檔　　號:
保存年限:

衛生福利部食品藥物管理署 函

地址：115021 臺北市南港區研究院路一段130巷109號
聯絡人：賴蔚榕
聯絡電話：(02)2787-7025
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電子郵件：luvkumara@fda.gov.tw

受文者：中華民國製藥發展協會

發文日期：中華民國114年9月17日
發文字號：FDA品字第1141106658號
速別：普通件
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份（A21020000I_1141106658_doc1_Attach1.pdf）

主旨：有關美國FDA發布印度原料藥廠Warning Letter乙案，請轉知所屬會員知照。

說明：

一、美國衛生主管機關Food and Drug Administration（FDA）查核印度原料藥廠「Hikal Limited」（廠址：72 - 82 / A Kiadb Industrial Area, Jigani, Karnataka, 560105, India），判定違反CGMP，並於114年8月20日發布Warning Letter（詳附件，114年9月9日公布於美國FDA官網）。

二、鑑於上述原料藥廠未符合GMP規定，具影響藥品製造品質之風險，請轉知所屬會員釐清國產及輸台製劑產品相關原料藥使用情形，並應依風險管理原則執行相關後續處置。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、台灣藥品行銷暨管理協會、台灣製藥工業同業公會、中華民國學名藥協會、中華民國製藥發展協會

副本：電子公文交換章 2025/09/17 16:22:16

WARNING LETTER

Hikal Limited

MARCS-CMS 709370 — AUGUST 20, 2025

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)

Delivery Method:
Via Email
Reference #:
320-25-102
Product:
Drugs

Recipient:
Dr. K Suresh Babu
Head – Corporate Quality and Regulatory Affairs
Hikal Limited
72 - 82 / A Kiadb Industrial Area
Jigani 560105 Karnataka
India

Issuing Office:
Center for Drug Evaluation and Research (CDER)
United States

Warning Letter 320-25-102

August 20, 2025

Dear Dr. Babu:

The United States Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hikal Limited, FEI 3003560263, at 72 - 82 / A Kiadb Industrial Area, Jigani, Karnataka, 560105, India, from February 3 to February 7, 2025.

This warning letter summarizes significant deviations from Current Good Manufacturing Practice (CGMP) for active pharmaceutical ingredients (APIs).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your APIs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your March 3, 2025 response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

1. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.

Inadequate root cause determination

Your firm failed to adequately determine the root cause of approximately 22 complaints since 2020 related to metal contamination in your APIs. For example, your investigation into a complaint of black particles in **(b)(4)** API identified this was the first lot manufactured after a facility modification. You stated some particles may have not been removed completely during equipment cleaning but concluded "no exact root cause identified." You also stated the particles were metallic in nature and were beyond the detection limit of your metal detector used to remove metallic particles in your API. However, our inspection determined you did not have a "**(b)(4)**" to adequately qualify your metal detector's performance for **(b)(4)** particles, even though most of your manufacturing equipment is composed of **(b)(4)**.

We also note your investigation determined the contamination to be technically unavoidable particles. You referenced an industry standard on technically unavoidable particles in excipients as applicable. According to this guideline, technically unavoidable particles are inherent to the product and are not foreign contamination introduced by incomplete cleaning. Not only is this standard not applicable to your active ingredient manufacturing process, it also specifies that appropriate evaluation of materials of construction and particle mitigation strategies are required. Based on your investigation indicating a cleaning deficiency as a likely root cause, you do not have evidence to support that the metallic particles present are inherent to the manufacturing process. Your firm remains responsible for establishing and following adequate cleaning procedures.

In your response, you state you have now obtained a "**(b)(4)**" and determined the metal detector is working satisfactorily. You then concluded there is "no impact on the performance of the metal detector."

Your response is inadequate. The current performance of the metal detector does not provide adequate assurance that previous API lots met established safety and quality standards. Also, your conclusion that your metal detector works adequately stands in contrast to customer complaints indicating contamination with metallic particles. Additionally, your investigation fails to adequately assess whether your manufacturing equipment's design and materials are suitable for API production without introducing contamination risks. Furthermore, you lack an adequate evaluation of your cleaning procedures and in-process controls to prevent the presence of metal particles in your API.

