Inspection Summary

Apotex Research Private Limited ARPL

Judgments of the Federal Court set aside import restrictions on APIPL and ARPL products, ordered a retraction of statements and declared amended terms and conditions on Apotex's Establishment Licence unlawful.

New Decision:

March 14, 2016: Health Canada undertook to make a new decision with respect to how to treat drugs fabricated at ARPL and APIPL. The decision, effective March 14, 2016, is made under the authority of the *Food and Drugs Act* and *Food and Drug Regulations*, and it imposes no terms and conditions on Apotex's Establishment Licences with respect to APIPL and ARPL.

Background

In September 2014, Health Canada took action to stop the import of health products from Apotex Research Private Limited (ARPL) based on new information from trusted international regulatory partners that raised serious doubts about the quality and safety of drug products produced at this site. In particular, the Department had significant concerns with the manner in which data generated at these sites was being collected and reported. Health Canada took the action as a precautionary measure to keep these products from continuing to reach the Canadian market due to underlying concerns with the integrity of the data.

Data Integrity

Manufacturers are required to perform testing at various stages of manufacturing to verify the quality of the health products being produced. Reliable and accurate data is critical to making decisions about the quality of a health product.

In October 2014, Health Canada amended the licences Apotex Inc. in Canada that import products from ARPL to require additional testing against the approved Canadian specifications prior to release of any medically necessary products to the Canadian market. This measure was put into place so that Canadians could have access to medically necessary products affected by the importation restrictions.

Corrective and Preventive Actions

Apotex has been implementing corrective and preventive actions (CAPA) at ARPL to address the data integrity concerns identified during a GMP inspection by a trusted international regulatory authority.

Corrective and Preventive Actions

CAPA are proposed by the manufacturer and reviewed by the regulator. Well-designed CAPA will correct the deficiencies and prevent the problems from re-occurring.

Health Canada has been receiving regular updates from Apotex Inc. on its progress in implementing the actions. Health Canada used this information, along with information

about the problems noted at ARPL, to develop an inspection plan to thoroughly assess whether the company's corrective and preventative actions address the core concerns and would prevent them from re-occurring.

In June 2015, Health Canada sent an inspection team, to conduct an onsite inspection of ARPL to assess the progress being made on the CAPA and verify whether Apotex's implementation would be both effective and sustainable.

Inspection Planning

Regulators rely on data generated by companies to have continued assurance that manufacturing processes consistently produce drugs that meet approved quality standards. In developing a CAPA inspection plan, Health Canada focused on the processes, practices and procedures that are in place to maintain the integrity of the data generated to meet regulatory requirements. Health Canada's inspection plan for ARPL focused on three main areas important for assessing systems around data integrity:

(1) Collecting and analyzing laboratory data: Testing data is collected by a drug manufacturer in order to assess the quality of a drug. The inspection plan included reviewing the systems and procedures used to collect, control and report this data.

(2) Investigation practices: When potential drug quality problems are identified during data analysis, it is critical for the manufacturer to investigate and address the root cause so that the problem does not re-occur. The inspection plan included reviewing investigation and remediation processes.

(3) Employee training: A qualified and well-trained workforce is critical to manufacturing high-quality drugs. The inspection plan included reviewing the training program and qualifications for employees who collect, analyze and review the data used to make quality-control decisions.

In each of these areas, the inspection team observed and interviewed employees performing their work, and reviewed procedures and data such as work instructions, laboratory books and electronic records.

Summary of Health Canada's Inspection Findings

Overall, the Health Canada inspection team found that satisfactory progress had been made in implementing the corrective actions at ARPL to address data integrity concerns previously identified. While the inspection team did not identify any critical issues, the inspection team observed some low impact items that required further monitoring and

follow-up by Apotex in order to ensure sustainability of the corrective actions, as production is ramped-up.

Re-assessment of Precautionary Steps

Based on the inspection findings Health Canada determined that because of the satisfactory progress made in implementing effective corrective actions at ARPL, importation of health products could resume provided additional safeguards are in place as the facility resumes full production and until until the action plan is fully implemented. The risk-mitigation measures include:

- **Re-testing in Canada:** As an additional safeguard until the corrective action plan is fully implemented, Apotex is required to re-test health products imported from ARPL at one of its GMP-compliant facilities in Canada; and
- **Reporting on testing and investigations:** Reporting to Health Canada of all deficient testing results at ARPL and in Apotex's Canadian testing facility with respect to ARPL products destined for the Canadian market, so that investigations can be monitored.

Next Steps

Apotex Research Private Limited (ARPL) has been requested to provide regular updates to Health Canada that outlines its continued progress on the implementation of corrective actions. Health Canada will actively monitor the progress until it is satisfied that the CAPA has been fully implemented. If at any time a risk to health is identified, Health Canada will take immediate action to protect the health and safety of Canadians.

Health Canada will be conducting a GMP inspection at an Apotex testing site in Canada in September 2015.

Finally, Health Canada is planning to do a complete GMP inspection of ARPL in early 2016 which will also include a confirmation of the corrective action implementation and sustainability.