
s only about 1/2 what is presented At 40 minutes, the mean pulse is
identical for sitting and standing at 72 7 but a change is noted as - 3 5
Again, the magnitude of the apparent discrepancy is

Would you please have these data checked? If these data presentations for
change are incorrect numerical values, please re-assess other numerical
change calculations to see what other data are incorrect so that we don't
have to wait for me to identify errors and ask for corrections

Please let me know if you have any questions

Would you please try to get the corrected tables (with the sign change) that
appear to have been omitted as soon as possible?

Would you also please confirm as soon as you receive this e-mail that you
did receive it and these issues are in the process of being addressed?

Thank you very much

Len

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: May 13, 2003

To: Andrea Miller	**From:** Teresa Wheelous
Company Bertek Pharmaceuticals Inc	Division of Division of Neuropharmacological Drug Products
Fax number (304) 285-6407	**Fax number:** (301 594-2859
Phone number. (800) 826-9526 x6869	**Phone number:** (301) 594-2850

Subject: NDA 21-264 Apomorphine HCl Injection Pharm/Tox Information Request

Total no of pages including cover 1

Andrea,
The following is a preclinical information request

In the chronic rat and monkey studies (— 9902 and — 9903) it is stated that the information on composition for the apomorphine was on file Please submit the Certificate of Analysis for the apomorphine batches used in these studies

Thank you,
Teresa

Document to be mailed: ☐ YES ☑ NO

Wheelous, Teresa A

From Kapcala, Leonard P
Sent Wednesday, May 07, 2003 12 48 PM
To Wheelous, Teresa A
Cc Kapcala, Leonard P, Roney, Paul L, Duan, John Z
Subject Apomorphine (NDA 21264) Data Analyses Requests

Hi Teresa,

Would you please forward the following data requests in the attached document to the sponsor? Please ask the sponsor to let us know if there are questions or need for clarification
Thanx

Len

APMDataRequests501 03 doc

We have the following requests for NDA 21264 for apomorphine If any of these specific data requests are already specified in the NDA as requested, please specify the volume and page where the information requested can be located

1. **For each of the following data requests, please specify the mean, median (50^{th}), 25^{th} percentile, 75^{th} percentile, and range (minimum and maximum) of the data Please provide the requested information for all patients treated with apomorphine In addition, please provide additional, cumulative subgroup data presentations based upon the duration of apomorphine treatment (i e $\geq$ 3 months, and $\geq$ 6 months, and $\geq$ 12 months) Note that patients treated for longer periods (e g > 12 months) would also be included in the dataset presentations of treatment duration of $\geq$ 3 months and $\geq$ 6 months Thus, these datasets should not be mutually exclusive of each other**

Please also provide separate, identical data presentations for all patients who participated in your pivotal studies (202, 301, 303) These presentations would be a subset of subgroup analyses of the analyses of all patients (complete dataset) who were treated with apomorphine

Specific Parameter Data Requests

- Hoehn and Yahr staging of Parkinson's disease
- Age
- Total UPDRS
- Total UPDRS motor score (subscale III)
- Total years since diagnosis of Parkinson's disease
- Daily "Off" hours
- Daily percent of "Off" during waking hours

A table show showing the format of how these data should be presented is attached You are welcome to use these tables and add the data if you like

Baseline Characteristics of Patients Treated with Apomorphine for Various Durations

	All Patients Treated with Apomorphine N =				Patients Who Participated (APM or Placebo) in Apomorphine Pivotal Trials (202, 301, 303) N =			
Parameter	Any Rx	Rx ≥ 3 months	Rx ≥ 6 months	Rx ≥ 12 months	Any Rx	Rx ≥ 3 months	Rx ≥ 6 months	Rx ≥ 12 months
H & Y stage N =								
Mean								
25 % ile								
50 % ile								
75 % ile								
range								
Age N =								
Mean								
25 % ile								
50 % ile								
75 % ile								
range								
Total UPDRS N=								
Mean								
25 % ile								
50 % ile								
75 % ile								
range								
UPDRS Motor Score III N =								
Mean								
25 % ile								
50 % ile								
75 % ile								
range								
Years with PD (since Dx) N =								
Mean								
25 % ile								
50 % ile								
75 % ile								
range								
Daily "Off" N =								
Mean								
25 % ile								
50 % ile								
75 % ile								
range								
Daily % "Off" of waking hrs N =								
Mean								
25 % ile								
50 % ile								
75 % ile								
range								

2 Please present the number and percentage of patients who demonstrated orthostatic hypotension at baseline (i e prior to ever receiving any apomorphine) according to the threshold categories specified here The percentage of patients should be calculated according to the total number of patients assessed for that specific threshold and orthostatic maneuver at baseline and the percentage should be shown in parentheses next to the number of patients Please provide separate data presentations according to various threshold including

1 systolic orthostatic hypotension **alone** (defined as $\geq$ 20 mm Hg decrease while changing from supine to standing)
2 diastolic orthostatic hypotension **alone** (defined as $\geq$ 10 mm Hg decrease while changing from supine to standing)
3 systolic orthostatic hypotension (defined as $\geq$ 20 mm Hg decrease while changing from supine to standing) **AND** diastolic orthostatic hypotension (defined as $\geq$ 10 mm Hg decrease while changing from supine to standing)
4 systolic orthostatic hypotension **alone** (defined as $\geq$ 20 mm Hg decrease while changing from sitting to standing)
5 diastolic orthostatic hypotension **alone** (defined as $\geq$ 10 mm Hg decrease while changing from sitting to standing)
6 systolic orthostatic hypotension (defined as $\geq$ 20 mm Hg decrease while changing from supine to standing) **AND** diastolic orthostatic hypotension (defined as $\geq$ 10 mm Hg decrease while changing from sitting to standing)

