

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR

APPLICATION NUMBER

21-264

Approval Letter(s)



NDA 21-264

Bertek Pharmaceuticals, Inc
Attention Andrea B Miller
Director, Regulatory Affairs
781 Chestnut Ridge Road
P O Box 4310
Morgantown, WV 26504-4310

Dear Ms Miller

Please refer to your new drug application (NDA) dated December 31, 2002, received January 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apokyn (apomorphine hydrochloride) 10 mg/ml Injection

We acknowledge receipt of your submissions dated

October 17, 2003	January 16, 2004	February 17, 2004	February 26, 2004
March 2, 2004	March 5, 2004	March 12, 2004	March 29, 2004
March 29, 2004	April 12, 2004	April 14, 2004	

The October 17, 2003 submission constituted a complete response to our July 2, 2003 action letter

This new drug application provides for the use of Apokyn (apomorphine hydrochloride) Injection for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Ampule and Pen Medication Guides) and submitted labeling (immediate container and carton labels submitted October 17, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

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submission “FPL for approved NDA 21-264 ” Approval of this submission by FDA is not required before the labeling is used

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred We are waiving the pediatric study requirement for this application

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitments submitted in your April 14, 2004 submission These commitments are listed below

PHARMACOLOGY/TOXICOLOGY

Commitment #1

You have committed to conduct one long term carcinogenicity study of subcutaneous apomorphine in rats to assess the carcinogenic potential of apomorphine Prior to study initiation, submit the proposed development plan for the carcinogenicity evaluation of apomorphine and the specific study protocol for the Agency’s review to assess whether or not the proposed study is adequate to meet scientific and regulatory requirements as well as the Agency’s expectations

Final Report Submission Date

May 2008

Commitment #2

You have committed to conduct one long term carcinogenicity study of subcutaneous apomorphine in mice to assess the carcinogenic potential of apomorphine Prior to study initiation, submit the proposed development plan for the carcinogenicity evaluation of apomorphine and the specific study protocol for the Agency’s review to assess whether or not the proposed study is adequate to meet scientific and regulatory requirements as well as the Agency’s expectations

Final Report Submission Date

May 2008

Commitment #3

You have committed to repeat the previously conducted in vivo micronucleus test using a multiple dosing regimen post approval Due to the nature of this request and the significance of the multiple dosing regimen on bone marrow/erythrocyte harvest and evaluation, the division will review the proposed study protocol to assess whether or not the design is adequate to meet scientific and regulatory requirements as well as the Agency’s expectations prior to study initiation

Final Report Submission Date

November 2004

Commitment #4

You have committed to conduct a reproductive toxicity study in rats to assess the potential effects of apomorphine on fertility and early embryonic development pursuant to guidelines set forth in ICH S5A (1994) and S5B (1996)

Final Report Submission Date May 2005

Commitment #5

You have committed to conduct a reproductive toxicity study in rats to assess the potential effects of apomorphine on embryo-fetal development in accordance with guidelines set forth in ICH S5A (1994)

Final Report Submission Date November 2005

Commitment #6

You have committed to conduct a reproductive toxicity study in rabbits to assess the potential effects of apomorphine on embryo-fetal development to assess the potential effects of apomorphine in accordance with guidelines set forth in ICH S5A (1994)

Final Report Submission Date November 2005

Commitment #7

You have committed to conduct a reproductive toxicity study in rats to assess the potential effects of apomorphine on prenatal and postnatal development including maternal function in accordance with guidelines set forth in ICH S5A (1994) Prior to study initiation, submit the proposed study protocol for the Agency's review to assess whether or not the proposed study is adequate to meet scientific and regulatory requirements as well as the Agency's expectations

Final Report Submission Date November 2005

Commitment #8

You have committed to the conduct of a ¹⁴C-apomorphine mass balance study in rats to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites

Final Report Submission Date May 2005

Commitment #9

You have committed to the conduct of a ¹⁴C-apomorphine mass balance study in mice to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites

Final Report Submission Date May 2005

Commitment #10

You have committed to the conduct of a ¹⁴C-apomorphine mass balance study in monkeys to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites

Final Report Submission Date	August 2005
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CLINICAL
Commitment #1

You have committed to the conduct of a clinical trial designed to assess the potential effects of apomorphine on the QTc interval. Due to the complexity of the design of this study, submit the protocol for review and discussion prior to study initiation.

Protocol Submission Date	October 2004
Study Start Date	April 2005
Final Report Submission Date	October 2006

Commitment #2

You have committed to the conduct of a randomized placebo-controlled trial to investigate the actual necessity for the use of concomitant trimethobenzamide to decrease nausea and vomiting in patients, who initiate and continue treatment with apomorphine. In addition this trial would also be designed to address the risk / benefits of trimethobenzamide 300 mg.

