CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022426Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

COMPLETE RESPONSE

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for alogliptin tablets (NDA 022271, dated and received December 27, 2007) and for alogliptin-pioglitazone fixed-dose combination tablets (NDA 022426, dated September 19, 2008, and received September 22, 2008).

We acknowledge receipt of your following amendments, as dated:

NDA 022271: February 20 and 22, March 21, April 1 and 24, May 7, 9, 16, and 30, June 26, July 22 and 31, August 5, 11, 25, and 29, September 5, October 3, 16, 17, and 29, November 10, 13, and 18, and December 17 and 18, 2008, January 19 and 21, March 4, 10, 16, and 25, April 9, May 6, 20, and 28, August 31, and October 28, 2009, January 21, February 11, March 15, April 13, May 7, June 21, and July 21, 2010, May 25, July 13 and 25, August 25, September 14, October 5, 6 and 11, November 7, 17, and 22, and December 2, 7 and 20, 2011, and January 20 (2), 23, and 24 (2), February 1, 9, 13, 14, and 22(2), March 6, 8, 13, 22, 23, 26, 27, 28, and 30, and April 4 and 5, 2012.

NDA 022426: October 6 and 29, and November 13 and 14, 2008, January 9, 19, and 28, March 30, April 14, May 6, 20, 22, 26, and 29, June 16, 18, and 30, and October 28, 2009, January 21, February 11, March 15, April 13, May 7, June 21, and July 21, 2010, April 19, May 25 and 31, July 13, 25, and 27, August 25, September 14, October 18 (2) and 28, November 7 and 17, and December 2, 7, 13 and 20, 2011, and January 20, 23, and 24, February 1, 9, 13, 14, and 22 (2), March 6, 8, 13, 22, 23, 26, 27, 28, and 30, and April 4, 5, and 12, 2012.

The submissions dated July 25, 2011, constituted complete responses to our action letters dated June 26, 2009, and September 2, 2009, for NDA 022271 and NDA 022426, respectively.

We also acknowledge receipt of your amendment dated September 9, 2011, to NDA 022426, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We also acknowledge receipt of the email from Dr. Thomas Harris dated April 21, 2012, providing updated liver analyses that incorporated data from ongoing Study 305. Those data were not previously submitted to NDA 022271 or NDA 022426 and were not reviewed for this action. You may include those data as part of your response to the deficiencies cited in this letter, as appropriate.

We have completed our review of these applications, as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

You have adequately addressed the deficiencies communicated in our action letters dated June 26, 2009, and September 2, 2009, for NDA 022271 and NDA 022426, respectively. However, we have identified a concerning signal for drug-induced liver injury with alogliptin based on our review of your July 25, 2011, complete response submissions. This new finding precludes approval of the alogliptin products at this time.

In the controlled phase 2/3 clinical trial database submitted to the alogliptin and alogliptin/ pioglitazone NDAs, there are numerical imbalances not favoring alogliptin for serum alanine aminotransferase (ALT) elevations >5X, >10X and >20X the upper limit of normal (ULN) compared to control. For example, eight alogliptin-treated patients but no comparator-treated patients had at least one markedly elevated serum ALT >10X ULN. Confounders were noted in all eight cases with serum ALT >10X ULN. However, randomization should result in a similar proportion of patients with confounders (e.g., as with hepatitis infection or alcohol consumption) in the control arm. As such, if these etiologies contributed to the ALT elevations, there should have been some cases observed in the control group, even after adjusting for the imbalanced randomization. You have raised the possibility that baseline imbalances in serum ALT elevations may account for these findings; however, 4 of the 8 patients who developed serum ALT elevations >10X ULN had normal or only mildly elevated serum ALT (<3X ULN) at baseline. Note that the NDA submissions for the approved dipeptidyl-peptidase (DPP)-4 inhibitors did not have imbalances in serum ALT elevations compared to control after adjusting for imbalances in randomization.

In addition, we have identified 5 probable cases of alogliptin hepatotoxicity among the estimated 219,000 patient-years of postmarketing experience in Japan, the only country where alogliptin is currently approved. These five cases are listed in Table 1, together with the assessments by our hepatologist and your hepatology consultants (b) (4) The assessments were based on the criteria set forth in the National Institutes of Health (NIH) Drug-Induced Liver Injury Network (DILIN) Study Group (Fontana RJ, Seeff LB, Andrade RJ, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010; 52: 73-742).