A table showing the format of how these data should be presented is attached You are welcome to use these tables and add the data if you like

APPEARS THIS WAY
ON ORIGINAL

Baseline Prevalence of Orthostatic Hypotension in Patients Treated with Apomorphine for Various Durations

	All Patients Treated with Apomorphine N =				Patients Who Participated in Apomorphine Pivotal Trials (202, 301, 303) N =			
Orthostatic Hypotension Threshold and Positional Changes	Any Rx	Rx ≥ 3 months	Rx ≥ 6 months	Rx ≥ 12 months	Any Rx	Rx ≥ 3 months	Rx ≥ 6 months	Rx ≥ 12 months
Systolic orthostatic hypotension **alone** (supine to standing)								
Diastolic orthostatic hypotension **alone** (supine to standing)								
Systolic **AND** diastolic orthostatic hypotension (supine to standing)								
Systolic orthostatic hypotension **alone** (sitting to standing)								
Diastolic orthostatic hypotension **alone** (sitting to standing)								
Systolic **AND** diastolic orthostatic hypotension (sitting to standing)								

- Systolic orthostatic hypotension (defined as ≥ 20 mm Hg decrease while changing from supine to standing or sitting to standing)
- Diastolic orthostatic hypotension (defined as ≥ 10 mm Hg decrease while changing from supine to standing or sitting to standing)

3. In the ISS (8-39-400 you noted that you had discovered that some investigators were not recording AEs that were present at baseline/pre-treatment and were recurring after initiating treatment with apomorphine How do you know that you captured all or most of the recurring AEs present at baseline when you asked investigators to record this information that had not been originally recorded? Upon what basis can you provide assurance that AEs not initially recorded by some investigators were comprehensively recalled by the investigator and comprehensively captured in your database?

4 Please conduct and present separate categorical analyses of orthostatic vital sign (VS) thresholds in tabular format for Studies 073, 302, and 303 The orthostatic VS thresholds are shown here

1) orthostatic decrease of systolic blood pressure by $\geq$ 20 mm Hg
2) orthostatic decrease of systolic blood pressure by $\geq$ 30 mm Hg to a level $\leq$ 90 mm Hg
3) orthostatic decrease of systolic blood pressure by $\geq$ 40 mm Hg
4) orthostatic decrease of diastolic blood pressure by $\geq$ 10 mm Hg
5) orthostatic decrease of diastolic blood pressure by $\geq$ 20 mm Hg
6) orthostatic decrease of diastolic blood pressure by $\geq$ 20 mm Hg to a level $\leq$ 50 mm Hg
7) orthostatic pulse increase by $\geq$ 15
8) orthostatic pulse decrease by $\geq$ 15

For Study 073, please tabulate the number and percent of each orthostatic threshold at each timepoint over time (0-270 minutes)

For Study 302, please tabulate the number and percent of each orthostatic threshold at each timepoint over time (0-90 minutes) for each treatment group (APM, APM + 2 mg, pooled Placebo)

For Study 303, please tabulate the number and percent of each orthostatic threshold at each timepoint over time (0-90 minutes) for each treatment group (oral medication, placebo, APM 2,4,6,8,10 mg)

Redacted 2

page(s) of trade secret.

and/or confidential

commercial information

(b4)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: April 9, 2003

To Andrea Miller	**From.** Teresa Wheelous
Company. Bertek Pharmaceuticals Inc.	Division of Division of Neuropharmacological Drug Products
Fax number. (304) 285-6407	**Fax number·** (301 594-2859
Phone number. (800) 826-9526 x6869	**Phone number** (301) 594-2850

Subject NDA 21-264 Apomorphine HCl Injection Microbiology Deficiencies

Total no of pages including cover

Andrea,
The following is a list of microbiology deficiencies and comments that should be addressed as soon as possible

Please answer the following question with regard to —— production at Vetter Pharma-Fertigung

a

b Please provide the following information regarding validation.

1)
2)
3)

c

d

Document to be mailed: ☐ YES ☑ NO

Wheelous, Teresa A

om	Kapcala, Leonard P
ent	Friday, April 04, 2003 1 49 PM
To	Wheelous, Teresa A
Cc	Kapcala, Leonard P
Subject	NDA 21264 apomorphine/

Hi Teresa,

Would you please send this response and additional clarification request to Bertek Pharma regarding NDA 21264 for apomorphine/

Thanx

Len

APMrequest4103ClarificationNDA.

APPEARS THIS WAY
ON ORIGINAL

Regarding NDA 21264 (apomorphine ——

We are responding to your request (4/1/03 FAX) for clarification of DNDP request # 5

- For study APO202, you are correct in interpreting our request as our desire that you add arithmetic mean treatment differences to the QTc tables and data that you have already presented

- For study APO303, you have already presented arithmetic treatment differences to show the differences between the mean QTc change from pre-dose on apomorphine compared to the mean QTc change from pre-dose for placebo Thus, there is no need to provide any additional presentation of the tabular data already presented

- You should also show the analogous mean arithmetic treatment differences between apomorphine treatment and placebo treatment for studies 302 and 303 also after you have recalculated all QTc data as we have requested

We have additional clarification of one (# 10 shown below) of our previous requests We neglected to include ISS table 96 into our request to show the incidence of orthostatic abnormal changes in VS **separately for patients studied while changing from supine to standing and from sitting to standing** ISS tables 96 and 97 apply your orthostatic criteria (# 1 and #2) Please also apply the new orthostatic criterion (#3) we requested (request # 9) in the revised tables to be submitted showing the data separately for the different orthostatic maneuvers

