**WARNING LETTER**

# Intas Pharmaceuticals Limited

**MARCS-CMS 662868 — NOVEMBER 21, 2023**

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**Delivery Method:**

Via Email

**Product:**

Drugs

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**Recipient:**

Mr. Nimish Chudgar

Chief Executive Officer & Managing Director

Intas Pharmaceuticals Limited

Plot No. 255, Magnet Corporate Park, Near Sola Bridge, S.G. Highway
Thaltej, Ahmedabad 380054 Gujarat
India

**Issuing Office:**

Center for Drug Evaluation and Research | CDER

United States

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**Warning Letter** 320-24-12

November 21, 2023

Dear Mr. Chudgar:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Intas Pharmaceuticals Limited, FEI 3003157498, at Plot No. 457- 458 & 191/218P, Sarkhej - Bavla Highway, Matoda - Sanand, Ahmedabad, from May 1 to May 12, 2023.

This warning letter summarizes significant violations of Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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 June 05, 2023 response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

**1. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).**

Your Quality Assurance (QA) and production departments failed to provide adequate oversight and ensure the reliability of data related to the quality of finished drug products manufactured at your facility. Since 2021, visual inspectors manipulated particle and other defect counts on manual visual inspection records in many instances, in order to keep the finished product batches within rejection limits. More specifically, the investigation found that operators manipulated the defect quantities "to keep the category wise rejections within limits to avoid a deviation and investigation."

In addition, multiple operators manipulated the reported defects, including **(b)(4)** attributes and particle counts, on manual visual inspection records to have identical numbers. This practice was repeatedly performed by at least nine different manual visual inspectors on trays of **(b)(4)**. The records, filled out by multiple operators, had an identical number of defects listed for all drug product defect categories.

Production managers including, but not limited to, front line supervisors failed to ensure reliable data, leading to significant data integrity deficiencies in your production records.

In addition, there was a lack of QA department review and oversight of visual inspection records, and your firm continued this egregious pattern of recording and altering defect counts. These findings indicated that your QA department was not exercising its basic responsibilities including, but not limited to, oversight and control over the adequacy and reliability of all CGMP data at your facility.

In your response, you acknowledge the discrepancies found in the visual inspection records and identify the contributing factors to these deviations as "inadequate data management processes, inadequate training and procedures, and inadequate quality oversight of the visual inspection operation." You state that "all the visual inspectors in this area have been disqualified" and "operators have been moved to the secondary packaging area and are not participating in GMP activities."

In addition, you also commit to working with a qualified consultant to perform a "data governance and integrity audit" and to establish a remediation plan. You commit to perform an assessment to evaluate injectable products that are within shelf life and are on the market to identify similar discrepancies in the visual inspection records.

We acknowledge your voluntary recall of batches of drug products due to particle contamination identified in product retain samples.

Your response is inadequate because you have not conducted a comprehensive evaluation of other CGMP records in which data may have been reported inaccurately or otherwise manipulated by your employees. You do not provide a comprehensive corrective action and preventative action (CAPA) plan with a systematic approach to correct these oversight deficiencies. Furthermore, although you indicate

that you have performed training for inspectors, QA, and managers, you fail to adequately address the managers' failure to act on observed data integrity lapses. In particular, you lack a comprehensive review of the management of your operations, including but not limited to ineffective supervision and governance in your production department (i.e., encompassing frontline supervisors through top operations managers).

In response to this letter, provide:

- An explanation why disqualified visual inspectors relocated to secondary packaging operations were characterized as not being involved in CGMP activities. Secondary packaging functions in a production department are performed under good manufacturing practices.
- A comprehensive assessment and remediation plan to ensure your QA department is given the authority and resources to effectively function. The assessment should also include, but not be limited to:

o A determination of whether procedures used by your firm are robust and appropriate
o Provisions for QA oversight throughout your operations to evaluate adherence to appropriate practices
o A complete and final review of each batch and its related information before the QA disposition decision
o Oversight and approval of investigations and discharging of all other QA duties to ensure identity, strength, quality, and purity of all products

