IDT Australia Ltd. 5/23/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter** 320-18-55
Return Receipt Requested

May 23, 2018

Dr. Graeme R. Kaufman
CEO, Acting, and Chairman of the Board of Directors
IDT Australia Ltd.
45 Wadhurst Drive
Boronia, Victoria, 3155
Australia

Dear Dr. Kaufman:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, IDT Australia Ltd. at 45 Wadhurst Drive, Boronia, from December 4 to 8, 2017.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) requirements for active pharmaceutical ingredients (API) and significant violations of CGMP regulations for finished pharmaceuticals, 21 CFR parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs 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 December 22, 2017, response in detail.

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

API Deviations

1. Failure to adequately investigate out-of-specification results and implement appropriate corrective actions.

Your firm rejected **(b)(4)** batch **(b)(4)** for assay failure on October 23, 2015. You opened an investigation the same day and subsequently closed the investigation a few months later on March 20, 2016. You determined the root cause of the failure to be **(b)(4)** from the **(b)(4)** in

March, 2016, but as of our December 2017 inspection, more than two years after the failure, you had not implemented a corrective action to address the root cause you identified. In the interim, your quality unit released at least **(b)(4)** batches of finished **(b)(4)** API.

Your response stated that you will reopen the investigation into this failure. You also stated that the **(b)(4)** subsequently released batches met specifications, and analytical trends were consistent with previously manufactured batches. However, you failed to include data supporting this statement.

In your response to this letter, provide a detailed summary of your investigations. Assess the risk of your decision to manufacture and release an additional **(b)(4)** batches even though you had not implemented any corrective action to resolve the problem your own investigation identified as the root cause for batch **(b)(4)**'s assay failure. Include any additional sampling and testing you performed between October 25, 2015, and December 2017 to support your release decisions.

In addition, provide an action plan with timeframes for a global assessment of your corrective actions performed over the past three years. Ensure this assessment identifies all investigations and the corrective actions and preventive actions that you initiated in response to your investigation findings, and that it shows how you determined that you expanded your investigations to other potentially affected batches.

2. Failure of your quality unit to ensure that critical deviations are investigated and resolved.

Your quality unit released **(b)(4)** batch **(b)(4)** on April 30, 2015, despite a total aerobic count of greater than **(b)(4)** colony forming units/gram (CFU/g). The specification is less than **(b)(4)** CFU/g. You sold this batch of **(b)(4)** to a firm that manufactures sterile finished drug products used to treat **(b)(4)** patients in the United States.

When you observed the failing result on April 15, 2015, you initiated an out-of-specification (OOS) investigation. When you closed the investigation on April 24, 2015, you concluded, without adequate evidence, that a biohazard cabinet was a potential source of contamination and released the batch.

Your response stated that you revised your SOP for handling OOS results to clarify resampling and retesting. However, the root cause you identified lacked scientific justification, and you did not provide evidence that supported your release of batch **(b)(4)**.

In your response to this letter, assess the risks of your decision to release batch **(b)(4)** despite the microbiological test failure and despite the inadequacy of your investigation into the cause of the failure. Provide your plans for addressing product quality and patient safety risks for any drugs still in distribution, including potential recalls or market withdrawals. Provide an updated OOS procedure that requires the speciation of microbes found as a result of any microbial analysis.

Finished Drug Violations

1. You firm failed to establish and follow adequate required laboratory control mechanisms, including any changes made to them which were drafted by the appropriate organizational unit and reviewed and approved by the quality control unit (21 CFR 211.160(b)).

Your firm reported multiple microbial test results for the **(b)(4)** system used to **(b)(4)** as ">80 CFU" when the actual number of CFU was too numerous to count. Days after you obtained these results, you resampled and diluted the new sample until colonies could be counted. If the diluted sample was within acceptable limits, you disregarded the original result. Your **(b)(4)** sample collection and test methods could have masked failing microbial results and your **(b)(4)** system may not have been suitable to **(b)(4)**.