Ineffective corrective actions and preventive actions (CAPAs)

Your firm failed to implement effective CAPAs after receiving numerous complaints of foreign material contamination of your APIs. For example, a customer reported foreign material contamination involving eight lots of **(b)(4)** API. Your investigation found CAPAs were implemented for similar complaints prior to the manufacture of the complaint lots. However, our inspection found approximately 28 additional complaints reporting foreign material contamination after you completed your investigation.

Inadequate investigations can result in unidentified root causes, ineffective CAPAs, and recurring problems that compromise your ability to manufacture safe and effective APIs.

We also note that during our review we found the risk assessment included in your complaint investigation is not scientifically sound, as you ranked this **(b)(4)** API complaint as an unlikely failure with the lowest probability of occurrence despite repeated similar complaints.

In your response, you state you hired a third-party consultant to evaluate contamination, investigations, risk assessments, and CAPAs related to foreign material contamination.

Your response is inadequate. You do not provide sufficient evidence of a comprehensive evaluation of potential contamination sources and process controls.

In response to this letter, provide:

- An action plan and timelines for conducting full evaluation of retain samples for particulate contamination to determine the quality of all lots of drug product distributed to the United States that are within retest dating as of the date of this letter.

- A summary of all results obtained from evaluating retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-specification (OOS) results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
- An evaluation of the suitability of equipment including, but not limited to, metal detectors, for intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality.
- A remediation plan that details your impact assessment of previously distributed lots for foreign contamination when your equipment was not properly calibrated.
- A detailed assessment of your methodology for categorizing complaints into low, medium, and high-risk categories that accounts for complaint frequency and provides clear escalation triggers for repeated complaints of the same nature. Summarize how your revised risk categorization system will prevent and respond to foreign material contamination complaints. Provide your timeline for implementing the revised risk categorization system, including appropriate training.
- A comprehensive review and reclassification, if necessary, of all contamination-related complaints related to APIs within expiry using your revised methodology. Identify any additional corrective actions that should be implemented based on any revised risk categorization.

2. Failure to have a system for evaluating suppliers of critical materials.

Your firm's supplier qualification procedure stated corrective action is required when a supplier's rejection rate exceeds **(b)(4)**% during incoming inspection. However, it did not incorporate mechanisms for re-evaluation of an approved supplier when quality deficiencies or complaints are detected after initial qualification.

This deficiency in your supplier qualification procedure allowed you to continue using materials from qualified suppliers after you determined their materials were found defective. For example, your firm received repeated customer complaints about particles in your APIs that you concluded most likely originated from your supplier of **(b)(4)** drums and lids. Despite notifying the supplier of these quality issues and continuing to receive customer complaints, your firm failed to implement timely corrective actions, such as qualifying alternate suppliers, enhancing supplier oversight, or discontinuing use of defective materials from this supplier.

An adequate supplier qualification program includes ongoing monitoring of supplier performance beyond incoming inspection and prompt implementation of corrective actions when quality issues are identified at any point in the manufacturing process.

In your response, you provide an updated supplier qualification procedure that accounts for quality issues identified during manufacturing and customer complaint investigations. You also state you have suspended the use of your drum supplier, and you are qualifying additional suppliers.

Your response is inadequate. You do not provide quality data for the new supplier, which you state was providing **(b)(4)**% of your drums prior to the inspection. Furthermore, you lack a comprehensive root cause analysis of your supplier qualification system’s failure to identify and respond to ongoing quality issues.

In response to this letter, provide:

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

- An independent, comprehensive review of your material system to determine whether all suppliers of components, containers, and closures, are appropriately qualified; materials are of consistently acceptable quality; and appropriate expiration or retest dates are assigned. Based on this systemic review, provide a summary of a systemic CAPA that remediates your supplier qualification program and prevents use of unsuitable components, containers, and closures.
- A summary of quality metrics of your new supplier of **(b)(4)** drums and lids including, but not limited to, incoming inspection data for **(b)(4)** drums and lids, with acceptance/rejection rates, defect types, complaint frequencies, and trending analysis in the previous three years.