- Describe how top management supports QA and reliable operations, including but not limited to, timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain contemporaneous, attributable, legible, complete, original, and accurate (ALCOA) records throughout your operation.
- Describe your plans to prevent manipulation and enhance control of all CGMP records. Specifically, describe your reconciliation and integrity improvements for all CGMP records that may be in loose form or otherwise vulnerable to manipulation. Based on an independent review by a qualified consultant, provide a gap analysis and specific CAPA measures you will take to safeguard integrity of records (e.g., recording data in logbooks, pre-paginated documents, and validated electronic systems).
- Your corrective action and preventive action (CAPA) plan to implement routine, operations management oversight of facilities and equipment. This plan should include, at a minimum:

o Improved production management oversight that ensures prompt detection of equipment, facility, and process performance issues
o Timely upgrades to equipment and facilities
o Adherence to appropriate preventive maintenance schedules
o Effective execution of repairs
o Allocation of appropriate resources, staffing, and competencies

o Appropriately qualified production supervisors and managers
o Improved systems for ongoing management review
o A provision(s) that appropriate actions are taken throughout the company network
o A thorough evaluation and risk assessment that addresses the suitability of your equipment for its intended use. Include an evaluation whether equipment is of appropriate design and your ongoing control and maintenance program is effective.

**2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).**

You failed to initiate or conduct adequate investigations into significant deviations in your aseptic processing manufacturing operations. You lacked investigations into visual inspection failures and non-viable particulates (NVP) exceeding your action levels. When investigations were conducted, they were often insufficient and lacked scientifically supported root cause(s).

A. Several investigations were opened due to batches that failed visual inspection rejection rate limits. These investigations were closed without identifying the particles or their sources. There was no characterization of the particulates found in the batch to determine if they were intrinsic, extrinsic, or inherent to the product.

For example, a deviation investigation was initiated for an **(b)(4)** injection batch intended for the European market, filled on the same aseptic processing line as that used to produce **(b)(4)** batches intended for the U.S. market. The batch exceeded the total rejection limit and the individual limits for white particles and glass particles. The investigation did not isolate or identify the white particles. In addition, there was no documented breakage of vials in the filling batch record. You closed the investigation without identifying the root cause or identifying the source of the white or glass particles.

In your response, you acknowledge your deviation investigation failed to characterize the particulates when a batch failed to meet established limits. You commit to revise procedures for manual inspections of filled and sealed vials, to perform particle characterization, and to identify sources of particles during investigations.

Your response is inadequate. Although you commit to perform particle characterization to identify the source of particulates during investigations, you do not commit to ensure appropriate definition and categorization of observed intrinsic and extrinsic particulates, and to fully evaluate visible particulate contamination.

It is important that any visible particulate contamination is appropriately evaluated and investigated. Visible particulates in injectable products should be avoided through appropriate preventive measures built into your design and production controls. When categorizing any visible particles, extrinsic or foreign matter should receive special attention, as it may indicate possible microbial contamination. Extrinsic or foreign particulate contamination should occur very infrequently, and be thoroughly investigated and appropriate CAPA implemented.

B. During aseptic filling, non-viable particle (NVP) count limits were exceeded in ISO 5 aseptic processing areas and no investigations were conducted because these excursions did not persist for more than **(b)(4)**, as stated in your procedure.

You lacked an adequate system for handling NVP counts exceeding your action levels of NMT **(b)(4)** particles ≥ 0.5 µm/ft$^3$ during aseptic processing operations. Line **(b)(4)** frequently failed to meet these ISO 5 limits. You routinely failed to investigate these high particulate levels in the ISO 5 aseptic processing operation.

For example, while manufacturing **(b)(4)** injection, a **(b)(4)** product produced for the U.S. market, the NVP probe at the filling station, the probe at the infeed **(b)(4)**, and the probe at the stoppering station failed the NVP count limit multiple times. In one instance, the filling machine automatically stopped as a result of these NVP alarms. There was no procedural requirement to clear any open product containers present at the time of the excursion. Your firm determined that no investigation would be done because the ISO 5 alarms did not individually persist for **(b)(4)**.

Excessive particulates in the ISO 5 environment can lead to non-viable or biological contamination of sterile drug products.

In your response, you state for NVP count excursions, removal of open containers will be added to the relevant SOP(s) to address this observation.

Your response is inadequate. There is no commitment to address the inappropriate **(b)(4)** timeframe to initiate a NVP deviation. The use of any timeframe-based criteria to initiate a NVP deviation is unacceptable. Any excursion or result outside of the classification limits should be investigated, and the intensity of those investigations should be consistent with the magnitude or frequency of the excursions. You should also trend data to identify and assess hazards and implement effective CAPA. In addition, you do not commit to perform a retrospective review of all batches with NVP levels outside the ISO 5 limits, including individual occurrences, as well as instances in which alarms occurred or the machine stopped during aseptic processing.

