CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21829

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.
Attention: Betsy Waldheim
Head, U.S. Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

Please refer to your new drug application (NDA) dated January 19, 2005, received January 28, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (rotigotine) 2mg/24 hr., 4 mg/24 hr., 6 mg/24hr., —— transdermal system.

We acknowledge receipt of your submissions dated:

25-May-2005	23-Jun-2005	29-Jul-2005	09-Aug-2005
10-Aug-2005	02-Sep-2005	06-Sep-2005	06-Sep-2005
09-Sep-2005	13-Sep-2005	23-Sep-2005	29-Sep-2005
05-Oct-2005	31-Oct-2005	09-Nov-2005	15-Dec-2005
21-Dec-2005	05-Jan-2006	26-Jan-2006	30-Jan-2006

We have completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

Clinical

Cardiac Arrhythmia

We request the following reanalysis of cardiac arrhythmia related adverse events:

All cardiac arrhythmia adverse events from any phase 2/3 trials that have been unblinded, regardless of indication, should be pooled in a comprehensive analysis. Please include the results of the high dose studies conducted in late stage Parkinson's Disease in this analysis. A broad net should be cast to include all potentially cardiac arrhythmia related AEs. For studies that used MedDRA, search terms should include those that fall into the MedDRA Higher Level Group Terms (HLGTs) "Cardiac arrhythmias" and "Cardiac disorder signs and symptoms" (under the Cardiac disorders System Organ Class [SOC]) and the Higher Level Terms (HLTs) "ECG investigations" and "Heart rate and pulse investigations" (under the Investigations SOC, Cardiac and vascular investigations HLGT). If you identify other MedDRA preferred terms (PTs) that would identify cardiac arrhythmia AEs, then those

should be included as well. For studies that used WHO-ART, search terms should be used that correspond to the categories listed above for MedDRA.

Narratives for the events should be written to include pertinent information, such as cardiac history, cardiac risk factors, pre-existing medications and medications initiated during study drug treatment, results of baseline and on-treatment ECGs, details of the adverse event, etc. The narratives, as well as the original ECGs, should then be examined by a cardiologist who is blinded to the patient's treatment assignment and who has not been previously involved with evaluating the cardiac AEs in the rotigotine development program. The blinded cardiologist should then recode the AEs to reflect the condition most accurately described by the narrative and ECGs. For example, an AE such as "ECG abnormal" or "Arrhythmia" can be assigned to a more specific PT. The frequencies of the various newly assigned PTs should then be calculated by treatment group. Additional analyses should also be conducted to look for a dose-response relationship and/or a relationship to duration of treatment.

Depending upon the results of these analyses, you may need to perform additional Holter monitoring studies.

Compulsive behavior

The CHMP Assessment report for Neupro included the following statement, "Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro" (bottom p. 42). We did not find a discussion of such events in the original NDA submission or safety update. Please identify any events in rotigotine treated subjects that represent compulsive gambling, compulsive eating, hypersexuality or any other compulsive behavior. For any such events please provide the rotigotine subject number, the number of the study where the event was identified, the preferred term to which the event was coded, and a brief description of the event.

Weight gain

We request an investigation of subjects who experienced increases in weight of more than 10% of baseline. Using any available clinical information, can it be established that the weight gain was due to benign causes such as improved appetite or to less benign causes such as fluid retention?

Laboratory abnormalities

1. For all patients who had declines in hemoglobin and/or hematocrit during a given trial (regardless of the degree of the decline), please provide individual patient profiles (either a table or a plot) showing what happened to the patient's hemoglobin/hematocrit over the course of the study. All subsequent hemoglobin/hematocrit values should be documented, including those drawn during de-escalation periods and open label extension periods.

   Please also provide such individual patient profiles for those patients with a decline in albumin.

2. Please submit narrative summaries for subjects receiving rotigotine who exhibited markedly abnormal laboratory values. The attached table lists just the initial abnormal measurement. There may have been subsequent abnormalities. The narrative summaries should include any relevant items in a subject's history and physical examination, concurrent medications and the results of any laboratory, imaging or other diagnostic work-up done to determine the cause of the abnormality as

well as the time profile of that analyte. Although their subject ID numbers are not listed in the table below, we also ask that you submit narrative summaries for patients assigned to other treatment groups who exhibited markedly abnormal lab values.

