U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Kyowa Hakko Kogyo Co., Ltd. 9/29/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

Via UPS Mail

WL: 320-10-009

September 29, 2010

Mr. Shigenori Ishizaki
Director of the Board/Plant Director
Yamaguchi Production Center
Kyowa Hakko Kogyo Co., Ltd.
1-1 Kyowa-cho
Hofu City, Yamaguchi
Japan, 747-8522

Dear Mr. Ishizaki:

During our June 21-25, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Kyowa Hakko Kogyo Co., Ltd. located at 1-1 Kyowa-cho, Hofu City, Yamaguchi, Japan, 747-8522, investigators from the Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations cause your APIs to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of July 14, 2010, and note that it lacks sufficient corrective actions.

Specific deviations observed during the inspection include, but are not limited, to the following:

1. Failure of your quality control unit/laboratory to thoroughly investigate and document out-of-specification (OOS) results obtained. For example,

a) Your firm's 2007 OOS investigation into high levels of **(b)(4)** found in **(b)(4)** lot **(b)(4)** was not completely documented, nor was the investigation extended to other lots. You indicated that the cause of the high levels of **(b)(4)** within **(b)(4)** lot **(b)(4)** was related to a component used in the manufacture of **(b)(4)** lot **(b)(4)** namely **(b)(4)** lot **(b)(4)**

The investigation did not document the testing of **(b)(4)** lot **(b)(4)** for **(b)(4)**, nor could the results be located or provided during our inspection. There were **(b)(4)** lots of **(b)(4)** and **(b)(4)** used in the production of **(b)(4)** lot but only one lot **(b)(4)** of **(b)(4)** was tested. This lot of **(b)(4)** was also used in the manufacture of **(b)(4)** lot **(b)(4)**, but you did not conduct further investigation into **(b)(4)** lot **(b)(4)**. Also, you did not evaluate **(b)(4)** lot **(b)(4)** for high levels of **(b)(4)** as a potential additional source of **(b)(4)** in **(b)(4)** lot **(b)(4)** .You also used **(b)(4)** lot **(b)(4)** in the manufacture of lot **(b)(4)**.

b) Your firm's OOS investigation relating to impurity levels for **(b)(4)**, lot **(b)(4)** , concluded that the root cause was a laboratory error, but the investigation did not identify what specific laboratory error occurred. Initial results for both Highest Individual Impurity (specification NMT **(b)(4)**%) and Total Impurities (specification **(b)(4)**%) were OOS at **(b)(4)**% and **(b)(4)**% respectively. The investigational checklist initially indicated that no problem was found with the analysis.

The investigational checklist you currently use is insufficient to detect and evaluate instrument problems and standard/sample preparation errors. You authorized retesting of **(b)(4)**, lot **(b)(4)**, without identifying a possible root cause. Instead, a new sample preparation was used to retest the product, which was found within specification. You used the passing retest results to invalidate the original OOS results, with no laboratory error attributed in obtaining the original result. This retesting approach lacks scientific justification.

Your response indicates that you will revise your procedure for conducting OOS investigations, YIS-HIN-0003, "SOP on OOS Investigation." Please note, that it is critical that your firm thoroughly investigate all OOSs to determine the root cause. Refer to the October 2006 Guidance for Industry-Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Products for additional information. Include in your response to this letter an English translation copy of the new procedure and the training documentation for this revised procedure. Additionally, we recommend that a retrospective review of all opened and closed investigations related to similar incidents where the original failing results were invalidated using a retest passing result. This retrospective evaluation should cover all products and lots intended for the US, and that remain within expiry.

2. Failure of your quality control unit/laboratory to ensure all sampling plans and test procedures are scientifically sound and appropriate to ensure that your APIs conform to established standards of quality and/or purity. For example,

a) Your chromatographic test methods do not include system suitability test requirements. There is no requirement that standards be injected prior to the start of or throughout a sequence. Your chromatographic sequences may last up to a week. You should have a requirement to perform a system suitability test to ensure the system is suitable throughout the entire sequence, thereby also ensuring the data's precision and reliability. Your QC manager indicated that you conduct system suitability tests **(b)(4)** per month on instruments used for the release of finished APIs, and once every **(b)(4)** months for non-release testing such as stability testing.

