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Warning letters and Indian pharma

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Greater emphasis on quality will allow India to participate more fully in existing global venues such as the International Council for Harmonisation (ICH) and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) – which will enable stronger collaboration and synergies among regulators. Quality is good for economic development, the market, and most importantly, patients and consumers everywhere.

On April 28, 2017, Vikshara Trading & Investments Ltd, from Gujarat has received warning letter from US Food and Drugs Administration (FDA). The US FDA during its inspection of its facility at Anup Engineering, Odhav Road, Ahmedabad on October 18, 2016, noted that its investigator documented that the firm delayed and limited an FDA inspection.

The US FDA noted that under the FD&C Act, as amended by the Food and Drug Administration and Innovation Act (FDASIA), section 707, 21 U.S.C. 351(j), the drugs are adulterated in that they have been manufactured, processed, packed, or held in an establishment where the owner or operator has delayed and/or limited an inspection.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. Because of the methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, the company's 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).

The US FDA has concluded that the violations cited in this letter are not intended as an all-inclusive list. The company is responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations. The FDA placed the firm on Import Alert 66-40 on February 8, 2017, and on Import Alert 99-32 on February 9, 2017.

The FDA further observed that until the company corrects all violations completely and it confirms their compliance with CGMP, FDA may withhold approval of any new applications or supplements listing the firm as a drug manufacturer. Failure to correct these violations may also result in FDA continuing to refuse admission of articles into the United States.

Similarly on April 13, 2017 Divi's Laboratories, over Rs 4100 crore company from Andhra Pradesh focused on developing new processes for the production of Active Pharma Ingredients (APIs) and Intermediates received warning letter from US FDA for its Unit II in located at Chippada village in Visakhapatnam district.

The US FDA team has visited the site of company for inspection from November 29 to December 6, 2016. During that inspection, its investigators documented that the firm limited and/or refused an FDA inspection. The investigators observed that the software the company has used to conduct high performance liquid chromatography (HPLC) analyses of API for

unknown impurities is configured to permit extensive use of the “inhibit integration” function without scientific justification.

Responding to these US FDA concerns, the company in its December 24, 2016 response to the FDA stated that it has made several corrective actions, including updating its procedure Peak Integration Techniques for Chromatography to include controls on the use of inhibit integration events. However, the response is inadequate in that it did not provide specific corrective action or supportive documentation for each drug’s chromatographic processing parameters, including API not cited on Form FDA 483. FDA noted that the firm has not shown how it will ensure that its test methods are appropriate to determine whether its API conform to established standards and specifications. Consequently, the summary data the firm provided does not demonstrate that previously released lots do not contain excessive levels of unknown impurities.

The FDA observed that if the firm is considering an action that is likely to lead to a disruption in the supply of drugs produced at its facility, FDA requested it to contact Center for Drug Evaluation and Research (CDER)’s Drug Shortages Staff, so that FDA can work with the firm on the most effective way to bring the firm’s operations into compliance with the law. It noted that contacting the Drug Shortages Staff allows the firm to meet any obligations the firm may have to report discontinuances or interruptions in the firm’s drug manufacture 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 the firm’s products. Meanwhile FDA placed the firm on Import Alert 66-40 and 99-32 on March 20, 2017.

Besides the above US FDA has issued as many as 87 warning letters to Indian companies since 2011. And 18 warning letters were issued by FDA during 2014 and 2015 each year. But this number has started to decline later from 14 in 2016 and 13 so far during this year.

Out of 87, in 18 cases the US FDA has issued closeout orders. In the last three years the number of companies receiving the closeout orders has increased. At the same time there is an increase in the number of companies receiving warning letters as well during this year. So far 13 companies got warning letters.

The FDA in its letter dated January 15, 2017 to Fleming Laboratories, a pharma company **in the business of manufacturing and supply of high quality generic Active Pharmaceutical Ingredients (APIs) to the global pharmaceutical industry observed that it has** completed an evaluation of the firm's corrective actions in response to its Warning Letter # GDUFA-14-016. Based on its evaluation, it appears that the company has addressed the violations contained in this Warning Letter. Future FDA inspections or regulatory activities will further assess the adequacy and sustainability of these corrections.

It may be recalled that the company has received warning letter on August 26, 2014 saying the company has failed to pay the appropriate facility fee as required by the Generic Drug User Fee Amendments of 2012 (GDUFA).

The FDA noted that the company’s facility at Shivampet Mandal Survey No. 270 on Kanukuna Road in Medal district, Andhra Pradesh is a drug manufacturing facility as defined under GDUFA. It was identified in a pending and/or approved Abbreviated New Drug Application (ANDA) on the dates for self-identification for fiscal year 2013 and fiscal year 2014, and on the dues dates for facility fees for fiscal year 2013 and fiscal year 2014. The facility has self-identified for 2013 and 2014 but, has not paid the 2014 facility fees as required by GDUFA. Therefore, all finished dosage forms of drugs or APIs, as well as drug containing an API, manufactured at the facility are misbranded.