Table 1. Probable cases of alogliptin hepatotoxicity			
Case	(b) (4)	(b) (4)	**FDA hepatologist**
TCI2011A04573	Unlikely	Possible	Probable to highly likely
TCI2011A06837	Probable	Probable	Probable
TCI2011A03640	Possible	Possible	Probable
TCI2010A05612	Possible	Possible	Probable
TCI2011A06481	Probable	Possible	Probable

Cases TCI2011A04573 and TCI2011A06837 were particularly concerning because of accompanying hyperbilirubinemia with marked aminotransferase elevations. In the case of TC12011A04573, the patient developed fulminant hepatic failure with increases in coagulation parameters and ultimately died from complications arising from the treatment of her hepatic failure. Drs. (b) (4) consider this case to more likely reflect autoimmune hepatitis because the patient had evidence of other autoimmune disease (Hashimoto thyroiditis) and responded to glucocorticoid therapy with a rebound in liver test elevations when the glucocorticoid dose was tapered. However, our view is that this case represents probable to highly likely alogliptin hepatotoxicity. The autoimmune serologies were negative, the liver test abnormalities were coincident with the use of alogliptin, and the serum ALT had improved considerably after alogliptin was discontinued and before glucocorticoid therapy was started. In addition, the rebound in liver test elevation does not convincingly coincide with the glucocorticoid taper because the serum ALT and total bilirubin slightly increased while the patient was still on prednisolone 60 mg daily and these laboratory tests improved after the prednisolone was reduced to 30 mg daily.

You have obtained Early Phase Postmarketing Vigilance data from Japan's Pharmaceuticals and Medical Devices Agency (PMDA) through November 2011 and concluded that alogliptin and sitagliptin have similar reporting rates of serious hepatic adverse drug reactions. However, your analysis is based on serious reports identified using the Standardised MedDRA Query (SMQ) for Hepatic Disorders. This broad analysis is based only on preferred terms and does not provide convincing evidence that alogliptin and sitagliptin have a similar propensity to cause drug-induced liver injury. For example, many of the identified preferred terms are non-specific (e.g., liver disorder, liver function test abnormal, Gamma-GT increased, hepatic function abnormal) or are not suggestive of drug-induced liver injury (e.g., bile duct stone, cholecystitis, cholecystitis acute). Including less severe or non-specific cases may dilute out and obscure an imbalance in more severe cases of drug-induced liver injury.

We conducted a more targeted search for postmarketing cases of potential drug-induced liver injury with the DPP-4 inhibitors. We used a MedDRA search strategy to identify cases with serious outcomes in our Adverse Event Reporting System (AERS) that were coded to Hepatic failure and associated disorders (High Level Term), Bilirubin conjugated increased (preferred term), Blood bilirubin increased (preferred term), Hepatic necrosis (preferred term), Hepatitis fulminant (preferred term), Hyperbilirubinemia (preferred term), Jaundice (preferred term), or Liver transplant (preferred term). We then performed a hands-on review of the identified cases and counted those that had at least a possible relationship to the DPP-4 inhibitor and a severity score of at least 3, based on the DILIN Study Group criteria mentioned above. Note that this

search strategy would detect the two probable cases with alogliptin that we find particularly concerning (TCI2011A04573 and TCI2011A06837). Therefore, it is reasonable to expect that our search strategy will detect potential liver cases with the other DPP-4 inhibitors that are similar to or more severe than the two most concerning alogliptin cases, if such cases exist. Our approach identified one possible AERS case of hepatotoxicity with sitagliptin from Japan and no probable, highly likely, or definite cases even though, as you note, there is about a 10-fold higher patient-year exposure there to sitagliptin than to alogliptin.

Furthermore, we have used the above-described strategy to conduct a search of worldwide liver reports in AERS to more comprehensively determine whether there are concerning cases of hepatotoxicity with the approved DPP-4 inhibitors. Based on this analysis, we have not identified a concern with the other DPP-4 inhibitors.

In summary, alogliptin has a concerning signal for drug-induced liver injury that is stronger than that seen with the other DPP-4 inhibitors. In addition, alogliptin has not been shown to have a unique benefit over the already approved DPP-4 inhibitors. Based on the available data, we have concluded that the potential benefit of alogliptin does not exceed its risk at this time.