Before

10 [ ]

Now (should read)

10 Please revise ISS Tables 96 and 97 to show the incidence and number of patients of orthostatic abnormal changes in VS separately for patients studied while changing from supine to standing and from sitting to standing Your analyses combine results from both different orthostatic maneuvers Please apply all 3 orthostatic VS criteria (i e your criteria 1 and 2 plus our 3rd criterion requested (request #9) to the new analyses for ISS Tables 96 and 97

Would you also please clarify if patients (study APO401), who had orthostatic VS (supine and standing) evaluated before and after apomorphine dosing at in-office dosing, were studied at a particular time after dosing? It does not seem that the protocol specified collecting data at a specific time after dosing Please indicate the time(s) post-dosing data were collected If post-dosing timed orthostatic VS measurements were not consistently collected at particular time(s), please describe how investigators dealt with this issue for data collection

Thank you for your attention to these issues

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE April 4, 2003

To Andrea Miller	Teresa Wheelous **From·**
Company· Bertek Pharmaceuticals Inc	Division of Division of Neuropharmacological Drug Products
Fax number (304) 285-6407	**Fax number:** (301 594-2859
Phone number. (800) 826-9526 x6869	**Phone number** (301) 594-2850

Subject. NDA 21-264 Apomorphine HCl Injection Clinical Reply to your Fax of 04/01/03

Total no of pages including cover 2

Andrea,
The following is a reply to your April 1, 2003 facsimile

Document to be mailed. ☐ YES ☑ NO

We are responding to your request (4/1/03 FAX) for clarification of DNDP request # 5

- For study APO202, you are correct in interpreting our request as our desire that you add arithmetic mean treatment differences to the QTc tables and data that you have already presented

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10 [ ]

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Thank you for your attention to these issues

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2003

To Andrea Miller	**From:** Teresa Wheelous
Company **Bertek Pharmaceuticals Inc**	Division of Division of Neuropharmacological Drug Products
Fax number (304) 285-6407	**Fax number** (301 594-2859
Phone number (800) 826-9526 x6869	**Phone number** (301) 594-2850

Subject NDA 21-264 Apomorphine HCl Injection Clinical Information Request

Total no of pages including cover 5

Andrea,

The following are clinical information requests

Document to be mailed: ☐ YES ☑ NO

We have the following requests to facilitate the review of NDA 21264

1 Please submit a new, overall, detailed, comprehensive table of contents (TOC) for section 8 (Clinical/Statistical) and the Safety Update This new, overall, detailed, comprehensive TOC will facilitate navigation throughout the NDA by providing the reviewer with a single, detailed index (in one site) that shows the specific location of most items throughout the NDA

- Whenever a final study report is presented, please incorporate and integrate the identical, complete TOC of this study report (including end of text tables, figures, and graphs, specified reference list, specified appendices, specified patient data listings, specified CRFs for deaths, other serious adverse events, and withdrawals, and individual patient data listings) Thus, all the detailed items listed in the final study report TOC should be integrated into the new, overall, detailed, comprehensive TOC

- For the ISE, please incorporate and integrate the identical, detailed TOC of the ISE

- For the ISS, please incorporate and integrate the identical, detailed TOC of the ISS

- For the tabular Appendices in the ISS, please incorporate and integrate the specific table numbers and respective titles

- For the patient profiles narrative summaries, and SAE reports in the ISS, please incorporate and integrate the patient identifiers (shown on the separating tabs)

- For the patient data listings, please incorporate and integrate the identical, specified patient data listings (shown on 11-i through 11-ix in volume 59 out of 111)

- For the patient CRFs, please incorporate and integrate the identical, specified TOC showing the location of CRFs for individual patients patient data listings (shown on 12-i through 12-ix in volume 73 out of 111)

- For the Safety Update, please incorporate and integrate the specified TOC on page i through x (volume 1 of the Safety Update) into the new, overall, detailed, comprehensive TOC

  - Please specify ISS table numbers and respective titles of the tabular Appendices (A-1-44 through A-5-574 contained within volumes 1 to 5 and representing Appendix 1)

  - Please incorporate and integrate the specific patient identifiers (shown on the separating tabs) of the patient profiles, narrative summaries, and SAE reports (A-6-1 through A-15-263 contained within volumes 6 to 15 and representing Appendix 2)

  - Please incorporate and integrate Appendices 3 to 8 (A-15-264 through A-15-373 contained within volume 15)

  - Please incorporate and integrate Study Report 302's TOC into the new, overall, detailed, comprehensive TOC In addition, include the titles of the specific references

shown on B-1-167 - 168 in volume 16 and the titles of the patient data listings shown for Appendices 16 4 1 1 - 16 4 4 on page B-3-382 in volume 18

- Please incorporate Study Report 303's TOC into the new, overall, detailed, comprehensive TOC along with the specified references and patient data listings requested above for Study 302

- Please incorporate and integrate the TOC for the Integrated ECG Report (volume 24) and the Appendices 1 - 4 containing titles of tables, listings, and figures (shown on pages ii - ix of volume 24)

- Please incorporate and integrate the Study Reports' (302 and 303) listings shown on pages vi - vii of volume 25

- Please incorporate and integrate the TOC for CRFs for deaths, other serious adverse events, and withdrawals for adverse events shown on pages i - iv in volume 27

All lines of text in the new, overall, detailed, comprehensive TOC should specify the location of the information according to the overall volume number on the outside of the volume and the page number of that specific volume