In response to this letter, provide:

- 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 oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
- An independent, retrospective evaluation of all ISO 5 NVP deviations, root causes, and a relevant CAPA plan.

**3. Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess (21 CFR 211.100 (a)).**

Your personnel qualification for the visual inspection of injectable products is deficient.

A. Your firm failed to provide adequate challenge test set vials to qualify your operators to perform the visual inspection of your drug products. The challenge test kit used to qualify manual visual inspectors was created using good and rejected vials from a previous batch, with unknown sizes of particles present in the vials. Additionally, a **(b)(4)** µm **(b)(4)** particle was added to the challenge kit but it is not representative of the types of particles found in your operation. You lacked assurance the test kit with unknown particle sizes can adequately assess if your inspectors have the competencies required to identify the particles that may be present in the vials. In addition, quality unit personnel have not maintained a defect library for training purposes or reference.

In your response, you commit to create a new visual inspection kit with known sizes of certified particle defects and revise procedures for kit preparation (e.g., to include particles with known particle sizes) and the inclusion of a reference defect library.

Your response is inadequate. You do not state how including the **(b)(4)** particle to your qualification kit is representative of your process to qualify visual inspectors.

B. Your firm failed to adequately validate the manufacturing process for **(b)(4)** mg **(b)(4)** tablets. Specifically, your process validation lacked inter-batch and intra-batch evaluation of **(b)(4)**, and process times for the **(b)(4)**. During production, **(b)(4)** processing times, **(b)(4)**, and **(b)(4)** were left to operators' discretion and variation of parameters were observed between batches.

In addition, you lacked scientific justification for the sample sizes collected at the **(b)(4)** operations to analyze for percent **(b)(4)**, dissolution, and appearance. Your firm has initiated deviations for OOS results of percent **(b)(4)**, and rough surfaces were also observed during **(b)(4)** of **(b)(4)**mg **(b)(4)** tablets. The process validation study, and commercial manufacturing data, did not provide sufficient assurance of that process consistency is maintained throughout production batch operations.

In your response, you acknowledge there is a lack of evaluation of inter- and intra-batch variability and insufficient guidance to the operators regarding process controls. You commit to performing an impact assessment on the **(b)(4)** on **(b)(4)** mg **(b)(4)** tablets **(b)(4)** and other drug products containing a **(b)(4)**. You also commit to revise your process validation procedures to ensure adequate samples are collected and performing statistical evaluations to understand the inter- and intra- batch variability with existing process validations. We acknowledge your firm's commitment to perform process validation for the **(b)(4)** stage of **(b)(4)** mg **(b)(4)** tablets.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established. Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

In response to this letter, provide:

- Provide a comprehensive, independent assessment of your validation program for ensuring an ongoing state of control throughout the product lifecycle, including the following elements:

o A description of the overall program (e.g., lifecycle process validation phases; equipment and facility qualification).

o A detailed description of how you ensure a rigorous process performance qualification studies. Include specific quantitative approaches with intensified sampling plans to fully assess all significant process steps, and explain how these extensive levels of sampling characterize the intra-batch uniformity at these steps to provide a high level of assurance that supports a decision on readiness for marketing.

o Vigilant ongoing monitoring of process performance and product quality throughout the lifecycle, with emphasis on:

 Mechanisms to ensure ongoing attention to both intra-batch and inter-batch variation

 Appropriate sampling methods and frequency throughout processing to ensure detection of process control lapses

 Scrutiny of raw material variability from suppliers

 Quality signals from both internal data and customers

 How your quality system integrates this ongoing knowledge of signals from process performance and product quality monitoring to identify areas of variation that need improvement.

o Based on this assessment, provide a CAPA to address any deficiencies in your process validation program.

- Improved in-process testing and monitoring to enhance detection of variation during production of each batch (including for both individual and average test limits). Include remediated in-process quality standards, including but not limited to enhanced sampling, that will more robustly monitor upstream process control. Describe how the improvements will ensure early detection of process variation and manufacturing defects, and prevent consumer exposure to substandard quality drug products.

**4. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113 (b)).**

A. Your procedures did not include a requirement for smoke studies to be performed in dynamic conditions in classified critical areas. There have been no smoke studies to determine whether the "**(b)(4)** LAF [laminar air flow]" can provide appropriate unidirectional air during dynamic activities, such as loading of the **(b)(4)** into the **(b)(4)** restricted access barrier systems (**(b)(4)**RABS). The mobile LAF was not evaluated during the smoke studies under dynamic conditions. For example, the operator removes the **(b)(4)** tub from the mobile LAF and carries them under the "**(b)(4)** LAF" (which is classified as an ISO 7 area) and then into the **(b)(4)**RABS.