Path Forward

You will need to provide additional postmarketing data from countries where alogliptin is approved as well as additional clinical trial data to provide reassurance that alogliptin hepatotoxicity is of limited clinical significance. The additional clinical trial data may come from your ongoing EXAMINE trial as well as other available clinical trials, such as Study 305. If the imbalances in serum ALT elevations in your controlled clinical trial database become less apparent with additional patient exposures and a true Hy's Law case is still not seen, we may have sufficient reassurance that alogliptin has an acceptable hepatic profile, particularly if additional postmarketing data do not identify further reports of severe drug-induced liver injury (e.g., leading to death or liver transplantation).

We strongly encourage you to perform enhanced pharmacovigilance (e.g., real-time follow-up to rule out alternative etiologies) for all potential cases of drug-induced liver injury reported with alogliptin to ensure that as much information as possible is obtained for these cases.

When presenting serum ALT elevations >3X, >5X, >10X and >20X ULN for your controlled phase 2/3 database in your resubmission, show baseline data only for those patients who received at least one dose of study medication and who have at least one post-baseline serum ALT value.

The extent of additional clinical trial and postmarketing data needed for the resubmission can be discussed at the End-of-Review meeting.

In addition, you could consider (b) (4)

(b) (4)

LABELING

We reserve further comment on your proposed labeling until the applications are otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

As described in our letter dated August 23, 2011, for NDA 022426, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for alogliptin-pioglitazone fixed-dose combination tablets to ensure that the benefits of the drug outweigh the risk of congestive heart failure in patients being treated with pioglitazone.

We note that your amendment dated September 9, 2011, to NDA 022426 contained a response to our letter dated August 23, 2011; that amendment was not reviewed for this action. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

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 nonclinical and clinical studies/trials 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/clinical trials 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

9. You identified 12 potential cases of interstitial lung disease based on a March 15, 2012, query of the alogliptin clinical trial and postmarketing database using the Interstitial Lung Disease SMQ. Provide an updated, comprehensive analysis of interstitial lung disease events in your resubmission.

ADDITIONAL COMMENTS

We have the following comments pertaining to your proposed pediatric plan. These comments are not a basis for our inability to approve your application.

(b) (4)

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

As described in our letter dated June 26, 2009, we have determined that, if this application is approved, you will be required to conduct a postmarketing trial to assess a signal of a serious risk of adverse cardiovascular events in patients taking alogliptin.

We acknowledge receipt of your May 15, 2009, proposed postmarketing clinical trial protocol to address this issue, which was submitted to IND 069707 for alogliptin. We will continue discussion of this ongoing clinical trial, as needed. If you complete this clinical trial prior to resubmitting your application, you should include the final report and relevant data sets in your Complete Response submission.

Any additional details of this required postmarketing clinical trial, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw these applications under 21 CFR 314.65. You may also request an extension of time in which to resubmit these applications. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before these applications may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

These drug products may not be legally marketed until you have been notified in writing that these applications are approved.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
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/

CURTIS J ROSEBRAUGH
04/25/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-426

COMPLETE RESPONSE

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, Ph.D.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Gupte:

Please refer to your new drug application (NDA) dated September 19, 2008, received September 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We acknowledge receipt of your amendments dated October 6 and 29, and November 13 and 14, 2008, and January 9, 19, and 28, March 30, April 14, May 6, 20, 22, 26, and 29, and June 16, 18, and 30, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form.

Before the application may be approved, it will be necessary for you to satisfactorily address the deficiencies listed below. These include the clinical deficiencies outlined in our action letter for NDA 22-271 for alogliptin, issued on June 26, 2009.

1. To support approvability, sponsors of unapproved drugs and biologics developed for the treatment of type 2 diabetes mellitus should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk, as recommended in the December 2008 Guidance to Industry, *Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.

   In the controlled phase 2/3 database included in NDA 22-271, there is a numerical imbalance in serious cardiovascular adverse events, not favoring alogliptin therapy. Based on the cardiovascular analyses requested by the Division of Metabolism and Endocrinology Products on January 11, 2009, and submitted by you on January 21, 2009, you have not ruled out an unacceptable increase in cardiovascular risk with alogliptin. Specifically, the upper bounds of the 95% confidence intervals

for the risk ratios comparing the incidence of major adverse cardiovascular events (MACE) with alogliptin to the incidence of MACE with placebo exceeded the 1.8 criterion recommended to support approvability. To resolve this deficiency, you should conduct a cardiovascular safety trial with alogliptin that satisfies the 1.8 upper bound criterion incorporating appropriate design features as described in the above mentioned guidance.