2 Please correct all tables showing all orthostatic VS changes (e g supine to standing or sitting to standing) using the standard method of calculation For example, you should subtract the initial, reference measurement (e g supine systolic BP 115) from the second measurement (e g standing systolic BP 125) Thus, the change would be + 10, not – 10 as would have been described by the unconventional method used (e g supine systolic BP 115 - standing systolic BP 125) and contained in the NDA data already submitted

3 **Please calculate one QT correction formula (i e the one that shows a "zero" slope when plotting QTc vs R-R interval) for each study based upon ECG data collected from patients included in each study prior to any apomorphine treatment (i e at baseline) and ECG data of patients treated with placebo only when there was no previous apomorphine treatment. This one QT correction exponent based on pre-treatment (i e , baseline) data for each study should be applied uniformly to correct all QT measurements performed in that study Please show the one QT correction formula along with the graphical display of each plot for each study**

We understand that the pre-dose data and "placebo" data you used to calculate each QT correction (for studies 073, 302 and 303) were derived from electrocardiographic data from patients, who had repeatedly been treated with apomorphine for weeks to months prior to collecting the electrocardiographic data used for the QT correction

4 **Please reanalyze and submit all ECG analyses contained in your 1/31/02 submission (detailed ECG analyses and report) and 2/5/03 submission (additional ECG analyses requested) calculated as described above in the preceding request.** Specifically, these analyses should include 1) tabulations of mean QTc changes from the "pre-dose" QTc for each treatment group in Studies 073, 302, and 303, 2) tabulations of mean maximal QTc

change from "pre-dose" QTc for each treatment group in Studies 073, 302, and 303, and 3) individual patient data listings of QTc

5 Please submit QTc analyses showing the mean arithmetic QTc treatment difference for each apomorphine treatment by subtracting the arithmetic mean respective placebo result from the arithmetic mean for each apomorphine treatment at each post-dosing timepoint in Studies 302 and 303

6 Please provide the most appropriate QTc correction formula selected and the graphical plots validating a "zero" slope used for each study (e g APO401, 202, 301, 101) in which QTc was analyzed but neither the specific QT correction formula nor graphic plot (i e QTc vs R-R interval) was provided If you did not use respective ECGs collected prior to ever receiving any apomorphine injection for calculating the appropriate QT correction (i e showing a "zero" slope) for each population of patients in each study, please calculate this correction exponent, correct all QT interval data, and reanalyze and present these recorrected data

7 Please calculate and present the maximal QTc change from baseline/pre-treatment for Study APO401 and any other studies when more than 2 ECGs were collected but these data were not previously submitted to DNDP

8 Please provide the missing data for the other treatment groups (e g 2, 4, 6, mg apomorphine, oral medication, and placebo treatment groups) from Tables 1 4 4 and 1 4 5 on pages D-1-146 and 147 These tables only show data for the 8 mg and 10 mg treatment groups It seems that data for the other treatment groups are missing

9 Please provide additional analyses for orthostatic VS for the ISS and studies 302 and 303 to characterize particular orthostatic changes in more detail Analyze all safety data involving orthostatic VS assessments with respect to showing additional, threshold changes 1) decrease of systolic blood pressure by $\geq$ 40 mm Hg regardless of absolute level, 2) decrease of diastolic blood pressure by $\geq$ 20 mm Hg regardless of absolute level, 3) pulse increase by $\geq$ 15, and 4) pulse decrease by $\geq$ 15 In addition, please show a further breakdown of your criterion 1 and criterion 2 by separately specifying the incidence of these changes for a systolic change and for a diastolic change Please provide a listing of all patients achieving any threshold change criterion, including the type of change, and the specific magnitude of the change

10 Please revise ISS table 97 to show the incidence of orthostatic abnormal changes in VS separately for patients studied while changing from supine to standing and from sitting to standing Your analyses combine results from both different orthostatic maneuvers

11 Considering all data submitted for this NDA, please specify wherever the term "baseline" is used in any table, figure, or listing and the term "baseline" does not indicate a timepoint/period prior to every receiving apomorphine Bertek Response # 6 (3/5/03 submission) indicated that the term baseline was not always used consistently according to the same definition (i e prior to ever receiving apomorphine) Occasionally, the term "baseline" was also used to indicate the "pre-dose" timepoint in patients who had been repeatedly been receiving apomorphine previously

If there is any problem with your complying with any of these requests, please contact us as soon as possible It is not necessary to comply with each request before submitting data. Although each request may be submitted separately when available, it would be desirable if all information requested for electrocardiographic parameters is submitted at the same time Thank you for your cooperation

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2003

To Andrea Miller	**From** Teresa Wheelous
Company Bertek Pharmaceuticals Inc	Division of Division of Neuropharmacological Drug Products
Fax number (304) 285-6407	**Fax number** (301 594-2859
Phone number (800) 826-9526 x6869	**Phone number** (301) 594-2850

Subject: NDA 21-264 Apomorphine HCl Injection No Filing Issues Fax

Total no of pages including cover 1

Andrea,

Please refer to your December 31, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apomorphine Hydrochloride Injection 10 mg/ml

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review Therefore, this application has been filed under section 505(b) of the Act on February 25, 2003 in accordance with 21 CFR 314 101(a)

At this time, we have not identified any potential filing review issues Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review

Document to be mailed ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE March 11, 2003

To Andrea Miller	**From** Teresa Wheelous
Company **Bertek Pharmaceuticals Inc**	Division of Division of Neuropharmacological Drug Products
Fax number (304) 285-6407	**Fax number** (301 594-2859
Phone number (800) 826-9526 x6869	**Phone number** (301) 594-2850

