U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via E-mail
Return Receipt Requested

May 4, 2023

Mr. Dilip Shanghvi
Managing Director
Sun Pharmaceutical Industries Limited
Sun House, 201 B/1
Western Express Highway
Goregaon (East), Mumbai
400063, India

Re: *United States v. Ranbaxy Laboratories, Ltd., et al.* (Civ. No. JMF-12-250 (D. Md.))

CONSENT DECREE CORRESPONDENCE / NON-COMPLIANCE LETTER

Dear Mr. Shanghvi:

From August 3 to 12, 2022, the U.S. Food and Drug Administration (FDA) inspected the drug manufacturing facility located at Unit 1 Plot A-41, Sez Industrial Area, Phase Viii A, Mohali, Punjab, 160071 India (FEI 3002807979) (hereafter, "Mohali facility"), owned by Sun Pharmaceutical Industries Ltd. ("Sun," "you," "your firm," or "the firm"), pursuant to the Consent Decree for Permanent Injunction ("Decree") entered in the above-referenced case on January 26, 2012.[1] The purpose of the inspection was to assess your firm's compliance with the Decree, the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. § 301 *et seq.*, and FDA regulations.

During this inspection, FDA investigators observed and documented significant violations of the Act and FDA's regulations, including significant violations of the current good manufacturing practice ("CGMP") requirements for drug products. These observations were documented on a Form FDA 483 issued to Sunil Yadav, Site Head, at the close of the inspection.

Paragraph XXVIII.F of the Decree states:

> If, at any time after entry of this Decree, FDA determines, based on the results of an inspection . . . that Defendants have failed to comply with the law or this Decree or that additional corrective actions are necessary to

[1] A copy of the Consent Decree is attached to this letter at Exhibit A. As you know, by letter dated September 12, 2013, FDA issued an order under paragraph XXIX of the Decree, adding the Mohali facility as a Covered Facility under the Decree. *See* Exhibit B. On March 13, 2017, FDA authorized Sun to resume drug manufacturing operations at the Mohali facility; however, the Mohali facility remains a Covered Facility under the Decree. *See* Exhibit C.

> achieve compliance with the law or this Decree with respect to any of . . . the Covered Facilities, . . . FDA may, as and when it deems necessary, notify Defendants in writing of the noncompliance and order Defendants to take appropriate corrective action including, but not limited to, ordering Defendants to immediately take one or more of the following actions: . . . any other corrective action(s) as FDA, in its discretion, deems necessary to bring Defendants into compliance with the law and this Decree or to protect the public health.

As set forth in detail below, FDA has determined that, based on the August 2022 inspection and your subsequent correspondence, your firm is not operating in compliance with the Act, applicable regulations, and the Decree at the Mohali facility. For those reasons, FDA is invoking its authority under Paragraph XXVIII of the Decree to direct Sun to take certain actions to ensure that the Mohali facility and the controls used to manufacture drug products there are established, operated, and administered in conformity with the CGMP requirements.

I. CONSENT DECREE VIOLATIONS

At the close of the inspection, FDA issued a six-item Form FDA 483, dated August 12, 2022. The most significant observations made during the inspection are as follows:

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).

Your firm's investigations into unexplained discrepancies were inadequate. Your quality unit ("QU") failed to thoroughly investigate all batches or employees associated with unexplained discrepancies. For example:

- Investigation 571594 was conducted on Clonazepam orally disintegrating tablet ("ODT") batches AA84106, AA84107, and AA97356. The investigation found evidence of cross-contamination with Clozapine, the API in a drug product previously manufactured on shared equipment. Detectable levels of Clozapine API were also found in five other batches of Clonazepam ODT. Your use of maximum allowable carry over ("MACO") calculations to establish acceptable levels of cross-contamination in the product is inadequate, and your investigation failed to identify the source of the contamination. You also failed to evaluate the effectiveness of the test methods used in your cleaning validation.

- On January 20, 2020, your Chief Data Reliability Officer ("CDRO") received Disclosure 2020-01 for two backdating incidents. Your CDRO interviewed the employees accused of backdating, assessed the effect of the two incidents on the drug product, conducted a risk assessment onsite, and initiated training. Your investigation was inadequate because you did not interview multiple quality assurance reviewers and did not fully investigate the extent of previous backdating incidents. Additionally, Disclosure 2020-03, also received by your CDRO, addressed a similar backdating incident over the same timeframe and was not thoroughly investigated.