Protocol Submission Date	October 2004
Study Start Date	April 2005
Final Report Submission Date	April 2007

Commitment #3

You have committed to submit the final Clinical Study Report for APO304 (Syringe to Pen Patient Transfer Study in 20 Patients) by June 2004.

Commitment #4

You have committed to submit a safety update for approximately 80 patients in APO-401 who have been switched from the ampule/syringe to the cartridge/pen by December 2004 (the date that the last patient will complete this study is October 2004).

Commitment #5

You have committed to provide the Agency a proposal and design and feasibility plan for a revised pen by October 2004.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

Commitment #1

You have committed to conduct a ¹⁴C-apomorphine mass balance study in 6 healthy humans to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites. This study will also determine the apomorphine plasma protein binding in these subjects.

Protocol Submission Date	December 2004
Study Start Date	April 2005
Final Report Submission Date	June 2006

Commitment #2

You have committed to perform a pharmacokinetic study addressing the differential effects of 250 mg three times a day (TID) versus 300 mg TID dosing regimens of trimethobenzamide on the pharmacokinetics of apomorphine. This study will only address the differential effect of the two trimethobenzamide dosing regimens on apomorphine and will not include patients treated with apomorphine without an anti-emetic.

Protocol Submission Date	July 2004
Study Start Date	October 2004
Final Report Submission Date	November 2005

Commitment #3

You have committed to conduct a pharmacokinetic and pharmacodynamic study to assess the drug interaction potential of apomorphine with alcohol and antihypertensives to include vasodilators (including short- and long-acting nitrates).

Protocol Submission Date	September 2004
Study Start Date	December 2004
Final Report Submission Date	6 months after study completion

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of DIVISION NAME and two copies of both the promotional materials and the package insert(s) directly to

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Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely Yours

A stylized handwritten signature consisting of a slanted line followed by a capital letter 'S' and another slanted line.

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple

4/20/04 07 18 41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-264

Approvable Letter (S)



NDA 21-264

Bertek Pharmaceuticals, Inc
Attention Andrea B Miller
Director, Regulatory Affairs
781 Chestnut Ridge Road
P O Box 4310
Morgantown, WV 26504-4310

Dear Ms Miller

Please refer to your new drug application (NDA) dated December 31, 2002, received January 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (apomorphine hydrochloride) 10 mg/ml Injection

We acknowledge receipt of your submissions dated

April 18, 2000	May 23, 2000	May 6, 2002	June 14, 2002
July 3, 2002	September 17, 2002	December 31, 2002	March 18, 2003
April 1, 2003	April 17, 2003	April 25, 2003	April 28, 2003
May 9, 2003	May 23, 2003	June 3, 2003	June 4, 2003
June 6, 2003	June 9, 2003	June 16, 2003	June 19, 2003
June 25, 2003			

We have completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, there are a number of issues for you to address.

CMC

DRUG SUBSTANCE

Specifications

- A The description of apomorphine hydrochloride is inconsistent with that provided in the Package Insert. We recommend that the description be limited to visually observed characteristics, and be revised to read "Minute, white or grayish white, glistening crystals or white powder." The _____ should be deleted from the description of the drug substance.
- B The proposed criterion for individual impurities (NMT $\frac{1}{100}$ % each) is not justified. Based upon the batch analysis data at release (max $\frac{1}{100}$ % for one batch and "None reported" for other batches), and stability of apomorphine HCl, we recommend that the acceptance criteria for individual impurities be tightened from NMT $\frac{1}{100}$ % to NMT $\frac{1}{1000}$ % each.

- C The proposed acceptance criteria for residual solvents (— NMT — ppm, — NMT — ppm and — ppm) are not supported by the batch analysis results. We recommend that the limits be revised as follow — ' NMT — ppm, — ppm and — NMT — ppm
- D No acceptance criteria for Heavy Metals have been established. We recommend a limit of — ppm, and testing by a USP <231> method
- E A chiral assay for apomorphine HCl drug substance has not been developed. We recommend that specifications for apomorphine HCl drug substance be revised to include a — assay or that you provide an explanation as to why you consider — testing unnecessary

DRUG PRODUCT

A Components/Composition

— included in the manufacturing of — by Vetter are not justified. We request that the standard operating procedures used to determine the amount of apomorphine HCl hemihydrate required for formulation be described in detail. Any — used in the manufacturing of the apomorphine HCl injection batches should be described and justified. Specifically, information should be provided on —