Subject NDA 21-264 Apomorphine HCl Injection Clinical Reply to your Fax of 1/23/03

Total no of pages including cover 1

Andrea,
The following is Clinical Pharmacology & Biopharm Information Request

"Please submit all raw pharmacokinetic/pharmacodynamic human subject data contained in the NDA in electronic format as a comma-delimited SAS Transport file "

If this information has already been submitted, please let me know the submission date

Thank you,
Teresa

Document to be mailed ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE March 10, 2003

To Andrea Miller	**From** Teresa Wheelous
Company Bertek Pharmaceuticals Inc	Division of Division of Neuropharmacological Drug Products
Fax number (304) 285-6407	**Fax number** (301 594-2859
Phone number (800) 826-9526 x6869	**Phone number** (301) 594-2850
Subject NDA 21-264 Apomorphine HCl Injection Pharm/Tox Information Request	
Total no of pages including cover 1 (ONE)	

Andrea,
The following is a preclinical information request

Please submit the ECG data from the 39-week monkey study (—— 6481-117, Mylan study No — 09903) It is unclear what data were recorded and what the timing of the recordings were Of special interest are data on QT, QTc and other quantitative data

Thank you,
Teresa

Document to be mailed: ☐ YES ☑ NO

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page(s) of trade secret.

and/or confidential

commercial information

(b4)

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

/s/

Thomas Broadbent
3/7/03 04 53 42 PM
CHEMIST

Maryla Guzewska
3/12/03 12 58 00 PM
CHEMIST

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Redacted 3

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE January 23, 2003

To Andrea Miller	Teresa Wheelous **From**
Company Bertek Pharmaceuticals Inc	Division of Division of Neuropharmacological Drug Products
Fax number (304) 285-6407	**Fax number** (301 594-2859
Phone number (800) 826-9526 x6869	**Phone number** (301) 594-2850

Subject NDA 21-264 Apomorphine HCl Injection Clinical Reply to your Fax of 1/23/03

Total no of pages including cover 5

Andrea,

The following is (1) a copy of your Jan 23, 2003 facsimile, and (2) Dr Kapcala's reply to your facsimile dated Jan 23, 2003 regarding Bertek's understanding of the clinical questions asked in a Jan 21,2003 telephone discussion

Document to be mailed ☐ YES ☑ NO

1 Where is the location of the "compelling argument" addressing the validity of electrocardiographic data collected from a 3-lead Holter with respect to QT evaluation? The pre-NDA meeting minutes (1/10/02) below request that the sponsor include a justification for using Holter monitor data instead of ECG data that had been recommended by DNDP

"The sponsor collected electrocardiographic data (desired by DNDP) in some studies using Holter monitors (3 lead) instead of standard 12 lead ECGs In previous discussions with DNDP about collecting desired ECG data (especially for QTc), discussion had focused on collecting data with ECGs The sponsor did not discuss the acceptability of collecting desired data with 3 lead Holter monitors Consequently, the sponsor must make a compelling, written argument why electrocardiographic data collected with 3 lead Holter monitors are valid for evaluating electrocardiographic effects (especially QTc) of

2 Where is the location of the graphical display of the plot of the QTc (specific correction formula) vs RR interval illustrating zero or nearly zero slope? The pre-NDA meeting minutes (1/10/02) cited below specify DNDP's request to show that QTc dose not vary with respect to heart rate (i e R-R interval)

"The sponsor should

Specify the QT correction formula selected and validate that it is appropriate by showing that QTc does not vary with respect to heart rate (i e R-R interval) "

3 Where is the location of the plot of QTc vs plasma blood concentrations? Note this reference (pp D-1-513 to D 1-517, Volume 24, December 31,2002 submission) was provided during the conversation DNDP agrees with this comment

4 Dr Kapcala inquired about specific data (tables or listings) for all the studies (e g 302, 303, 073, 401) that described the maximal QTc change per subject by dose, by time and/or by study visit, and the resulting mean maximal QTc change by these various parameters It appears that the maximal QTc change over a study period was only analyzed and shown for study 302 The pre-NDA meeting minutes (1/10/02) cited below specify DNDPs' request to show the maximal QTc changes over a treatment period by dose and study visit

"The sponsor should

Show maximal change of electrocardiographic data (e g QTc) over a treatment period with respect to dose and study visit "

5 Has the sponsor submitted the information/analyses for all the bulleted items requested by DNDP at the pre-NDA meeting and specified below in the meeting minutes?

"The sponsor should

- *Tabulate the total number of AEs/SAEs for potentially orthostatic hypotensive-related symptoms by dose received when AE/symptoms occurred or when orthostatic hypotension was observed*

- *Indicate how frequently orthostatic hypotension was symptomatic and asymptomatic*

- *Tabulate the frequency of orthostatic VS data by mean daily dose of —— and mean daily frequency of —— dosing*

- *Consider how to present and analyze various coding terms (e g light-headedness, dizziness, postural light-headedness or dizziness, vertigo, near-syncope, syncope, etc) that might be associated with orthostatic hypotension "*

6 Clarify the term "baseline" on page C- 1-178, and the difference between baseline and pre-dose for example page D-1-I50 Is the term "baseline" always meant to indicate the change from a measured parameter **that was collected before the patient ever received any apomorphine (i e ——) dose?**

7 Clarify the terms "Predose" and "Post" in the columns labeled "Predose Mean" and "Post Mean" as ii relates to each of the time points for each treatment for example pages D-1-28 and D-1-137 If the "Dosing" timepoint indicates the time immediately prior to dosing with oral medication or injection, how can you calculate mean data for "Change From Predose" for the "Dosing" timepoint?