Listing of Subjects Assigned to Rotigotine in Pools S1 and S6 with Marked Abnormalities in Laboratory Tests

Subject id	Test	Visit number	Result		Criteria for marked abnormality
506000282	PLATELET	6	53	G/L	<=100
506000308	BUN	7	14.64	mmol/L	>=14.28
506000326	WBC	6	2.7	G/L	<=3
506000704	HEMOGLOBIN	4	96	g/L	<=85% LLN
506000704	HEMATOCRIT	8	29.2	%	<=85% LLN
506001003	WBC	8	2.8	G/L	<=3
506001027	PLATELET	6	614	G/L	>=600
506001031	HEMATOCRIT	4	33.5	%	<=85% LLN
506001031	HEMOGLOBIN	4	103	g/L	<=85% LLN
506001207	PLATELET	8	93	G/L	<=100
506001276	SGPT	6	145	U/L	>= 3*ULN
506001654	BUN	6	14.64	mmol/L	>=14.28
506001656	BUN	6	14.64	mmol/L	>=14.28
512010201	SGPT	9	319	U/L	>= 3*ULN
512011102	MONOCYTES	9	30	%	>=20
512011102	HEMATOCRIT	23	26.9	%	<=85% LLN
512011102	HEMOGLOBIN	23	87.8	g/L	<=85% LLN
512011502	POTASSIUM	4	9	mmol/L	>=6
512011506	POTASSIUM	11	9	mmol/L	>=6
512011901	WBC	13	2.8	G/L	<=3
512012803	WBC	5	2.9	G/L	<=3
512013603	BUN	24	15.5	mmol/L	>=14.28
512013608	HEMATOCRIT	5	34.7	%	<=85% LLN
512015307	SGPT	7.001	160	U/L	>= 3*ULN
512015307	MONOCYTES	8	22.2	%	>=20
513100203	MONOCYTES	23	23	%	>=20
513100808	BUN	5	23.7	mmol/L	>=14.28
513100808	HEMATOCRIT	5	28.9	%	<=85% LLN
513100808	HEMOGLOBIN	5	95.049	g/L	<=85% LLN
513100811	HEMOGLOBIN	8	98.271	g/L	<=85% LLN
513101106	POTASSIUM	15	3	mmol/L	<=3
513101703	HEMATOCRIT	8	21.8	%	<=85% LLN
513101703	HEMOGLOBIN	8	62.829	g/L	<=85% LLN
513101703	PLATELET	8	611	G/L	>=600
513101903	WBC	21	3	G/L	<=3
513102003	WBC	15	2.9	G/L	<=3
513102601	MONOCYTES	21	21.7	%	>=20
513102601	WBC	21	2.4	G/L	<=3
513104504	WBC	18	2.7	G/L	<=3
513105604	SGPT	5.2	159	U/L	>= 3*ULN
513105911	HEMOGLOBIN	8	113.576	g/L	<=85% LLN
513106005	PLATELET	15	93	g/L	<=100
513106101	HEMATOCRIT	5	29.2	%	<=85% LLN

Listing of Subjects Assigned to Rotigotine in Pools S1 and S6 with Marked Abnormalities in Laboratory Tests

Subject id	Test	Visit number	Result		Criteria for marked abnormality
513106101	HEMOGLOBIN	5	95.049	g/L	<=85% LLN
513106301	POTASSIUM	8	3	mmol/L	<=3
513106905	POTASSIUM	15	3	mmol/L	<=3
513108006	POTASSIUM	21	8.2	mmol/L	>=6
513108205	WBC	18	3	G/L	<=3

3. We request a comprehensive laboratory dataset consisting of all laboratory investigations performed in all unblinded clinical studies of transdermal rotigotine of at least 14 days exposure for all indications including Phase 1 studies. The specifications for this dataset are given in the following table.