2. Your firm failed to document at the time of performance required laboratory control mechanisms and to record and justify any deviations from required laboratory control mechanisms (21 CFR 211.160(a)).

You failed to provide sufficient evidence to demonstrate that water samples were collected on multiple occasions at the times and locations documented by your quality control employee. Your procedure SOP000494, *Monitoring of Raw Water, Potable Water, Hot Potable Water, Purified Water and Process Steam Condensate*, states that water sampling shall be performed at the sampling point and documented at the time of sampling. Numerous purified water sample collections were documented at a specific time and purified water sampling port, but, according to badge access records, the employee responsible for the water sampling was located in a different building during the same time. You have not adequately identified the scope or root cause of this incident.

3. Your firm failed to establish adequate 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, and your firm's quality control unit did not review and approve those procedures, including any changes (21 CFR 211.100(a)).

You failed to adequately validate your drug product manufacturing process for ranolazine extended release ("ER") 500 mg and 1000 mg tablets. Your firm rejected 17 ranolazine ER finished tablet batches from 25 out-of-specification ("OOS") dissolution testing investigations between January 2020 to July 2022. Your firm continued to manufacture ranolazine ER tablets throughout 2021 through 2022, despite failing dissolution results that produced calculated process capability ("Cpk") values below your acceptable criteria of (b) (4) (desirable level greater than (b) (4) at the (b) (4) and (b) (4) timepoints. Your corrective action in September 2021, to increase (b) (4) at th (b) (4) stage, did not appear to increase Cpk values to a desirable level. Furthermore, ased (b) (4) on your (b) (4) value did not appear to be evaluated at the time of your change.

Your subsequent correspondence about the observations listed on the Form FDA 483, which FDA received on September 2, 2022, did not adequately address the deficiencies observed during the inspection. Specifically, your corrective actions and investigations into deviations failed to address the full scope and impact of these CGMP deficiencies, as well as the associated risks, to all batches.

II. CORRECTIVE ACTIONS

Due to your noncompliance with the FD&C Act and the Decree provisions applicable to the Mohali facility, FDA hereby orders you, pursuant to paragraph XXVIII of the Decree, to take the following corrective actions at the Mohali facility before you release any finished product batches for distribution into the United States.

You must immediately retain, at your expense, an independent person or persons (the "CGMP Expert"), as set forth in paragraph XVI.A.2 of the Decree, to inspect the Mohali facility to determine whether its methods, facilities, and controls are operated and administered in

conformity with CGMP requirements and to conduct batch certifications of drugs manufactured at the Mohali facility, as set forth below.

Batch Certification and Auditing Requirements

The CGMP Expert shall submit to FDA for approval a written batch certification protocol ("certification protocol") applicable to all drugs Sun manufactures and tests at the Mohali facility for distribution into the United States and shall not commence batch certification until FDA has approved the certification protocol in writing. In no circumstance shall FDA's silence be construed as a substitute for written notification.

Once FDA has approved the certification protocol, the CGMP Expert shall immediately begin witnessing the manufacture and testing of all drugs at the Mohali facility intended for distribution to the United States.

You shall obtain from the CGMP Expert a written certification for each of the drugs for which he or she has witnessed the manufacture and examined the manufacturing and control records, and the raw data associated with such records for each drug, in accordance with the FDA-approved certification protocol, and determined that each batch has the identity, strength, quality, and purity it purports and is represented to possess. You shall submit such certifications, signed by the CGMP Expert and a responsible company employee who has also reviewed the respective batch-specific manufacturing records, to FDA prior to releasing the respective finished product batches for distribution to the United States.

For all drugs, this third-party batch certification shall be performed in accordance with the FDA-approved certification protocol for a period of no less than twelve months from the start of the initial batch.

If the CGMP Expert determines that any particular batch of drugs failed to have the identity, strength, quality, and purity it purports and is represented to possess, the CGMP Expert shall provide to FDA a written explanation for the batch failure and all relevant supporting data within 30 days of the failure. No drug from such batch may be introduced into the United States.