Hence FDA has placed the facility on a publicly available GDUFA facility arrears list for failure to pay required fees in 2013 and 2014. As per GDUFA, failure to correct these violations promptly may result in regulatory action, including but not limited to seizure or injunction without further notice. Besides the facility may also be placed on import alert such that any drug the facility manufactures will be refused admission into the United States.

Similarly Sharp Global Limited, got the closeout order from FDA on February 21, 2017. The company received warning letter in October 15, 2014 from the authorities after their inspection of the manufacturing facility located at Sharp House, Plot No. 9, 1st Floor, Part 1, Sagar Centre, Gujranwala Town, New Delhi, on March 6, 7, and 10, 2014. In its warning letter, FDA observed that its investigator observed specific deviations during the inspection, including, but not limited to, the following: Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data; Failure to have appropriate controls for issuance of batch records; Failure to have appropriate documentation and record controls and Failure to validate non-compendial analytical test methods. Besides other observations, the inspection found that batch records related to non-US products were not completed at the time key operations were performed for batches that were subsequently distributed for use. The company has received positive note from the US regulatory after gap of over 30 months of responded to it by sending its action taken report.

According to Edelweiss report titled “cGMP Warning Letter resolution: How steep is the task?” “a deep dive into the statistics

of the US FDA inspections in past eight years and warning letters issued and resolved in recent years, paints a disturbing picture. Since GDUFA's implementation (Oct 2012), FDA inspections have doubled in India and China (20% versus 11% of total inspections earlier), which led to considerable increase in issuance of warning letters (55% versus 33% of total earlier). Warning letter resolutions have become longer and rarer ? only nine out of 108 warning letters have been sorted taking an average of ~500 days. Data for India and China is even bleaker with just one resolution out of the 64 warning letters issued in past 52 months. Cadila Healthcare's Moraiya unit (426 days) looks poised to be resolved soon post its recent re?audit that had no FDA observations. While data suggests that Sun Pharma's Halol unit (432 days) and Dr Reddy's (474 days) are closer to resolution timeframe, the concern is that the warning letters are not easy to resolve."

The report further says that since GDUFA, ~55% of the current Good Manufacturing Practice (cGMP) related warning letters issued by Center for Drug Evaluation and Research (CDER) division of FDA were issued to facilities in India/China. However, just one out of the total nine resolutions during the period was from India/China. This threat is set to increase going forward as over the next three years, the agency will inspect the pending ~190 Indian facilities which it hasn't inspected in past five years. Last eight years' data highlight that while overall warning letters issued by CDER have not shot up dramatically, contribution from cGMP related ones have increased significantly. Last year, ~70% of warning letters issued were cGMP related.

None of the facilities inspected since June 2014 (33 months ago) and subsequently receiving warning letters have had resolution. Since GDUFA, the nine resolutions done took an average of ~500 days post warning letter issuance. Cadila Healthcare's Moraiya unit (426 days) looks poised to be resolved soon post its recent re?audit that had no FDA observations. While data suggests that Sun Pharmas' Halol unit (432 days) and Dr Reddy's (474 days) are closer to resolution timeframe, the concern is that the warning letters are not easy to resolve. Other facilities of listed companies under Import Alert due to inspections post GDUFA include Wockhardt's 4 units, IPCA's units and Sun Pharma's Karkhadi unit, the Edelweiss report added.

US FDA in India

To ensure that food and medical products exported from India to the US are safe, are of good quality, and are effective, US FDA opened the India office in New Delhi in 2008.

FDA's goals in India are to obtain information to help make better regulatory decisions about the products from India that are being developed and exported for the US market. This includes medical products being reviewed for marketing authorization in the US, and the safety assessment of products that are already on the US market. In addition, the India Office helps verify that foods being imported into the US are safe. FDA's India Office is well-positioned to help the Partnership and India explore how best to meet these goals.

Sharing her views on blogs.fda.gov, Mary Lou Valdez, FDA's Associate Commissioner for International Programs who was in India recently to participate in Indian Pharmaceutical Alliance (IPA) Second Forum, titled "Towards Excellence in Quality noted "Over the past decade, the Indian pharmaceutical market has grown by nearly 14 per cent and continues to experience massive growth. However, in order to fully realize the nation's potential as an important player in the global pharmaceutical industry, India's regulatory infrastructure must keep pace to ensure that global quality and safety demands are met. Quality issues are an ongoing challenge for the Indian pharmaceutical industry. Of 42 warning letters issued by FDA's Office of Manufacturing Quality last year, nine went to Indian facilities. The IPA is working to communicate to its diverse members why quality matters and how to achieve it."