One record per subject per visit per laboratory test				
Varname	**Label**	**Type**	**Format or Decode**	**Comment**
STUDYID	Clinical Study	char	$3.	3 digit representation of Clinical Study Identification. Use the same code for open-label extensions as the original controlled study
USUBJID	Unique Subject Identifier	char	$9.	
AGE	Patient age at study entry	num		
SEX		char		
INDICTN	Treatment Indication	char	EP LP RL HV OT	EP- Early Parkinson's LP- Late Parkinson's RL- Restless Legs HV- Healthy Volunteer (Phase I) OT- Other
TRTSAFN	Treatment Code for Safety	num	0,1,or 2 (3 and greater)	Numeric form of SUBJECT.TRTSAF: 0='Placebo' 1='Rotigotine' 2='Ropinirole' , (>2 for other active controls)
TRTASSN	Original Treatment Assignment	num	same as TRTSAFN	
DOSEASN	Assigned dose	num		For fixed-dose studies only. Set to zero for placebo and missing for variable-dose studies
DOSEMOD	Modal Dose for Subject	num		Dose received most often for corresponding part of study
DOSEREC	Most Recent Preceding Dose	num		Last Dose received before laboratory value was obtained
LBTESTCD	Short Name of Test	char	$4.	
LBTEST	Verbatim Name of Test	char	$25.	
LBDTM	Date of Specimen Collection	num	Date9.	
STARTDT	Date of first treatment	num	Date9	Date when study treatment was initiated. Should be uniform for each subject regardless of Study Phase
STARTROT	Date of first rotigotine exposure	num	Date9	Same as STARTDT for subjects originally randomized to rotigotine; First date of rotigotine exposure for subjects receiving placebo or active control in the controlled trial; Set to missing for subjects never exposed to rotigotine
TYPE	Study Type	char	CNTL UNCTL	CNTL- controlled study UNCTL- Uncontrolled study or extension of controlled study
PHASE	Phase of Study	Char	PRE TI MN DE POST OLE	PRE- Before initiation of study treatment TI- Titration (if applicable) MN- Maintenance DE- De-Escalation (if applicable) POST- After discontinuation of study treatment OLE- Treatment with rotigotine during open-label extension
LBSTRESN	Numeric Result	num	8.2	Actual laboratory evaluation.
LBSTRESU	Standard Unit	char	$6.	Standard laboratory units.
LBINTP	Interpretation of Specimen Result	char	Low High Normal	If the laboratory evaluation LBSTRESN is below or above the normal range for that laboratory value then LBINTP is either "Low" or "High", respectively. Otherwise, LBINTP is "Normal".
BASEVAL	Baseline Value	num	8.2	Last value obtained before beginning study treatment

Dose Response Analysis of Adverse Events in Study 506

The following requests pertain to analyses of adverse events, laboratory results, and vital sign results for Study 506.

1. Analyze and present the incidence of treatment-emergent (TE) AEs, SAEs, and study discontinuations according to **randomized** treatment (placebo, 4.5, 9, 13.5, or 18 mg rotigotine and **any** rotigotine dose). For each of the 3 types of analyses (i.e. TEAEs, TE-SAEs, TEAEs causing study discontinuation), please provide separate analyses based upon: 1) the development of an event during the **whole, 4 week titration period**; 2) the development of an event during the **whole, 7 week maintenance period**; 3) the development of an event in the 4 week titration period and persistence into the 7 week maintenance period. You will need to define this last category (e.g. when it is considered "persistent" such as if an

event starting in the titration period persists > 7 days into the maintenance period). In these analyses, also show the total number of specific events and the total number of patients experiencing these events.

Tabular analyses showing this information should be conducted without respect to severity or causality of TEAE and should show results for all 5 randomized treatments (and any rotigotine treatment if possible) on the same page. For example, the reader should be able to see the frequency of nausea for placebo and all 4 randomized rotigotine treatments (and any rotigotine treatment if possible) on the same page.

2. Analyze and present laboratory data for ALL analytes according to each randomized treatment. Please try to show all results for each visit along with each randomized treatment on a single page and present results for all subsequent visits of each single analyte on consecutive pages. In this manner, the reader would see all results over time for one analyte (e.g. Hgb) on consecutive pages and the next section for a different analyte would show all results (according to each randomized treatment) over time for the next analyte (e.g. Hct) on consecutive pages.

   - Present tables showing laboratory results for mean results and mean change from baseline for each laboratory analyte over time according to randomized, treatment (placebo, 4.5, 9, 13. 5, 18 mg). Tables should show multiple parameters including N, mean, SD, minimum, median, and maximum.

   - Present shift tables (e.g. shift from low, normal or high at baseline to low, normal or high during treatment at a specific time/visit) showing laboratory results for each laboratory analyte over time according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg).

   - Present markedly abnormal laboratory result shift tables (e.g. tables showing shift from markedly low, markedly high, or not markedly low or high at baseline to markedly low, markedly high, or not markedly low or high at a specific post-treatment time/visit). Present markedly abnormal shift table results over time according to treatment (placebo or rotigotine dose at the time). Please apply the markedly abnormal criteria recommended by DNP and applied for the markedly abnormal analyses in the last Safety Update.