8 Dr Kapcala asked Bertek to clarify the convention used to calculate blood pressure changes from sitting to standing for example the calculations used to derive the "Change from Predose Off' on pages B-1-154 and B-1-156

It appears that the sponsor followed an unusual convention and used the standing value as the reference timepoint for calculating orthostatic changes instead of the sitting value that is always used as the reference value when studying orthostatic effects upon standing For example, when studying changes of orthostatic VS, the first measurement (e g supine when comparing supine and sitting, sitting when comparing sitting and standing, supine when comparing supine and standing) is always used as reference value Thus, if systolic BP sitting was 120 and standing was 130, the normally calculated change would be (130 while standing minus 120 while sitting) **+10** indicating an incremental change It appears that the sponsor's method would show a change of **-10** suggesting a decremental change This, convention is particularly confusing when in the same table a change from pre-dosing at + 20 minutes is compared to the pre-dosing or the initially measured value/reference value For example, if the pre-dosing systolic BP was 120 and the +20 minute systolic BP was 130, the change from pre-dosing would be **+10** Consequently, in the same table a similar change in systolic BP from 120 (initially measured or reference value) to 130 would be indicated by a different sign as an incremental change However, according to the sponsor's unusual convention, the change from sitting to standing would be **-10** Thus, a similar change in systolic BP from 120 to 130 (due to a 10-mm Hg increment) in the same table would depict by a different sign One change would show a + sign suggesting an increment but the same change would also show a - sign suggesting a decrement

These contrasting conventions appeared to be used for all orthostatic VS analyses and are often utilized in the same table These analyses make it very difficult conceptually to think about what is happening and reflected by the data/analyses

9 Dr Kapcala also questioned why the "Treatment Difference" was described as Least Squares Mean instead of Mean

10 Dr Kapcala questioned why the subtraction of mean positional blood pressures is not exactly reflected by the resultant Change from baseline in mean positional blood pressures (example page C-1-199)

In addition, a few other questions or need for clarification have arisen

11 Were the statistical analyses used to analyze safety data (e g ECG/QTc and orthostatic VS) pre-specified for study 302? If so, where?

12 In the statistical analyses for study 303, it is noted below some tables that if the effect was significant, one model was used, and if it was not significant, a different model was used What are the factors used in the final model? For example, please see footnote in Table 1 4 2 on page D-1-141

13 Does the mean for (Active Change) - (Placebo Change) as shown in Table 1 4 5 on page D-1-147 indicate the mean change for subtracting the mean placebo change at a particular timepoint from the mean change for a dose of apomorphine at the same timepoint? Thus, this is the arithmetic treatment difference at particular timepoints

14 The following issue/question was also raised by Dr Kapcala in an e-mail (1/21/02) to Andrea Miller at Bertek

"As I've gone through some of this most recent submission it seems that most (if not all) of the controlled data on orthostatic VS (i e blood pressure and pulse) involve changing from a sitting to standing position As I recall (I don't have access to these minutes at home but I'm pretty sure that supine and standing were recommended/specified) in the meeting minutes of previous telecons, DNDP had recommended studying orthostatic VS in supine and standing positions Such manipulations allow for potentially seeing a maximal orthostatic VS effect Ideally, it's best to be able to evaluate changes relative to all 3 positions (e g supine to sitting, sitting to standing, and supine to standing It seems to me that the NDA does not contain controlled orthostatic VS data for evaluating changes from supine to standing Is this correct? Are there data within the NDA that address this issue of orthostatic VS changes from supine to standing?"

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commercial information

(b4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 52,844

Mylan Pharmaceuticals Inc
Attention Frank R. Sisto
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P O Box 4310
Morgantown, WV 26504-4310

Dear Mr Sisto

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for —— (apomorphine HCl) Injection

We also refer to your October 23, 1998, request for fast track designation submitted under section 506 of the Act

We also refer to a June 1, 1999 Agency letter denying your fast track designation request

Finally we refer to a June 23, 1999 telecon between Mylan Pharmaceutical representatives and Dr Robert Temple, Office of Drug Evaluation I Director

Based on a re-consideration of the issues, we are changing the designation of —— (apomorphine HCl) Injection for use as 'off" episodes of — Parkinson's Disease to a fast track product

If you pursue a clinical development program that does not support use of —— (apomorphine HCl) Injection for use as 'off" episodes of — Parkinson's Disease, we may not review the application under the fast track development program

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850

Sincerely,

/S/

{See appended electronic signature page}

Russell Katz, M D
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
6/27/01 01 52 06 PM

MODE = MEMORY TRANSMISSION START=SEP-06 10 03 END=SEP-06 10 04

FILE NO = 088

STN NO	COM	ABBR NO	STATION NAME/TEL NO	PAGES	DURATION
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-FDA/DNDP

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FOOD AND DRUG ADMINISTRATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD 120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859

Telecopier Cover Sheet

DATE	**September 6, 2000**
TIME	**10 00 AM**
DELIVER TO	**Frank Sisto**
FAX #	**(304) 285-6407**
FROM	**Teresa Wheelous, R Ph**
	Senior Regulatory Management Officer

Total number of pages, including cover page
If you do not receive all pages or have any problems with receiving call (301) 594-2850
Frank,

The following are comments from the Office of Post-Marketing Drug Risk Assessment regarding NDA 21-264 container labels and carton labeling

A CONTAINER LABEL (2 mL)

1 The expression of strength should be revised on all labels and labeling to indicated the total contents of the ampule The following is suggested 20-mg/2 mL (10 mg/mL)
2 Revising and increasing the prominence of the statement For subcutaneous Injection to read FOR SUBCUTANEOUS USE ONLY'

