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Decoding FDA's Ranbaxy inspections

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WASHINGTON: Last week-end, numerous reports in the media emerged that attempted to interpret the findings of the U.S. Food and Drug Administration in its inspections of the manufacturing facilities of India-based generic pharmaceuticals giant Ranbaxy, located in Toansa, Punjab.

Many of these reports, including wire service accounts that were widely published, focussed on the FDA's Form 483 inspection finding that "Too Numerous To Count (TNTC)" flies were found in a sample storage room, and there was inadequate control over samples and non-adherence of procedures in sample analysis.

Yet, what is evident from a closer reading of the full Form 483, which *The Hindu* obtained via a Freedom of Information Act request from the FDA, is that the bulk of the report was, in fact, about what could be interpreted as deliberate falsification of data, rather than any involuntary slip-ups in adhering to current Good Manufacturing Practices (cGMP).

For example, 'Observation 1' on the first page of the report, said that the inspection, carried out during January 5-11, 2014, discovered that "finished API [Active Pharmaceutical Ingredient] analytical results found to be failing specifications or otherwise suspect are retested until acceptable results are obtained [and] failing or otherwise suspect results are not reported".

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In the same page, the FDA inspectors noted that this "practice of overwriting electronic raw data files for ongoing sample sequences until acceptable results are achieved," occurred so many times during the review of five months worth of data that the number of such cases of falsification "could not be quantified during our inspection due to the large amount of data."

The following four or five pages of the 11-page report comprise detailed examples of specific instances of data falsification, typically involving Ranbaxy personnel overwriting the results of various drug tests recorded electronically on an earlier date.

The second key observation made on page six of the inspectors' report was that "samples were not analysed according to established laboratory test method procedures," under which the FDA again found numerous results not reported, and a lack of written procedures and documentation of test results.

Additional observations made during the inspections include "Appropriate controls are not established over computerised systems," "records are not completed contemporaneously," the latter suggesting that Ranbaxy analysts and other personnel were "back-dating" testing records or log books.

Under the fifth observation made by the inspectors, that "Laboratory samples are not adequately controlled to prevent mix-ups," the report seemed to hint at deliberate attempts made to avoid detection of any drug or test quality issues.

The Food and Drug Administration report notes under this observation that despite the inspectors' request on a previous day for the Ranbaxy personnel to retain two vials in the "QC analytical laboratory, "Upon return to the laboratory... we found that these two vials had been discarded [and] during the course of our inspection the identity/fate of these... vials could not be determined."

The final three observations, bringing the total of what appear to be serious deviations from cGMP to eight, "the FDA inspectors discovered inadequate laboratory facilities, incomplete records on the maintenance of manufacturing equipment and inappropriately calibrated analytical instruments."

The latest action taken by the FDA to halt all imports into the U.S. from Ranbaxy's Toansa facility comes in the wake of the company being fined $500 million last May for seven felony charges relating to manufacturing fraud, to which the firm pled guilty.

While two Ranbaxy facilities, in Paonta Sahib, Himachal Pradesh and Dewas, Madhya Pradesh, had faced import restrictions and curtailment by the FDA prior to that settlement, a third facility, in Mohali, Punjab, was hit with a similar import alert last September when the FDA found tablets with embedded with a black fibre that could have been a hair from an employee's arm or tape fragments.

The founders of the firm, Malvinder and Shivinder Singh sold Ranbaxy to Japanese Daiichi-Sankyo in 2008 for about $4.6 billion, though the FDA's investigation suggests that the company acknowledged violations of cGMP regulations with regard to a U.S.-distributed drug Sotret, in 2003.

The subsequent case against the firm brought by the U.S. Department of Justice was built on a large trove of evidence collected by whistleblower and former Ranbaxy Director Dinesh Thakur.

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