   - Present analyses showing the incidence of low and high abnormalities for each analyte and the incidence of markedly low and markedly high abnormalities for each analyte according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg). Please try to show results for all 4 abnormal laboratory categories for each analyte for the whole 4 week titration period (week 2/visit 3 AND week 4/visit 4), for the whole 7 week maintenance period (week 7/visit 5 AND week 11/visit 6), for, and for the whole study treatment period (all 11 weeks) according to all randomized treatments on a single page.

3. Analyze and present various orthostatic vital sign analyses a according to each randomized treatment based upon the example tables shown in the appendix. Please complete the requested analyses in the tables provided so that results for each table (Tables 2 – 7) can be viewed on a single page with the exception of Table 1 that may need to show all results on 2 pages. Please also provide separate tabular analyses for orthostatic vital sign data collected at 1 minute after standing, at 3 minutes after standing, and after 1 and 3 minutes after standing for each of the tables requested. You had presented similar analyses of the pooled data for the 3 pivotal trials at 1, 3, and 1 and 3 minutes after standing. Data source tables that would be used to compile summary results for each of the appended tables should also be submitted.

   Please let us know if you would like an electronic copy of these summary tables for insertion of the data.

4. Provide analyses of TEAEs, TE-SAEs, and TE study discontinuations for AEs/SAEs that are suggestive of falls or orthostatic hypotension/postural dizziness. Please show these analyses according to **randomized** treatment (placebo, 4.5, 9, 13.5, or 18 mg rotigotine and **any** rotigotine dose) and show results for all treatment (and any rotigotine dose if possible) on the same page. These analyses of special interest represent a conservative approach of assessing the possible frequency of particular events of interest that may not have been captured as a particular event because of AE coding vagaries. These analyses include :

   - **Events possibly suggestive of falls.** Search for a variety of AE terms that might be suggestive of a fall despite the fact that the AE had not been coded as a fall. AE terms (**e.g. some examples but not a complete list**) that might be included in this search are fall, abrasion, laceration, fracture, hematoma (any type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb. You should consider such events possibly suggestive of a fall unless there is information to suggest that the event was not a result of a fall. Present the incidence, total number of events, and total number of patients for events that may have been suggestive of a fall for TEAEs, TESAEs, and study discontinuations for a TEAE (further broken down as to whether the event was an SAE or non-serious AE).

   - **Events possibly suggestive of orthostatic hypotension / postural dizziness.** Search for a variety of AE terms that might be suggestive of orthostatic hypotension / postural dizziness despite the fact that the AE had not been coded as such. AE terms (**e.g. some examples but not a complete list**) that might be included in this search are hypotension, postural hypotension, decreased blood pressure, syncope, dizziness, vertigo, postural dizziness, light-headedness, postural light-headedness, impaired balance, and feeling drunk. Present analyses as described for events possibly suggestive of falls.

Clinical Pharmacology

Please adopt the following proposed dissolution method, specifications, and acceptance criteria for rotigotine transdermal systems as the regulatory method.

Table 1 Proposed Regulatory Dissolution Method, Specifications, and Acceptance Criteria for Rotigotine Transdermal Systems

Applicable Strengths:	4.5 mg / 10 cm^2 9.0 mg / 20 cm^2 13.5 mg / 30 cm^2	
Apparatus:	Paddle over Disk (Apparatus 5)	
Test medium:	Phosphate Buffer pH 4.5	
Volume:	900 mL	
Temperature:	32 ± 0.5 °C	
Speed:	50 rpm	
Sampling Times:	0.25, 1.0, 2.0 hours	
Specifications:	***Sampling Times (Hours)***	***% Labeled Content***
	0.25 1.0 2.0	— — NLT —
Acceptance Criteria:	Per USP XXIX / NF 24 <724> Acceptance Table 4	

Non-Clinical

1. The in vivo micronucleus test (0309FD15.001) in mouse was conducted using i.v. bolus administration. Since the clinical route of administration (transdermal patch) results in sustained plasma levels of rotigotine, it is unclear that an i.v. bolus study would be an adequate test of in vivo clastogenicity. Subcutaneous administration in mouse was demonstrated to provide fairly sustained plasma levels of rotigotine, and, on face, would seem to be a more relevant route for testing the in vivo clastogenicity of rotigotine. If you have additional data that would justify the use of i.v. bolus in this assay, please provide it. If such data are not available, this study will need to be repeated as a Phase 4 commitment.