2. Both NDAs 22-271 and 22-426 contain only uncontrolled data beyond week 26, substantially limiting interpretability. Your complete response must contain controlled data for at least 500 patients with at least one year of total exposure to alogliptin to supplement the approximately 2,000 patients with uncontrolled one year of exposure to alogliptin included in the 120-day safety update and to provide additional assurance regarding safety for this therapy that will be used chronically, if approved. These data can be derived from the cardiovascular safety trial and/or from other appropriate trials, such as the one-year trial comparing alogliptin to titration of pioglitazone in patients on background metformin plus pioglitazone therapy and the one-year trial comparing alogliptin to sulfonylurea in elderly patients.

3. In Study SYR-322-006, entitled "An Open-Label, Parallel-Group Comparison Study of Single-Dose Pharmacokinetics of SYR110322 in Subjects with Mild or Moderate Renal Impairment and Healthy Volunteers," submitted to NDA 22-271, mean exposure to alogliptin, as assessed by the area under the time-concentration curve (AUC), was increased by approximately 70% in patients with mild renal impairment compared to patients with normal renal function. This finding suggests there may be a need to adjust the dosage of alogliptin in patients with mild renal impairment. In your complete response to both NDAs 22-271 and 22-426, you should include analyses of the controlled phase 2/3 program comparing safety and tolerability in patients with normal renal function to those with mild renal impairment. Present the data in two ways; one using the Cockcroft-Gault formula to categorize renal function and another using the Modification of Diet in Renal Disease (MDRD) equation to categorize renal function.

4. In NDA 22-426, greater incidences of elevations in blood urea nitrogen, serum creatinine and urinary albumin/creatinine ratios were observed with the combination alogliptin/pioglitazone treatment group compared to the individual alogliptin and pioglitazone treatment groups. In addition, more subjects in the combination drug treatment group experienced a shift from normal to mild or moderate renal impairment, as calculated by both the Cockcroft-Gault and MDRD formulas, when compared to the individual treatment groups. These observations raise concern in your proposed dosage strengths (b) (4)

(b) (4)

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory compliance with Current Good Manufacturing Practices for Drugs is required for all manufacturing and testing facilities listed in the NDA before this application may be approved.

SAFETY UPDATE

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 nonclinical and clinical studies/trials 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/clinical trials 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

9. In addition, provide updated analyses and narratives of adverse events that are of interest for all dipeptidyl-peptidase (DPP)-4 inhibitors, including alogliptin (hypersensitivity reactions including angioedema, hepatotoxicity, pancreatitis, infections, skin reactions, and renal safety). For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging reports should be included in the narratives.

POSTMARKETING REQUIREMENTS UNDER 505(0)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

As stated in our June 26, 2009, letter under NDA 22-271, we have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of adverse cardiovascular events in patients taking alogliptin (or alogliptin-containing) tablets.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this signal of serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of adverse cardiovascular events. Therefore, based on appropriate scientific data, FDA has determined that, if the application for NDA 22-271, which will serve as the basis for approval of this NDA, is approved, you

will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following trial to assess a signal of serious risk of adverse cardiovascular events in patients taking alogliptin (or alogliptin-containing) tablets.

> A randomized, double-blind, controlled clinical trial evaluating the effect of alogliptin on the incidence of major adverse cardiovascular events in adults with type 2 diabetes mellitus.

The primary objective of this trial will be to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with alogliptin to that observed in the control group is less than 1.3. Because renal impairment is an important complication of diabetes, you should ensure that there is a minimum of one year of exposure for at least 200 alogliptin-treated patients with moderate renal impairment and at least 100 alogliptin-treated patients with severe renal impairment. These data can be obtained in the required cardiovascular trial or in dedicated renal safety trials. The specific details of this required postmarketing trial will be described more fully in the approval letter for this application, if it is approved.

OTHER

We remind you that adverse events of interest for dipeptidyl peptidase-4 (DPP-4) inhibitors include hypersensitivity reactions including angioedema, hepatotoxicity, pancreatitis, infections, skin reactions, and renal safety. These adverse events should be captured and analyzed in all future clinical trials evaluating the alogliptin/pioglitazone fixed-dose combination tablet.

We also remind you of your product quality agreement submitted on June 18, 2009.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the May 2009 FDA Guidance for Industry *Formal Meetings Between the FDA and Sponsors or Applicants* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf).

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

If you have any questions, call Julie Marchick, M.P.H., Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CURTIS J ROSEBRAUGH
09/02/2009