If an OOS result is obtained, Sun shall conduct an investigation and the CGMP Expert shall review the investigation results. If Sun determines that the batch may be distributed to the United States, it must provide its investigation and the CGMP Expert's review to the Agency. Additional information may be requested by the Agency regarding the final disposition of the batch.

After the CGMP Expert has completed at least twelve months of batch certifications, the CGMP Expert shall perform the functions of the "CGMP Auditor" as set forth in paragraph XXIII of the Decree. The procedures set forth in this letter shall continue until FDA is satisfied that the Mohali facility is operating in compliance with CGMP.

Independent Review Requirements

Within thirty (30) days after the CGMP Expert is retained, he or she shall also conduct an

independent, retrospective review of all drug product batches at or from the Mohali facility that have been offered for sale or commercially distributed in the United States. Within thirty (30) days after completing the review, the CGMP Expert shall provide a comprehensive report to FDA with a proposed timeline for addressing each of the following issues:

1. A comprehensive review and remediation plan for the OOS result investigation systems at the Mohali facility. The corrective action and preventive action (CAPA) plan should address, but not be limited to, the following:
   - Quality unit oversight of laboratory investigations
   - Identifying adverse laboratory control trends
   - Resolving causes of laboratory variation
   - Initiating thorough investigations regarding potential manufacturing causes whenever a laboratory cause cannot be conclusively identified
   - Adequately scoping each investigation and its CAPA
   - Revising OOS investigation procedures with these and other remediations

2. A comprehensive review of OOS results (including in-process and release or stability testing) for products, irrespective of whether the batch was ultimately distributed in the United States, for the 3 years prior to August 3, 2022, and a report summarizing the findings of the analysis, including the following for each OOS:
   - Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
   - For investigations that conclusively establish laboratory root cause, provide a rationale to ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
   - For all OOS results found by the review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment, facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Provide a summary of potential manufacturing root causes for each investigation and any manufacturing operation improvements.

3. A procedure for water system monitoring that specifies routine microbial testing of water to ensure its acceptability for use in each batch of drug products produced at the Mohali facility.

4. A procedure governing the program for ongoing control, maintenance, sampling integrity, and monitoring that ensures the system consistently produces water that meets Purified Water, USP monograph specifications and appropriate microbial limits. This procedure should include steps to ensure all data documenting employee activities are accurate and reliable.

5. An assessment of each drug product process to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that the production processes will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in monitoring and testing systems, quality of input materials, and reliability of each manufacturing process step and control.

6. Timelines for completing additional process performance qualification studies on remediated processes for marketed drug products for which a state of control has not been adequately established.

7. A comprehensive process capability assessment of manufacturing processes, with special emphasis on the capability of each major operational stage including, but not limited to, granulation and blending.

8. A remediation program that provides for an ongoing statistical assessment of processing line performance to vigilantly monitor state of control. Specifically, include the program for statistical process control of each batch of drug products manufactured at the Mohali facility to monitor intra-batch and inter-batch variation, and promptly detect a drift in process control.

9. 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 attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation.

III. PROVIDE COPY OF THIS CORRESPONDENCE TO ASSOCIATED PERSONS

Additionally, under paragraph XXVIII of the Decree, FDA is ordering you to do the following: within fifteen (15) days after your receive this correspondence, provide a copy of this correspondence, by personal service, personal delivery via electronic mail with acknowledgment of receipt, return receipt email, or certified mail (restricted delivery, return receipt requested), to each of your Associated Persons, as that term is defined in paragraph XXXV of the Decree; and within thirty (30) days after you receive this correspondence, provide to FDA an affidavit of compliance, signed by a person with personal knowledge of the facts, stating the fact and manner of compliance with the provisions of this paragraph and identifying the names, addresses, and positions of all persons who have received a copy of this correspondence.

This letter will be posted on FDA's web page with appropriate redactions. Once FDA has posted this letter on its web page, the Agency requests that you include a link to the letter on your official web page to inform the public about the results of your most recent FDA inspection.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3002807979 and ATTN: Joseph Lambert, Pharm.D., Compliance Officer.

Sincerely,

Francis Godwin -S Digitally signed by Francis Godwin -S
Date: 2023.05.05 12:03:52 -04'00'

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