Your response stated that you will modify the sample size to ensure a proper count at each sampling event. Your response is inadequate. You failed to evaluate how your practice of disregarding original results may have affected the reliability of data about your **(b)(4)**system.

In your response to this letter, provide the scientific rationale for your modified **(b)(4)** sample collection and test methods. In addition, assess the product quality and safety risks of using potentially contaminated **(b)(4)**.

2. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards. (21 CFR 211.194(a)).

Our review of your laboratory records revealed that you failed to report non-conforming test results on multiple occasions in multiple parts of your operations.

Analytical Testing
During testing of **(b)(4)** exhibit batch **(b)(4)** in March 2016, three consecutive identity test failures occurred. The fourth test passed and you reported this conforming result. You did not include the three failures in the data package submitted to the quality unit for review or your application submission for this product. You did not conduct an investigation into the non-conforming results. At the time of the inspection, you were unaware that your analysts had not reported the failing results to your quality unit for review.

Your response stated that you will revise your procedures and train your analysts to assure that all data is reported. Your response is inadequate. You failed to investigate the nonconforming identity test results. You also failed to evaluate other **(b)(4)** test records to identify other unreported nonconformances. You also failed to determine whether there were unreported nonconformances for commercial products that you released for distribution.

Microbial Testing
During microbial testing of your cleaning water, results for samples collected on November 23, November 24, and December 1, 2017, were not reported before the **(b)(4)** plates were destroyed. Your firm stated that the plates were destroyed because the incubator had failing temperature mapping results. Your investigation into the failing temperature mapping results stated the plate results were passing but no individual plate counts were recorded.

In your response, you stated that you have reviewed all 2017 results and found them to be complete. Your response is inadequate. You did not explain your rationale for limiting your review to a single year, nor did you include sufficient details to support your conclusion that 2017 records were complete. You also have not evaluated the effects of your incomplete microbial test records on the quality and safety of your products.

3. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-

process materials, packaging materials, labeling, and drug products, and the authority to review production records to assure that no errors have occurred, or if errors have occurred, that they have been fully investigated. (21 CFR 211.22(a)).

Your quality unit failed to review high performance liquid chromatography (HPLC) assay data for release and stability of your **(b)(4)** product.

During review of your HPLC's electronic data, we discovered at least 100 "test" injections. Your analytical procedures and methods do not discuss "test" injections. Your laboratory supervisors did not review these injections prior to submitting the data packages for approval. You informed our investigator that, per procedure, your laboratory supervisors and quality unit only review the chromatograms printed and submitted to them by the analysts. Because your analysts did not print the chromatographic results of "test" injections, neither laboratory supervisors nor your quality unit reviewed these injections. Your procedure did not require review of the underlying electronic records or data by either laboratory supervisors or the quality unit to ensure their accuracy or completeness. Accordingly, your quality unit relied on incomplete data for batch disposition decisions. Your quality unit failed to ensure the adequacy of procedures for assessing the quality of your drug products.

We observed other examples of your quality unit's failure provide adequate data management and review procedures, including the following:

- Your analysts performed manual integration of chromatograms without instructions that describe when manual integration is permitted and how it is to be done.
- You did not have procedures for reviewing audit trails or electronic data for the Fourier-transform infrared spectroscopy or ultraviolet systems.

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. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

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 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 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:

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

Conclusion

Deviations and violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations and deviations, for determining the causes, for preventing their recurrence, and for preventing other violations and 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) and 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.

Until you correct all deviations and violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations and violations may also result in FDA refusing admission of articles manufactured at IDT Australia Ltd., 45 Wadhurst Drive, Boronia, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of 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 that you contact Kent Bui by email at Kent.Bui@fda.hhs.gov, within five working days of receipt of this letter to schedule a regulatory meeting.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and deviations and to prevent their recurrence. 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 or mail your reply to:

Karen D'Orazio
Consumer Safety Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3000219354.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research