Thorough smoke studies are essential to evaluate and qualify your aseptic processing operations and ensure appropriate implementation of needed design remediations.

In your response, you indicate your procedures were revised to include instructions for conducting smoke studies under dynamic conditions. You state you have now performed smoke studies under dynamic conditions for the **(b)(4)** tub loading process including the mobile LAF and "**(b)(4)** LAF." You commit to an assessment for all filling lines of parenteral drug products to evaluate execution of smoke studies in static and dynamic conditions.

Your response is inadequate. You do not provide the smoke study video and report evaluating unidirectional airflow patterns under dynamic conditions for the **(b)(4)** tub loading process, including mobile LAF and "**(b)(4)** LAF."

B. The qualification of the **(b)(4)** cycle of the **(b)(4)** equipped with transport ports failed to ensure adequate decontamination and worst-case locations in the **(b)(4)** used in manufacturing. Specifically, the **(b)(4)** transport port **(b)(4)** used to transport components to the **(b)(4)** was not assessed with biological indicators at the **(b)(4)** of the **(b)(4)**. In addition, the investigator observed an overlap and fold in the **(b)(4)** of the **(b)(4)** near the area where the **(b)(4)** attaches to the **(b)(4)** for which the qualification failed to address if this area can be reproducibly decontaminated by **(b)(4)**.

In your response, you acknowledge the observation that chemical and biological indicators were not placed at the **(b)(4)** of the **(b)(4)** transfer port and **(b)(4)** for **(b)(4)**. We note a requalification was performed on the **(b)(4)** cited during the inspection and a report was provided. You commit to evaluating all **(b)(4)** and **(b)(4)** for appropriate sample locations. You commit to reviewing the qualification protocols and reports for all remaining **(b)(4)** to ensure the **(b)(4)** are adequately sampled. As a result of this inspection, you conducted a retrospective review and discovered five other **(b)(4)** that did not have chemical and biological indicators at the **(b)(4)** of the **(b)(4)** for **(b)(4)**-decontamination.

As acknowledged in your response, further evaluations are needed to identify and assess the potential weak spots in your **(b)(4)** decontamination process. Your strategy appears to emphasize use of chemical indicators. However, biological indicators are essential to any evaluation to identify and evaluate locations that may lack assurance of sufficient **(b)(4)** exposure.

In response to this letter, provide:

- Comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:

o All human interactions within the ISO 5 area
o Equipment placement and ergonomics
o Air quality in the ISO 5 area and surrounding room
o Facility layout
o Personnel Flows and Material Flows (throughout all rooms used to conduct and support sterile operations)

- A detailed remediation plan with timelines to address the findings of the contamination hazards risk assessment. Describe specific tangible improvements to be made to aseptic processing operation design and control.

**Data Integrity Remediation**

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers

We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include these elements:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A commitment to have a qualified consultant conduct extensive annual audits, for at least two years, to assist in evaluating CAPA effectiveness after you have executed your data integrity remediation protocol.
- Inform FDA if you will be hiring a Chief Integrity Officer who is fully empowered to maintain anonymity of employees who report data integrity concerns and with authority to investigate

potential breaches.

- A status report for any of the above activities already underway or completed.

**Repeat Observations at Facility**

In a previous inspection, including the inspection of July 22 to August 02, 2019, FDA cited similar CGMP observations. You proposed specific remediations for these observations in your responses. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

**Ineffective Quality System**

Significant findings in this letter demonstrate that your firm does not operate an effective quality system in accord with CGMP. In addition to the lack of effective production and laboratory operations oversight, we found your quality unit is not enabled to exercise proper authority and/or has insufficiently implemented its responsibilities. Executive management should immediately and comprehensively assess your company's global manufacturing operations to ensure that your systems, processes, and products conform to FDA requirements.

**Conclusion**

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

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.

FDA placed your firm on Import Alert 66-40 on November 14, 2023.

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

Failure to address any violations may also result in the FDA continuing to refuse admission of articles manufactured at, Intas Pharmaceuticals Limited, at Plot No. 457- 458 & 191/218P, Sarkhej - Bavla Highway, Matoda - Sanand, Ahmedabad, Gujarat, India 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).

We request you email Temeka Moore, Temeka.Moore@fda.hhs.gov, within five days of receipt of this letter to schedule a regulatory meeting.

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 violations 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 3003157498 and ATTN: Erika V. Butler.

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.