B CARTON LABELING (5 X 2 mL)

1 See comment 1 under CONTAINER LABEL
2 Relocate the net quantity statement so it does not appear in conjunction with the product strength
3 Relocated the route of administration to the front panel to give it more prominence and revise to read as recommended above
4 Delete the terminal zero from "1 mg", which appears in the Each mL contains statement

FOOD AND DRUG ADMINISTRATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859

Telecopier Cover Sheet

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DATE	August 14, 2000
TIME	9 30 PM
DELIVER TO	Frank Sisto
FAX #	(304) 285-6407
FROM	Teresa Wheelous, R Ph
	Senior Regulatory Management Officer

Total number of pages, including cover page 2
If you do not receive all pages or have any problems with receiving, call (301) 594-2850
MESSAGE

Frank,
This is a 2-page fax containing Microbiology deficiencies and comments regarding NDA 21-264

List of Microbial Deficiencies and Comments

A Microbiology Deficiencies

1 The applicant should be more specific in describing

i should also be provided

2 The applicant should provide the for the validations to insure that they are comparable to the production specifications

3 The applicant should provide

validations The applicant should also list the manufacturer, and expiration dates for the biological indicators used in this validation

are the same for the validation and production runs, the applicant should provide the for each of the used in the validation run to ensure that none exceeds the minimum If the validation exceeds the minimum the biological indicator data for the validation run is not valid

4 The applicant should provide up to date data and indicate the size of the containers, closures (if any), and volume/container used for these fills The applicant should explain why validations

5 The applicant should

MEMORANDUM OF TELEPHONE CONVERSATION
NDA # 21-264

Drug: ——— (Apomorphine) Injection
Sponsor: Mylan
Date November 14, 2002
Conversation Between
FDA
Dr R Katz – Division Director
Dr L Kapcala - Medical Reviewer
Dr J Feeney – Team Leader
Ms T Wheelous – Project Manager

Mylan Pharmaceuticals Attendees & Titles
Dr P Bottini – Exec Director, Clinical Research
——— – Consultant
Andrea Miller, Esq – Assoc Director, Reg Affairs

Purpose To inform the sponsor that the rolling NDA is not yet complete

Discussion
Clinical Submission

- The September 23, 2002 submission was provided as the last piece of this rolling NDA However, upon review of this submission the expected EKG data from study #303 was not included

- The NDA states that this essential information would be provided at a later date (in about 2 months) in the safety update

- Since this data is a necessary piece of the review material, the division has decided to wait for the receipt of the EKG data before starting the 6-month review clock

- The sponsor expects to have the EKG data available for submission in a couple of weeks

- Additionally, EKG data from study #302 will be submitted at the same time as the required EKG data from study #303

Action Item
When the sponsor submits the required EKG data as the final piece of this rolling NDA the 6-month review clock will begin

MEETING MINUTES

DATE: **January 31, 2003**

LOCATION **WOC II conference Room E**

APPLICATION **NDA 21-264 APOMORPHINE HCl INJECTION**

TYPE· **Internal – Completeness of Rolling NDA**

ATTENDEES

Dr Russell Katz – Division Director
Dr John Feeney – Group Leader
Dr Leonard Kapcala – Medical Reviewer

BACKGROUND·

As a follow-up to a November 4, 2002 telecon with the sponsor in which the sponsor was notified that the NDA was incomplete, Bertek Pharmaceuticals submitted a December 31, 2002 amendment which provides a safety update and a final report compiling the ECG observations from all applicable studies This purpose of this meeting is to determine whether or not the December 31, 2002 submission completes the application as requested

The ECG information requested in the January 2002 pre-NDA meeting has not yet been provided The following is an excerpt from the January 10, 2002 pre-NDA meeting minutes regarding ECG data required for the NDA

ECG Data

- *The sponsor collected electrocardiographic data (desired by DNDP) in some studies using Holter monitors (3 lead) instead of standard 12 lead ECGs In previous discussions with DNDP about collecting desired ECG data (especially for QTc) discussion had focused on collecting data with 12-lead ECGs The sponsor did not discuss the acceptability of collecting desired data with 3 lead Holter monitors Consequently, the sponsor must make a compelling, written argument why electrocardiographic data collected with 3 lead Holter monitors are valid for evaluating electrocardiographic effects (especially QTc) of* ——

- *The sponsor should not mix or integrate electrocardiographic data collected with 3 lead Holter monitors with data collected using 12 lead ECGs In addition, the sponsor should always specify whether electrocardiographic data presented were collected with 3 lead Holter monitors or 12 lead ECGs*

DISCUSSION:

- A facsimile was sent to the sponsor on January 23,2003 In that facsimile , among other items, the following information was requested

    1 Where is the location of the "compelling argument" addressing the validity of electrocardiographic data collected from a 3-lead Holter with respect to QT evaluation? The pre-NDA meeting minutes (1/10/02) described above request that the sponsor include a justification for using Holter monitor data instead of ECG data that had been recommended by DNDP

    2 Where is the location of the graphical display of the plot of the QTc (specific correction formula) vs RR interval illustrating zero or nearly zero slope? The pre-NDA meeting minutes (1/10/02) cited below specify DNDP's request to show that QTc does not vary with respect to heart rate (i e R-R interval)

    "The sponsor should

    Specify the QT correction formula selected and validate that it is appropriate by showing that QTc does not vary with respect to heart rate (i e R-R interval) "

- The fundamental information, validating the 3-lead holter data, has not been provided and the application should be viewed as incomplete