Additional API CGMP Guidance

FDA considers the expectations outlined in ICH Q7 when determining whether APIs are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API at https://www.fda.gov/media/71518/download.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, you should engage a consultant qualified to evaluate your operations to assist your firm in meeting CGMP requirements.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Conclusion

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of any deviations and for preventing their recurrence or the occurrence of other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct any deviations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any deviations.

Failure to address any deviations may also result in the FDA refusing admission of articles manufactured at Hikal Limited, Jigani, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority that appear to be adulterated may be detained or refused admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days[1]. Specify what you have done to address any deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3003560263 and ATTN: Matthew Jensen.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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1 Under program enhancements for the Generic Drug User Fee Amendments (GDUFA) reauthorization for fiscal years (FYs) 2023-2027, also known as the GDUFA III Commitment Letter, your facility may be eligible for a Post-Warning Letter Meeting to obtain preliminary feedback from FDA on the adequacy and completeness of your corrective action plans.

檔　　號:
保存年限:

衛生福利部食品藥物管理署 函

地址：115021 臺北市南港區研究院路一段130巷109號
聯絡人：黃萱閔
聯絡電話：02-27877139　分機：7139
傳真：(02)2787-7023
電子郵件：hsuanmin@fda.gov.tw

受文者：中華民國製藥發展協會

發文日期：中華民國114年9月30日
發文字號：FDA品字第1141106785號
速別：普通件
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊1份 (A21020000I_1141106785_doc2_Attach1.pdf)

主旨：有關美國FDA發布印度原料藥廠「Hikal Limited(廠址：72 - 82 / A Kiadb Industrial Area, Jigani, Karnataka, 560105, India)」不符合GMP相關訊息乙案，請轉知所屬會員知照。

說明：

一、美國衛生主管機關Food and Drug Administration (FDA)於114年2月3日至7日查核旨揭原料藥廠，判定其違反CGMP並於114年8月20日正式發布Warning Letter (詳附件，美國FDA業於114年9月9日公布於其官網)(本署114年9月17日FDA品字第1141106658號函諒達)。經查，旨揭原料藥廠輸臺原料藥品項如下：

(一)ACEBUTOLOL (HCL)；

(二)ACEBUTOLOL HCL；

(三)BUPROPION HYDROCHLORIDE；

(四)CINNARIZINE；

(五)FLUNARIZINE；

(六)FLUNARIZINE (HYDROCHLORIDE)；

(七)FLUNARIZINE HCL (FLUNARIZINE 2HCL)；

(八)GABAPENTIN；

(九)GEMFIBROZIL；

(十)PENTOXIFYLLINE；

(十一)PIRACETAM；

(十二)QUETIAPINE FUMARATE；

(十三)TRIPROLIDINE HCL；

(十四)TRIPROLIDINE HCL MONOHYDRATE；

(十五)VENLAFAXINE HYDROCHLORIDE。

二、鑒於旨揭藥廠相關原料藥之製造品質恐無法符合GMP之要求，使用其原料藥可能對藥品製造品質帶來影響與衝擊，基於源頭管理及風險管理的原則，請轉知國內製藥廠，應配合辦理下列事項，相關資料留廠備查：

(一)應取得佐證資料進行評估以釐清其品質疑慮，必要時，暫停使用旨揭藥廠所生產之原料藥。

(二)已使用旨揭藥廠相關原料藥生產之產品，應全面進行品質檢討，並有文件化資料可佐證。

(三)新購原料藥部分，應優先考量其GMP符合性現況為原則。

正本：中華民國學名藥協會、中華民國製藥發展協會、臺灣製藥工業同業公會
副本：電子公文交換章 2025/09/30 15:54:39

WARNING LETTER

Hikal Limited

MARCS-CMS 709370 — AUGUST 20, 2025

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)

Delivery Method:
Via Email
Reference #:
320-25-102
Product:
Drugs

Recipient:
Dr. K Suresh Babu
Head – Corporate Quality and Regulatory Affairs
Hikal Limited
72 - 82 / A Kiadb Industrial Area
Jigani 560105 Karnataka
India

Issuing Office:
Center for Drug Evaluation and Research (CDER)
United States

Warning Letter 320-25-102

August 20, 2025

Dear Dr. Babu:

The United States Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hikal Limited, FEI 3003560263, at 72 - 82 / A Kiadb Industrial Area, Jigani, Karnataka, 560105, India, from February 3 to February 7, 2025.