B Specifications

- 1 Sampling plans for production batches and selection of sub-samples for analyses are not described
- 2 The description of the drug product includes unnecessary information (—). We recommend that the description be revised to read —
- 3 The proposed limits for related compounds apomorphine — (NMT — %), impurity — (NMT — %), impurity — (NMT — %), and any individual unknown impurity (NMT — %) are not justified. Based on the batch analysis results and according to ICH Q3B requirements, we recommend that the limits be tightened as follows:
 - Chemistry Assessment Section
 - Apomorphine — NMT —
 - Apomorphine Impurity — NMT —
 - Apomorphine Impurity — NMT —
 - Individual Unknown Impurity NMT — each
- 4 The structures assigned to apomorphine impurities — are inconsistent throughout the submission. (See NDA pp 4-3-2, 4-10-130, 4-3-382, 4-3-384 and Amendment of 9/17/03 p 3-1-140) We request consistent and unambiguous structure assignments for the impurities —

C Stability

- 1 The proposed expiration period of — months is not supported by the data provided for the apomorphine HCl injection in cartridges (—). Please propose a justifiable shelf-life
- 2 The proposed shelf-life specifications for the drug product are different from the release specification, and therefore not acceptable. Per the ICH Q6A guidance, the regulatory acceptance

criteria should be the same from release throughout shelf-life, unless separate shelf-life criteria can be justified

ESTABLISHMENT INSPECTION

The inspection of _____ facility (drug substance manufacturer) has not been completed. Satisfactory inspection will be required before this application may be approved.

LABELING

A Proprietary Name

As you are already aware, the proposed proprietary names, _____ were found not acceptable by the Division of Medical Errors and Technical Support (DMETS)

B Package Insert

- 1 The "Description" section includes two different names for the active component of the drug. We request deletion of the first name, _____ and retention of the second name, "6 α -Aporphine-10,11-diol hydrochloride hemihydrate "
- 2 In the "How Supplied" section, the word "cartridges" is misspelled ("Cartons of five 3mL cartridges"). The spelling should be corrected and spaces should be inserted in "3mL" and "2mL" to separate the numbers from "mL"
- 3 The proposed storage temperature range _____ does not conform to recommendations of the current stability guidance. We recommend that it be revised to read

"Store at 25°C (77°F)
Excursions permitted to 15-30°C (59 to 86°F)
[See USP Controlled Room Temperature]"

C Container Labels

The container labels need revisions to incorporate a new proprietary name, and the storage temperature range recommended by the Agency.

PHARMACOLOGY / TOXICOLOGY

- 1 You will need to assess the carcinogenic potential of apomorphine by conducting carcinogenicity studies in mice and rats post-approval. _____
- 2 You will need to conduct and submit the reproductive toxicity studies specified in ICH guidelines, you may submit the results of these studies post approval.
- 3 You have set specifications for two degradants that are above the threshold of qualification. If you are unable to lower the specification for these products, you will need to conduct qualification studies of the degradants prior to approval of the drug product.

- 4 Prior to approval, you will need to conduct and submit results of an in vitro HERG channel assay in which you have examined effects of a wide range of apomorphine doses. You should include positive and negative drug controls in each assay.
- 5 As a phase 4 commitment, we ask that you repeat the in vivo micronucleus test using a multiple dosing regimen which would more closely resemble the intended clinical use.
- 6 You should determine the metabolism of apomorphine by conducting mass balance studies in mice, rats and monkeys, this should be done prior to approval.
- 7 Finally, we ask that you review the preclinical literature for information supporting the safety of Tigan administered chronically.

CLINICAL

- 1 **Indication** You are seeking a claim for the treatment of two types of Off periods: end-of-dose wearing Off and spontaneous Off. In the initial phase of APO202, you induced Off periods by withholding PD medication overnight. Such induced Off periods may well approximate end-of-dose Off periods, but we believe spontaneous Off periods may be more complex, given that they occur unrelated to time of dosing. In APO301 and APO302, patients received their morning doses of PD medication and were followed until their first Off of the day (at least 1 hour post dosing). Whether the results of APO301 and 302 address the efficacy of apomorphine for spontaneous Off periods depends on the distributions of time-to-Off in those studies. If many studied Off periods occurred well before the end of the usual dosing interval, the results would bear on spontaneous Off periods. If, however, the great majority of Off periods occurred close to the end of the usual dosing interval, then the results bear more on end-of-dose Off. We therefore ask you to examine APO301 and APO302 to determine each patient's time-to-apomorphine-dosing and compare this to the patient's usual dosing interval. Please categorize patients based on whether the treated Off period best represents end-of-dose wearing Off or spontaneous Off.
- 2 **Clinical Trials** In APO303, the between-group difference was 5 in the first period and 12 in the second period. This compares with a between-group difference of 24 in APO202, 18 in APO301, and 17 in APO302. We are less impressed by the results of APO303 because of this and therefore we do not believe the results should be described in labeling.
- 3 **QT Prolongation** There appears to be an effect of apomorphine on the QTc interval, with doses of 8-10mg associated with a 2-8 msec prolongation in APO303. No cases of torsades were identified during the NDA review, but there were cases of syncope and sudden death (not unexpected in this patient population), and 3 patients experienced post-dose QTc interval of >500 msec. The effect on QTc interval will need to be described in labeling. We ask that you provide additional analyses from APO302, characterizing the effect of dose on QTc. If there is an adequate distribution of patients by dose, such analyses may support the QTc results obtained by 3-lead Holter in APO303. The data from APO303 suggests QTc prolongation at doses greater than 6mg. In any event, we believe you will need to perform a formal, randomized, placebo controlled trial to evaluate the effects of the full dose range of sc apomorphine on the QTc interval, this study may be performed after approval.