She further said "No one wants resources wasted on ineffectual development and weak processing or manufacturing systems that could actually impede product success. We all want greater competition, increased options for consumers and patients, and more affordable alternatives to comparable products."

Industry is of the opinion that achieving quality requires regulators and industry alike to champion and advance a quality culture throughout the product life-cycle, by effectively employing the use of data and science and requiring greater transparency.

Mary Lou Valdez observed "While I was in India, it was really gratifying to witness the high-esteem and trust Indian regulators and industry have for FDA, and our India Office. In turn, whether it is through their response to inspectional observations, their participation in trainings and seminars or their readiness to share strategic information, we see India committing to quality and compliance. Indian regulators and industry both recognize that a quality culture is imperative if India is to increase productivity, reduce compliance risk, lessen rework, and minimize supply interruptions that result in lost revenue and increased risks to public health."

This greater emphasis on quality will also allow India to participate more fully in existing global venues such as the International Council for Harmonisation (ICH) and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) – which will enable stronger collaboration and synergies among regulators. “Quality is good for economic development, the market, and most importantly, patients and consumers everywhere. FDA’s Office in New Delhi looks forward to continued collaboration with our Indian regulatory colleagues to champion a culture of quality,” Mary Lou Valdez concludes.

FDA activities in India

· Conducting inspections of medical products and foods facilities that export to the US

· Engaging with Indian regulatory authorities to build confidence in each other and develop quality standards

· Partnering with Indian counterpart agencies on bilateral initiatives

· Assisting and training Indian regulators, Indian pharmaceutical and foods industries and stakeholders on developing and maintaining the quality, safety and effectiveness of medical products and foods

· Building and strengthening relationships with the government of India by supporting the mission of the US Embassy

Warning Letters –Issuing offices (since 2011)

Baltimore District Office

Center for Devices and Radiological Health - 6

Center for Drug Evaluation and Research - 60

Center for Food Safety and Applied Nutrition -9

Chicago District Office

Detroit District Office

Kansas City District Office – 2

Minneapolis District Office

New England District Office -2

New Jersey District Office

Philadelphia District Office

San Juan District Office

Seattle District Office

Reasons for issuing warning letters

Acidified Foods/Emergency Permit Control/Adulterated -12

CGMP Food/Prepared, Packed or Held Under Insanitary Conditions/Adulterated

CGMP/Acidified Foods/Adulterated

CGMP/Active Pharmaceutical Ingredient (API)/Adulterated

CGMP/Active Pharmaceutical Ingredient (API)/Adulterated/Failure to Register

CGMP/Active Pharmaceutical Ingredient (API)/Adulterated/Misbranded

CGMP/Active Pharmaceutical Ingredient (API)/Adulterated/Refused Inspection

CGMP/Adulterated

CGMP/APIs and Finished Pharmaceuticals/Adulterated

CGMP/APIs/Adulterated – 2

CGMP/Drugs/Adulterated

CGMP/Finished Pharmaceuticals/Adulterated - 28

CGMP/Finished Pharmaceuticals/Adulterated/HPLC - 2

CGMP/Manufacturing, Packing or Holding Human Food/Adulterated/Insanitary Conditions

CGMP/QSR/Medical Devices/Adulterated - 5

CGMP/QSR/Medical Devices/Adulterated/Misbranded

CGMP/Unapproved New Drugs/Dietary Supplements/Adulterated/Misbranding/Labe ling

Failure to pay GDUFA Fees

Failure to Register and List – 2

Generic Drug User Fee Amendments of 2012 (GDUFA) - 2

Labeling/Promotional Claims False & Misleading/New Drug

Labeling/Promotional Claims False & Misleading/New Drug/Misbranded

Medical Device Reporting/Adulterated/Misbranding

Medical Device/Adulterated/Misbranded/Lacks PMA and/or 510(k)

New Drugs/Cosmetics Labeling and Marketing with Drug Claims

New Drugs/Dietary Supplements/Food Labeling/Misbranded

Seafood HACCP/CGMP for Foods/Adulterated -5

Seafood HACCP/CGMP for Foods/Adulterated/Insanitary Conditions 2

Unapproved and Misbranded New Drugs

Unapproved new drug/Misbranded – 5

No of warning letters received by Indian companies since 2011

year	warning letters
2011	1
2012	6
2013	15
2014	18
2015	18
2016	14
2017	13

Source: fda.gov

No of closeout orders issued by US FDA (last 6 years for Indian companies)

Year	No closeout
2012	2
2013	1
2014	2
2015	1
2016	5
2017	7

Source: fda.gov

Companies receiving 2 or more warning letters

Sal Pharma, Unimark Remedies, USV and Sun Pharmaceutical (2)

Pan Drugs and Wockhardt (3)

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