Your response indicates that you have begun to perform system suitability testing throughout the run, and that revisions to the following SOPs will be completed: HIS-HIN-KI-011, "System Suitability Test of Chromatography," and HIS-HIN-BUN-003, "Analysis Method of **(b)(4)**."

Include in your response to this letter an English translation copy of the revised SOPs. Also, include your scientific justification for these new system suitability requirements, as well as the specific timelines of when you intend to implement the revision to your procedures and complete the training of your analysts. Provide copies of the training documentation generated for these revised procedures.

b) Your firm does not sample incoming components/raw materials in a manner that represents the batch for the determination of acceptance or rejection of the material. Your firm fails to have a scientific justification for the sampling approach used for incoming materials. For example, you only sampled 3 **(b)(4)** of drums of a batch of **(b)(4)** received in February 2007 (less than **(b)(4)**

samples). Your firm also lacks a written procedure describing the material sampling process.

In addition, your site personnel do not conduct sampling on incoming material. Your Quality Assurance (QA) Manager indicated that your vendors sample the materials prior to shipping to your site, and that the supplied samples are then tested by your facility. These samples are also composited by your vendors. Your sampling practices are unacceptable for the following reasons:

- Your approach provides limited or no information regarding the material's variability
- In the case that the material fails to meet the established specification, the root cause determination may be limited by the sampling approach
- You have no information on how your vendor conducts the sampling with no assurance that the samples were properly collected by your vendor
- There is no assurance that the samples were collected from the batch of incoming material received
- The sample is composited, without justification
- The actual effect of transportation on the batch within its container is not assessed, such as segregation or contamination that may occur during transportation.

We are concerned that you do not sample, examine, or test incoming material you use for the manufacture of API in a manner that would verify the incoming lot's integrity. Your current process is deficient because of your inability to demonstrate that you have a controlled and secure supply chain when you rely on limited samples collected and shipped by a source independent to your quality unit.

Your response states that your firm will investigate the homogeneity of incoming materials, and that you will revise the appropriate procedure. Describe in your response to this letter the number of containers to be sampled, the portion of the container to be sampled, sample size to be collected, material variability, and approach to prevent contamination of the material. Your training documentation, related to this issue, will be evaluated in a future inspection.

3. Failure of your quality control unit/laboratory to ensure your analytical methods used to evaluate the stability of your APIs are validated to be stability indicating.

For example, you have not validated the method you currently use to test the stability of **(b)(4)** to ensure it is stability indicating. You use this **(b)(4)** of several **(b)(4)** in the finished drug product **(b)(4)**. You provided no supporting documentation to demonstrate that the current **(b)(4)** method can detect the presence of **(b)(4)** or unknown impurities/related substances. Also, you performed forced degradation studies on all **(b)(4)** individually, not on the **(b)(4)** of **(b)(4)**. We consider these forced degradation studies incomplete. They should include the forced degradation of the to ensure selectivity of the method in the presence of all **(b)(4)**, and their related impurities/related substances and degradation products.

Your response indicates that you will review the forced degradation studies of each individual **(b)(4)** making up **(b)(4)** and that you will establish another assay method for this product if any **(b)(4)** or impurity is found to increase. Again, this action lacks the evaluation of all being present during forced degradation. As a result, there can be no evaluation of how this **(b)(4)** could degrade, or the effect of the **(b)(4)** degradation on the method's selectivity. There may be a difference in how individual **(b)(4)** degrade within a of other **(b)(4)**. Include in your response to this letter an evaluation of the forced degradation of the **(b)(4)**, and your justification for continuing to use the current method for stability of **(b)(4)**.

4. Failure of your quality control unit/laboratory to ensure your analytical methods are appropriately validated, and to assess method modifications to verify that any modifications to a validated method continue to produce results that are accurate and reliable as compared to the established method.