2. There is concern regarding the adequacy of the subcutaneous embryo-fetal development studies conducted in rat, mouse and rabbit. In these studies, there were few or no malformations detected, particularly in the rat (no external, visceral, or skeletal malformations reported) and mouse (no visceral or skeletal malformations and only one external malformation reported). The historical control data lists primarily or exclusively external malformations; the paucity of visceral and skeletal malformations seems somewhat unusual. Please provide any available information that would demonstrate the laboratory's ability to detect a full range of malformations expected in the species and strains. If such information cannot be provided, either the rat or mouse study will need to be repeated (only one rodent embryofetal development study is required); the selection of species would need to be justified. If repeat studies are needed, they may be conducted post-approval.

   The rabbit study will need to be repeated due to the lack of dose-limiting toxicity at the high dose (15mg/kg). Data from the dose range-finding study in rabbit indicated that the high dose of 25 mg/kg

was well-tolerated; therefore, in all probability, doses higher than 25 mg/kg could be used. The repeat study may be conducted post-approval.

For each study to be conducted post-approval, you would need to provide a time line for completion of the study and submission of the final study report.

3. Two transdermal studies (LPT Report 16332/02) were conducted in Goettingen minipigs in order to assess the potential for rotigotine to induce preneoplastic changes at the site of administration; the clinical patch formulation was used in both studies. In the initial study, two 10 cm2 (4.5 mg) (or placebo) patches were applied daily to the same site. This dosing regimen resulted in unacceptable local toxicity and premature termination of the study. In the repeat study, one 10 cm2 (4.5 mg) patch (or placebo) was applied to different sites, with administration to the same site only once every 8 days. It is not clear that higher doses could not have been used; the majority of local effects were characterized as minimal or mild and no systemic toxicity was observed. In addition, the study provides no safety margin since only the lowest dose clinical formulation was tested. Since this study is the only one to assess preneoplastic potential, it is particularly important that the adequacy of this study be established. You need to provide additional information to demonstrate that higher doses could not have been achieved (e.g., by applying the patch to the same sight more often than every 8 days). If substantially higher doses could have been tolerated, a repeat study may be needed. A response to this issue needs to be provided prior to approval.

4. You propose that the degradation of rotigotine to (3.2.S.3.2) includes the concomitant production of According to published studies, are mutagenic . We are unaware of any genotoxicity data on Therefore, you need to either specify a limit in the drug product specification that would result in a dose of this degradant µg/day or demonstrate that this degradant does not exhibit genotoxic potential (i.e., negative in the Ames assay and either an in vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay (with colony sizing)). If is negative in these assays, the limit would need to be set at or below the qualification threshold unless you can provide data demonstrating that this degradant has been adequately qualified in nonclinical or clinical studies. This issue needs to be addressed prior to approval.

CMC

1. Please include on the carton label

2. Two alternate HPLC methods are proposed to establish the identity of the active in the drug product release specification, whereas the ICH Q6A guidance recommends that a combination of two such non-specific methods be used. The drug product release specification will need to be amended to reflect this.

3. The proposed drug product impurity acceptance criteria need to be revised so that they are more in line with that recommended in the ICH Q3B(R) guidance - that is, a identification threshold and qualification threshold based on a maximum daily dose of ng. This will apply to and the unspecified impurities

4. You propose for some of the drug product impurities. This is not appropriate, as

[redacted] The limits need to be revised so that the numerical percentage is the same for each strength.

5. Your proposed [redacted] degradation pathway of rotigotine to [redacted] 3.2.S.3.2) includes the concomitant production of [redacted] Provide data on levels of this degradant at release and through the drug product expiry period, together with analytical validation data for its detection. Additionally a separate limit will need to be specified and justified for this degradant in the drug product specification that addressees the concerns outlined in Non-Clinical Item # 4 (above).

Additional CMC Comments

1. The stability data provided in the application does not support the proposed 24-month expiry period. Please provide an update of long-term stability results in your response.

2. The carton label [redacted]

3. In light of the relatively large number of cases of partially detached patches found in the clinical studies, we recommend that that [redacted] be developed that will be more predictive of the actual adhesion performance of the drug product in the patient population through the expiry period.

4. We suggest that you determine whether a relationship exists between the extent of patch detachment found in the clinical studies (using the current patch formula) and [redacted] This may provide some insight to the [redacted] properties of the delivery system over time.

In addition, you must submit final printed labeling (FPL) for the drug.

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 Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

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

Appendix