This warning letter summarizes significant deviations from Current Good Manufacturing Practice (CGMP) for active pharmaceutical ingredients (APIs).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your APIs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your March 3, 2025 response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

1. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.

Inadequate root cause determination

Your firm failed to adequately determine the root cause of approximately 22 complaints since 2020 related to metal contamination in your APIs. For example, your investigation into a complaint of black particles in **(b)(4)** API identified this was the first lot manufactured after a facility modification. You stated some particles may have not been removed completely during equipment cleaning but concluded "no exact root cause identified." You also stated the particles were metallic in nature and were beyond the detection limit of your metal detector used to remove metallic particles in your API. However, our inspection determined you did not have a "**(b)(4)**" to adequately qualify your metal detector's performance for **(b)(4)** particles, even though most of your manufacturing equipment is composed of **(b)(4)**.

We also note your investigation determined the contamination to be technically unavoidable particles. You referenced an industry standard on technically unavoidable particles in excipients as applicable. According to this guideline, technically unavoidable particles are inherent to the product and are not foreign contamination introduced by incomplete cleaning. Not only is this standard not applicable to your active ingredient manufacturing process, it also specifies that appropriate evaluation of materials of construction and particle mitigation strategies are required. Based on your investigation indicating a cleaning deficiency as a likely root cause, you do not have evidence to support that the metallic particles present are inherent to the manufacturing process. Your firm remains responsible for establishing and following adequate cleaning procedures.

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Your response is inadequate. The current performance of the metal detector does not provide adequate assurance that previous API lots met established safety and quality standards. Also, your conclusion that your metal detector works adequately stands in contrast to customer complaints indicating contamination with metallic particles. Additionally, your investigation fails to adequately assess whether your manufacturing equipment's design and materials are suitable for API production without introducing contamination risks. Furthermore, you lack an adequate evaluation of your cleaning procedures and in-process controls to prevent the presence of metal particles in your API.

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- A remediation plan that details your impact assessment of previously distributed lots for foreign contamination when your equipment was not properly calibrated.
- A detailed assessment of your methodology for categorizing complaints into low, medium, and high-risk categories that accounts for complaint frequency and provides clear escalation triggers for repeated complaints of the same nature. Summarize how your revised risk categorization system will prevent and respond to foreign material contamination complaints. Provide your timeline for implementing the revised risk categorization system, including appropriate training.
- A comprehensive review and reclassification, if necessary, of all contamination-related complaints related to APIs within expiry using your revised methodology. Identify any additional corrective actions that should be implemented based on any revised risk categorization.

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This deficiency in your supplier qualification procedure allowed you to continue using materials from qualified suppliers after you determined their materials were found defective. For example, your firm received repeated customer complaints about particles in your APIs that you concluded most likely originated from your supplier of **(b)(4)** drums and lids. Despite notifying the supplier of these quality issues and continuing to receive customer complaints, your firm failed to implement timely corrective actions, such as qualifying alternate suppliers, enhancing supplier oversight, or discontinuing use of defective materials from this supplier.

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Your response is inadequate. You do not provide quality data for the new supplier, which you state was providing **(b)(4)**% of your drums prior to the inspection. Furthermore, you lack a comprehensive root cause analysis of your supplier qualification system’s failure to identify and respond to ongoing quality issues.

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- A summary of quality metrics of your new supplier of **(b)(4)** drums and lids including, but not limited to, incoming inspection data for **(b)(4)** drums and lids, with acceptance/rejection rates, defect types, complaint frequencies, and trending analysis in the previous three years.

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CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, you should engage a consultant qualified to evaluate your operations to assist your firm in meeting CGMP requirements.

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Conclusion

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If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

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This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days[1]. Specify what you have done to address any deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3003560263 and ATTN: Matthew Jensen.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

---

1 Under program enhancements for the Generic Drug User Fee Amendments (GDUFA) reauthorization for fiscal years (FYs) 2023-2027, also known as the GDUFA III Commitment Letter, your facility may be eligible for a Post-Warning Letter Meeting to obtain preliminary feedback from FDA on the adequacy and completeness of your corrective action plans.