For example, the validation of your **(b)(4)** assay method does not include an evaluation of the minimally required validation elements. You have not evaluated accuracy and specificity (including forced degradation) as part of the **(b)(4)** assay method validation. Furthermore, you initially validated this method in 1995, and then again in March 2008, to cover additional validation elements such as LOQ. However, throughout this method's use, changes to the gradient method have been made without evaluating how these changes might affect the validation status of the method. Our investigators found that the gradient is different for every instrument you currently use for this method, compared to the original validated gradient. These changes greatly exceed the allowable gradient variations suggested by USP <621> Chromatography.

Your response indicates that you will validate the assay method according to ICH Q2B. We expect that you validate the method with the appropriate gradient for each instrument type you plan to use for this assay method because the method's gradient is required to be so different on the various instruments you use. This does not normally apply if the gradient variations are within those limits listed in USP <621> Chromatography.

5. Failure of your quality control unit/laboratory to institute and use a control system for the issuance of laboratory records to ensure the integrity and reliability of laboratory raw data.

For example, your laboratory does not use bound notebooks or worksheets with a unique identifier controlled by the quality unit to record raw data, such as sample weights, etc. We expect you to record and retain all original raw data.

This is a repeat observation from your August 2007 FDA inspection. Your response indicates that you corrected the issue indentified on the August 2007 FDA-483, to uniquely indentify laboratory issued equipment log sheets. Your response further states that QA will uniquely identify each laboratory record, log sheet, calibration record, OOS investigation report, record of calculation, etc.

This observation is considered a repeat observation because you initially only addressed the specific example that was listed on the August 2007 FDA-483. Your correction was not applied globally to all areas in which original raw data should be recorded and retained. It is your company's responsibility to apply corrective actions to all deficiencies at your facility, whether or not they are listed in a FDA-483 or a Warning Letter. Provide an English translation copy of the procedure that describes how your quality unit will control the issuance of all laboratory records to ensure the integrity and reliability of laboratory raw data. Also provide the training documentation for this procedure.

6. Failure of your quality control unit/laboratory to include the complete data derived from all tests conducted to ensure compliance with established specifications and standards.

For example, your laboratory does not record reagent information (such as expiration dates of solutions) or balance information (such as sample/standard weights) you use for analytical testing. The inspection also revealed that the actual raw data weights are not used for the result calculations. The facility uses the theoretical sample and standard weights described in the procedure as the weights to calculate sample results. Furthermore, you do not use the actual purity of a standard. Instead, if the standard purity is 99.5% or higher, it is rounded to 100%, which would also be the value you use for the result calculation.

Your response states that you have just installed a new LIMS system to record laboratory activities such as sample/standard weights, equipment identification, lot numbers, expiry dates of solutions, etc. It further states that for the raw data that is not recorded by the LIMS system, you will revise other SOPs to describe the recording procedures of this additional data. Include in your response to this letter a description of all procedures revised to correct this deviation. Also include an explanation of how data will be captured at the time it is generated, if this data is meant to be captured only in the LIMS system. We expect you to record data at the time of the occurrence.

7. Failure of your quality control unit to ensure cleaning procedures are validated.

For example, your firm has no cleaning validation (cleaning and drying for reuse) for the large flexible bags you use to hold the **(b)(4)** of the **(b)(4)** after the **(b)(4)** step, and before the **(b)(4)** step. Although you use these bags to hold material from the different **(b)(4)** manufacturing processes executed at your site, you have not performed a validation of the current cleaning procedure. These bags are also not dedicated to a specific process or **(b)(4)**. In addition, you do not follow the current cleaning procedure as written. Examples of inconsistencies between the procedure itself, HES-III-SEI-514, "SOP for Cleaning of the Flexible Large Bags and what your employees actually perform include, the **(b)(4)** of the bags in **(b)(4)** for **(b)(4)** minutes and "Hand washing" is not define as using **(b)(4)** on the **(b)(4)** of the bag.