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

/s/

Russell Katz
2/28/03 10 25 00 AM

MEETING MINUTES

ATE: **January 10, 2002**

IME **11 am**

LOCATION **WOC II conference Room E**

APPLICATION ———

TYPE **Pre-NDA**

ATTENDEES

FDA

NAME	TITLE & DIVISION
Dr Russell Katz	Division Director HFD-120
Dr John Feeney	Group Leader HFD - 120
Dr Leonard Kapcala	Clinical Reviewer
Dr Barry Rosloff	Pharmacology Team Leader HFD-120
Dr Lois Freed	Pharmacology Reviewer HFD-120
Dr Hong Zhao	Clinical Pharmacology & Biopharmaceutics Team Leader HFD-860
Dr Kun Jin	Biometrics Team Leader HFD-710
Dr Sharon Yan	Biometrics Reviewer HFD-710
Dr Maryla Guzewska	CMC Team Leader
Ms Teresa Wheelous	Senior Regulatory Management Officer

MYLAN / BERTEK PHARMACEUTICALS

NAME	TITLE
Sherron Wiechert	RAC Director, Regulatory Affairs, Bertek Pharm
James Mauzey	President & CEO, Bertek Pharm
Dr Peter Bottini	Exec Director, Clinical Research, Bertek Pharm
——	Consultant
Dr John O'Donnell	Exec Vice President, Research and Quality Control
Dr Mei-Ying Huang	Exec Director, PK and Drug Metabolism, Mylan Pharm
Dr Thomas Clark	Medical Director, Mylan
Dr Jeffrey Smith	Pharmacologist / Toxicologist, Bertek

BACKGROUND

Mylan Pharmaceuticals NDA 21-264 submitted April 17, 2000 was refused to file in an Agency letter dated June 16, 2000 The sponsor has conducted additional studies and would like to re-submit the NDA during the 3rd quarter of this year as a rolling NDA

DISCUSSION QUESTIONS

Rolling NDA Submission

- CMC and preclinical data may be submitted as early as January-February 2002 and data for other disciplines will follow

- The sponsor expects that most of the safety data will be submitted at the time of the main clinical data submission (April-May 2002) These data (including CRFs) should cover > 400 total patient exposures, ~ 290 patients followed for ≥ 4 months, > 100 patients followed for ≥ 12 months

- The 6-month review clock will not begin until data for all disciplines have been submitted including all efficacy data and the bulk of the safety data outlined earlier.

- The remaining safety data comprising the safety update will consist of additional CRFs for SAEs and deaths These additional data (expected approximately 3 months after the review clock starts) should be submitted as soon as possible and should consist of > 300 patients followed for at least 6 months An expectation of the sponsor and DNDP is that the safety update will not consist of a large volume of data

- Under normal circumstances, DNDP noted that the best that can usually be expected with a fast-track 6-month review clock is to receive an approvable letter It is unlikely that labeling could be negotiated within that rapid timeframe

- 

- DNDP requested submission of clinical and statistical data as soon as possible It may be helpful to receive protocols and amendments separately prior to submission of data for potential early review

CMC

- A separate meeting will be held on January 16, 2001 to discuss CMC issues

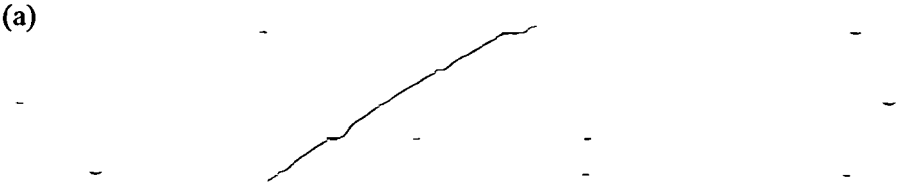
- Mylan desires to market both pens and ampules containing [redacted]

- Mylan will evaluate and compare the ease and accuracy of using the pen in patient caretakers, technicians, and patients

PRECLINICAL

- Mylan plans to submit the NDA as a rolling submission, with the nonclinical section to be submitted during Jan-Feb, 2002

- Mylan indicated that the following nonclinical studies would be submitted in the NDA
  (a) chronic toxicity studies in rat [26-wk] and monkey [39-wk] The sponsor indicated that TK data were not collected in either study
  (b) a 13-wk combination (+TK) study [apomorphine + levodopa/carbidopa] in rat
  (c) 7 in vivo PK/TK studies
  (d) waiver requests for reproduction and carcinogenicity studies

- Mylan was informed that
  (a)  The Division will consider the sponsor's request for waivers regarding the reproduction and carcinogenicity studies
  (b) at the December 10, 2001 meeting, the sponsor committed to submitting the nonclinical portion of the NDA in electronic format The Division re-affirmed interest in Mylan doing so, and recommended that the sponsor contact Dr Randy Levin for guidance in formatting their electronic submission

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

- The Human Pharmacokinetics and Bioavailability section of the NDA will consist of study reports, and a description of apomorphine pharmacokinetics compiled from literature reports

- The Human Pharmacokinetics and Bioavailability section of the NDA is scheduled to be submitted in February 2002

- Mylan did not describe the purpose of Study APOM-0073 According to the study protocol, it was designed to evaluate the multiple-dose pharmacokinetics and dose proportionality of apomorphine in patients and to identify pharmacokinetic and pharmacodynamic relationships in apomorphine activity

- In the Office of Clinical Pharmacology & Biopharmaceutics' review of August 3, 2000, it was pointed out that the effect of levodopa on pharmacokinetics and pharmacodynamics of apomorphine was not evaluated Mylan has conducted two studies (a 2- and 13-week study in rats) to evaluate the potential toxicity of a