We request that you submit all ECGs (for our review) conducted in patient # 41/003 who showed large QTc increments (including a QTc of 514 msec) after dosing of 6 mg apomorphine in study APO302

- 4 **Concomitant Tigan** The exposure to Tigan in the NDA needs to be fully characterized prior to approval While we know that essentially all patients received Tigan, we do not know how Tigan was used over time Please provide information bearing on this issue It would be helpful to break down the apomorphine exposure into time with and without Tigan Specifically, determine the number of patients who were able to successfully taper off of Tigan and continue apomorphine Once off Tigan, did patients need to resume Tigan?
- 5 The dose of Tigan used in the apomorphine development project was 250mg tid This dose is no longer marketed in this country, the marketed dose is 300mg It will be a matter of judgment as to whether the 50mg increment could interfere with the efficacy of apomorphine at the approved doses or alter the safety profile seen in the NDA We ask you to explain why you believe a 50mg increment in dosing for Tigan will not significantly alter the experience with apomorphine
- 6 After approval, you should conduct a randomized, parallel group, placebo-controlled trial to investigate the actual necessity for the use of concomitant Tigan to decrease nausea and vomiting in patients who initiate and continue treatment with apomorphine While we are describing the concomitant use of Tigan in our version of labeling, we believe that more definitive evidence of the benefit of Tigan should be accrued
- 7 Please address the capability of the intended patient population to self-administer apomorphine by subcutaneous injection We recognize that patients have been supplied with ampules/syringes in your studies to date, but we are interested in knowing whether self-administration or administration by a caregiver was usual Please address the capability of patients with advanced Parkinson's disease to use the dosing pen
- 8 Please justify the use of the benzyl alcohol formulation, you have presented no data about the safety of this formulation other than single 2 mg doses in normal volunteers

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

- 1 As discussed in the Pharmacology/Toxicology section above, it is not clear what the predominant circulating species is (are) in humans and what it was in the preclinical toxicity studies This information should be available prior to approval There is insufficient evidence to show the role of auto-oxidation in apomorphine elimination, although the apparent clearance of 230 L/h is higher than hepatic blood flow, which supports the existence of auto-oxidation of apomorphine The assumption that auto-oxidation occurs in tissues at the same rate as in plasma has not been validated Further, auto-oxidation could not account for most of the apomorphine eliminated You should conduct a mass balance study to show the major elimination route and the percentage of elimination that each route accounts for
- 2 The basis for the labeling statement regarding plasma protein binding is not clear You did not conduct the protein binding study Based on the literature, plasma protein binding of apomorphine was estimated at greater than 99.9% over a range of 1257 ng/mL to 3112 ng/mL However, these concentrations are much higher than the therapeutic concentration (about 10 ng/mL) You should

conduct a protein binding study using the clinically relevant concentration _____

- 3 The antiemetic Tigan (trimethobenzamide) was administered during the clinical trial, but no formal pharmacokinetic drug interaction study has been conducted. You should conduct such a study and, in that study, address the differential effect of Tigan 250mg and Tigan 300mg on the pharmacokinetics of apomorphine.
- 4 Drug interaction studies with alcohol and with vasodilators (including short- and long-acting nitrates) should be considered.

In addition, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

- 1 Describe in detail any significant changes or findings in the safety profile.
- 2 When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- 3 Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
- 4 Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

- 5 Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data
- 6 Provide a summary of worldwide experience on the safety of this drug Include an updated estimate of use for drug marketed in other countries
- 7 Provide English translations of current approved foreign labeling not previously submitted

In addition, submit three copies of the introductory promotional materials that you propose to use for this product Submit all proposed materials in draft or mock-up form, not final print Send one copy to this division and two copies of both the promotional materials and the package insert directly to

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110 If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65 Any amendment should respond to all the deficiencies listed We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved

The drug product may not be legally marketed until you have been notified in writing that the application is approved

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

Sincerely Yours



Robert Temple, M D
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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

/s/

Robert Temple

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