Your response indicates that you will revise HES-III-SEI-514, "SOP for Cleaning of the Flexible Large Bags," and you will validate the cleaning

procedure. Include in your response to this letter an English translation copy of the revised procedure, the training documentation for this procedure, and an English translation copy of the validation protocol for this cleaning procedure. Also, if you plan to validate the cleaning of these bags using a matrix approach based on the worst case (e.g. hardest to clean) **(b)(4)** include a justification for the choice of the selected worst case **(b)(4)**.

8. Failure of your quality control unit to ensure that critical parameters and inprocess attributes that could affect the quality attributes of your APIs are identified and validated.

For example, your firm reuses **(b)(4)** during the manufacture of your **(b)(4)** products, but failed to justify or validate the calculation used to determine the number of times that **(b)(4)** are used during production. Each **(b)(4)** master batch record (MBR) contains this calculation for use by the manufacturing operators to determine the acceptability of the recycled **(b)(4)**. However, you lack supportive data to justify your rationale.

Your response states that you will re-investigate the suitability of the calculation. Operations that may affect the quality attributes of your API must be properly validated.

Include in your response to this letter the summary of your investigation into the suitability of this calculation and indicate how this calculation was correlated to the current validation of your manufacturing processes regarding the number of times that your recovered **(b)(4)** can be reused. Also include in your response information to demonstrate that the quality attributes of the APIs produced by your firm with reused **(b)(4)** have not been compromised by the presence of impurities and by-products that may be formed by reusing. Furthermore, provide information to support that the recovered **(b)(4)** met the appropriate standards before being reused.

9. Failure of your quality control unit to ensure records for equipment cleaning are maintained.

For example, your firm does not maintain cleaning records for the accessories of the **(b)(4)** used to remove **(b)(4)** of different **(b)(4)**, including, but not limited to, the **(b)(4)** process. This equipment is not dedicated to a single manufacturing process, increasing the importance of recording the use (including at a minimum: date, time, product, and batch number) and cleaning (including at a minimum: date, time, product, batch number, and the person who conducted the cleaning, type of cleaning procedure performed) of this equipment.

Your response states that you will revise HIS-P-2005, "SOP on Cleaning Procedure in **(b)(4)** Facilities," to require the recording of the following information related to the accessory cleaning: temperature and duration. You will also revise the form you use to document the cleaning to record the same information. Include in your response to this letter an English translation copy of the revised form. Your firm's procedures and training documentation will be evaluated in a future inspection.

Your response also indicates that your firm will increase the number of internal audits from annually to quarterly. This commitment appears appropriate and should allow your firm to be more proactive in discovering GMP concerns, prior to regulatory inspections.

The deviations detailed in this letter are not intended to be an all-inclusive statement of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations. If you wish to continue to ship APIs to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, failure to correct these deviations may result in FDA refusing admission of articles manufactured at Kyowa Hakko Kogyo Co., Ltd. located at 1-1 Kyowa-cho, Hofu City, Yamaguchi, Japan, 747-8522 into the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381 (a)(3)] in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct deviations. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI #3002807424.

If you have questions or concerns regarding this letter, contact Brian L. Belz (CDER), Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-4279

Sincerely,

/Concepcion Cruz/
for Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

ADDENDUM to Warning Letter

VIA E-mail

Re: WL 320-10-009

To: Kyowa Hakko Bio Co., Ltd.

Date: October 29, 2010

Subject: Warning Letter 320-10-009 from the Food and Drug Administration

WL 320-10-009 was issue with the firm's previous name: Kyowa Hakko Kogyo Co., Ltd.

The current and correct name of the firm is: Kyowa Hakko Bio Co., Ltd.

The firm's address remains:

1-1 Kyowa-cho
Hofu City, Yamaguchi
Japan, 747-8522

WL-320-10-009, issued on September 29, 2010, applies to the facility named Kyowa Hakko Bio Co., Ltd., located at the address above, which is also the address listed within WL-320-10-009.

Links on this page: