DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	4/11-15/2022 FEI NUMBER 3002807424

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Yoshihisa Fujiwara, Senior Executive Officer General Manager

FIRM NAME	STREET ADDRESS
Kyowa Hakko Bio Co., Ltd.	1-1, Kyowa-cho
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Hofu-city Yamaguchi 747-8522 Japan	API Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Quality System

Observation 1
The responsibilities and procedures applicable to the quality control unit are not fully followed.
Specifically, SOP HIS-QC-0006, Procedure for Handling Laboratory Errors; effective since September 1, 2021 requires that if a "remarkable trend" is identified it should be reported and corrective actions must be implemented to address the trend. Review of laboratory incidents for the year 2021 and 2022 revealed the following:
a) In 2022 the following incidents during endotoxin testing, involved poor calibration curves, however the root cause is not established and no CAPA was issued to address this issue.
LE2022-HB-002 2022/01/06
LE2022-HB-004 2022/01/12
LE2022-HB-018 2022/02/07

b)SOP YMS-QA-0119, effective July 15, 2021 requires that evidence of investigations should be retained together with the records of deviation. In addition SOP YIS-QA-0039-01, requires a risk a assessment for determining if a deviation has any impact on product quality. However review of deviation DV-21-0072; "Inadequate endotoxin interfering response" and associated investigation revealed that no risk assessment was present as part of the documentation. This deviation was classified as major and no CAPA was initiated.

c)SOP YIS-QA-0039-02, effective 01/01/2022 does not state the criteria for extending deviations. Review of deviations revealed that several deviation were opened for more than 90 days, the examples below provide the longest time for deviations (see below).

DV-21-0591 Complete 275 day(s)
DV-21-0093 Complete 252 day(s)
DV-21-0307 Complete 219 day(s)

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	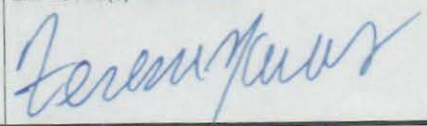	Teresa I. Navas, Investigator	04/15/2022

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DV-21-0832 Complete 194 day(s)
DV-21-0377 Complete 192 day(s)
DV-21-1147 Complete 174 day(s)
DV-21-0070 Complete 134 day(s)
DV-21-0911 Complete 126 day(s)
DV-21-0896 Complete 119 day(s)
DV-21-1018 Complete 117 day(s)
DV-21-1243 Complete 111 day(s)
DV-21-1214 Complete 104 day(s)
DV-21-0955 Complete 103 day(s)
DV-21-1223 Complete 1101 day(s)
DV-22-0018 Open since 28-Dec-2021 94 day(s)
DV-22-0045 Open since 06-Jan-2022 85 day(s)
DV-22-0087 Open since 13-Jan-2022 78 day(s)
DV-21-1596 Open since 17-Dec-2021 105 day(s)

d) Investigations of deviations with potential product impact such as deviation DV-1596 (presence of unwanted microorganism) do not show that a proper investigation was performed to support the conclusions. The investigation was lacking risk assessment as well as root cause investigation.

e) Review of the quality system revealed that as of April 2022 the firm has over 300 open change controls. The same trend of time exceeding 100 days was observed for CAPAs and complaint investigations. Although the change control SOP YIS-QA-0035 requires to check on the status of changes that have been open for an extended period of time. Review of change control documents showed that there is no documentation for all changes and their progress status. The following are examples of the time frame for change controls that exceed 300 days:
CC-21-0261 Active 23-Apr-2021 343 day(s)
CC-21-0280 Active 28-Apr-2021 338 day(s)
CC-21-0315 Active 10-May-2021 326 day(s)
CC-21-0318 Active 10-May-2021 326 day(s)
CC-21-0323 Active 10-May-2021 326 day(s)
CC-21-0325 Active 10-May-2021 326 day(s)

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CC-21-0326 Active 10-May-2021 326 day(s)
CC-21-0342 Active 12-May-2021 324 day(s)

Observation 2
a)The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. Specifically, impact and risk assessment for CC-21-0292 which involved installing (b)(4) holding tanks for the DIW water system did not take into consideration the time the system was shutdown when evaluating risk for microbial growth. In addition, the implementation plan did not include justification for not increasing monitoring practices after the system was placed back into service.

b) Your firm did not evaluate the potential impact of proposed changes on the quality of intermediates or APIs. Specifically, your firm changed the storage conditions of API (b)(4) from 25°C to (b)(4) °C ±(b)(4) °C by enacting Change Control CC21-0305. The change control only considered adding the new storage requirements to the label. However, your assessment for this change control did not evaluate if batches that were shipped with labels that contained no storage requirements were transported or stored at the required conditions. In addition, your firm was aware that the storage requirements for all grades of (b)(4) should be (b)(4) °C ±(b)(4) °C since 2015 and did not include this information on the label until May 2021.

Observation 3
Materials System
Your firm does not have evidence to demonstrate that the current monitoring frequency and specifications for water (PFW) used in the manufacture of APIs ensure the water is suitable for its intended use. Specifically, there are no specifications for monitoring absence of objectionable microorganisms.

Laboratory System
Observation 4
Your firm laboratory controls procedures are inadequate.
Specifically,

a) Samples that were completed in January have not been disposed and your SOP for sample disposition does not

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state the length of time the sample can continue to be stored inside the QC lab after analysis has been completed.

b) Not all Microbiology samples for TAMC stored in incubator G9012 were logged into the logbook.

c) Employees identified as classified to perform audit trail reviews in empower as part of routine QC review of data are unable to demonstrate proficiency of audit trail reviews.

Observation 5
Production System:
Your procedures do not classify alarms that are observed in DCS system (process monitoring system) thus, operators do not have enough information to establish which alarms are critical for the process and should be documented during process monitoring.

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