Inopak Ltd 2/21/19

Division of Pharmaceutical Quality Operations I
10 Waterview Blvd, 3rd FL
Parsippany, NJ 07054
Telephone: (973) 331-4900
Fax: (973) 331-4969

WARNING LETTER
CMS # 569465

February 21, 2019

VIA UPS OVERNIGHT
Mr. John L. Polite
Chief Executive Officer
Inopak Ltd.
24 Executive Parkway
Ringwood, NJ 07456

Dear Mr. Polite:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Inopak Ltd. (FEI: 1000122232) at 24 Executive Parkway, Ringwood, New Jersey, from July 11 to 20, 2018.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 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 August 8, 2018, response 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 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 manufacture drug products such as antiseptic hand wash and antiseptic foam marketed for use in hospital settings and "before contact with a person under medical care or treatment." FDA tested your antibacterial foaming hand wash, Inofoam, batch #7302, collected in February 2018 and notified you that it failed microbial limit testing. As a result, you retested batch #7302 and confirmed that the drug product failed microbial limit testing. You then recalled this lot prior to FDA inspection.

During the inspection you informed us that you believed your failing retest results were invalid due to testing error, and because you had recalled the material you planned "no further action."

Your response is inadequate because you did not propose any corrective actions and preventive actions (CAPA) to address your failure to conduct and document thorough investigations into out-of- specification (OOS) test results. In addition, you did not extend the OOS investigation to other batches.

In response to this letter, provide:

- A comprehensive independent assessment of your overall system for investigating deviations, atypical events, complaints, OOS results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness.
- A retrospective assessment of all invalidated OOS test results including microbiological testing associated with each drug product you produce for the U.S. market, and all lots within expiry. Assess whether the scientific justification and evidence for each invalidated OOS result was conclusive. For investigations that establish laboratory root cause, ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For each lot that does not meet its purported quality standards, provide your plan to take appropriate action (e.g., notifying customers or product recalls).
- A review and remediation of your system for investigating OOS results. Provide a CAPA plan to improve OOS handling. Your CAPA plan should ensure that your revised OOS investigation procedures include:
    - Enhanced quality unit oversight of laboratory investigations
    - Identification of adverse laboratory control trends
    - Resolution of causes of laboratory variation
    - Investigations of potential manufacturing causes when a laboratory cause cannot be conclusively identified

2. Your firm failed to assure that the drug product bore an expiration date that was supported by appropriate stability testing (211.137(a)).

During the inspection, you were unable to provide stability data to support the labelled three-year expiration dates for your Inofoam, Derma Gel, and Saniguard drug products. Without stability data, you cannot assure the quality of your products throughout their labeled shelf lives.

Your response stated that you were "exploring options" and would update FDA of your plans by October 2018.

Your response is inadequate because you have not provided an interim plan or a commitment to conduct stability studies.

In response to this letter, provide:

- Your plan for conducting stability studies, including a procedure describing your stability program, stability-indicating methods, and stability studies to support each drug product in its container- closure system before distribution is permitted.
- A retrospective assessment of the stability of batches produced for the U.S. market within expiry. Include a list of all batches, the date each was released, and the date you conducted analysis. Provide the type of testing conducted for each batch and the test results. Indicate the actions you will take if you find that any of the batches you released were OOS for strength, identity, or any other attribute.

3. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit (21 CFR 211.22(d)).

You have not established a written procedure for annual product review, nor have you completed annual product reviews of drugs manufactured since 2016. Manufacturers are required to conduct an annual evaluation of quality standards for each drug

product. Failure to perform annual product review of each of your drug products compromises your ability to evaluate the adequacy of controls over manufacturing and adherence to appropriate quality standards for each of your drug products.

Your response stated that you will create a new procedure for annual product review, and that you have sufficient details from August 2017 onwards to conduct annual product reviews.

Your response is inadequate because you did not provide a timeline for completing your annual product reviews, or for evaluating information available for drugs in distribution manufactured before August 2017.

In response to this letter, list all the quality unit procedures that you have created and/or revised. Also provide your timeline to perform annual product reviews for drug products manufactured in 2016, 2017, and 2018.

See FDA's guidance document, *Quality Systems Approach to Pharmaceutical CGMP Regulations*, for help implementing modern quality systems and risk management approaches to meet the requirements of CGMP regulations (21 CFR, parts 210 and 211), at **https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM07 (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070337.pdf)0337.pdf. (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070337.pdf)**

4. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a))

You have not validated the processes you use to manufacture your drug products. You have not demonstrated that your manufacturing process is capable of consistently producing drugs of uniform character and quality.

Your response stated that you will validate your manufacturing process for all your drug products once you have completed the validation of your water system.

Your response is inadequate because it failed to evaluate the impact of manufacturing your products using unvalidated processes and procedures, and you provided no interim corrective actions.

In response to this letter:

- Provide the protocols for your process validation activities. Also describe how you will monitor sources of variability in your operation throughout the drug lifecycle to minimize batch variation and assure consistent product quality.
- Assess all distributed drug products within expiry. Provide your plans to address product quality and patient safety risks for any drugs still in distribution.
- Commit to control and monitor of your purified water system such that it consistently produces water that meets the purified water USP monograph specifications and appropriate microbial limits.

Repeat observations at facility
In a previous inspection, dated March 8 to 24, 2017, FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response. These repeated failures demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate.

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

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction.
Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

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 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 response to **orapharm1_responses@fda.hhs.gov. Your written notification should refer to the Warning Letter Number above (569465). (mailto:orapharm1_responses@fda.hhs.gov)**

If you have any questions, contact Compliance Officer Barbara Wilimczyk-Macri at **barbara.wilimczyk@fda.hhs.gov or 973-331-4951. (mailto:barbara.wilimczyk@fda.hhs.gov)**

Sincerely,
/S/
Diana Amador-Toro
Program Division Director
Office of Pharmaceutical Quality Operations - Division I

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