August 4, 2016

DEL Bulletin #2

Good manufacturing practices requirements for foreign buildings conducting activities in relation to active pharmaceutical ingredients destined for Canada or used to fabricate finished dosage forms destined for Canada

This DEL Bulletin serves as a reminder of the *July 31, 2015, Notice to Stakeholders - Updates to drug establishment licence applications and good manufacturing practice evidence requirements for active pharmaceutical ingredients* ("July 2015 Notice"). As indicated in the July 2015 Notice, as of November 8, 2016, in relation to buildings conducting activities related to Active Pharmaceutical Ingredients (APIs) used in the manufacture of drugs listed on the Prescription Drug List, Scheduled under the *Controlled Drugs and Substances Act* (Schedules I, II, III, IV, or V inclusively), or defined as a "narcotic" under the *Narcotic Control Regulations,* importers will be expected to have Good Manufacturing Practices (GMP) compliance evidence based on inspections by Health Canada or by one of the following recognised regulatory authorities / organizations:

- Regulatory partners with whom Health Canada has established equivalence under Mutual Recognition Agreements (MRA);
- Regulatory partners whose inspection system has been assessed and found comparable under the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/s);
- Organizations such as the European Directorate for the Quality of Medicines and Healthcare (EDQM) and the World Health Organization (WHO), which inspect against ICH Q7 guidelines.

Consultant or corporate audits, and other GMP evidence should not be used to demonstrate the foreign building's compliance with GMP in relation to the above-noted categories of drugs.

It is important to note that importers of selected consumer health products and importers of APIs intended for use in those products continue to be covered under the pilot project outlined in the *Notice to Stakeholders – Good Manufacturing Practices for Active Pharmaceutical Ingredients – Implementation Pilot Project for Selected Consumer Health Products* ("pilot project")**.**

Please be reminded that GMP evidence in support of sterile APIs and the release testing of APIs on behalf of the Finished Dosage Form (FDF) fabricator should continue to be submitted as before, in accordance with the guidelines outlined in *Health Canada's Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080).*

Further, there will be no changes to the current Drug Establishment Licence application process. Health Canada will continue to seek clarification with respect to Table A, as applicable, and assess the GMP

compliance evidence of foreign buildings during the inspection of an importer, during the off-site paper assessment, or during the foreign on-site inspection.

The following sections clarify documents that will enable Health Canada to further assess the GMP compliance of foreign buildings:

A. Foreign buildings inspected by the above-noted recognised regulatory authorities and organizations

- most recent, available, signed inspection report issued by Health Canada or by a recognised regulatory authority;
- copy of the GMP certificate issued by the recognised regulatory authority, stating the outcome of the inspection above (if available);
- corrective actions taken, signed by the foreign building's responsible official (if applicable);
- copy of the Site Master File, or a similar document (such as a quality manual); and
- copy of the quality/written agreement between the foreign building's responsible official and the Canadian establishment

B. Foreign buildings which have not been inspected by the above-noted recognised regulatory authorities and organizations

- most recent (within last 3 years) corporate or consultant audit, signed and dated by the lead auditor;
- justification for using a consultant/corporate audit report (e.g. only available GMP evidence);
- qualifications and experience of the auditor(s);
- scope of the inspection (including activities being performed, drugs/APIs covered, and specific building address);
- evidence that the consultant or corporate audit was conducted against all applicable sections of Part C, Division 2 of the *Food and Drug Regulations*;
- corrective actions taken, signed by the foreign building's responsible official and assessed by the auditor for adequacy (if applicable);
- copy of the Site Master File, or a similar document (such as a quality manual); and
- copy of the quality/written agreement between the foreign building's responsible official and the Canadian establishment

Health Canada is considering other approaches for certain APIs that are of lower risk and widely used outside of the pharmaceutical industry.

Importer responsibilities

Importers are responsible for monitoring the GMP compliance of their foreign buildings, and for ensuring they have up-to-date written agreements and required GMP evidence. If the foreign buildings' GMP evidence is not based on inspections by recognised regulatory authorities or organizations, in order to meet the required GMP evidence by November 8, 2016, you should:

1. Source APIs from an alternate supplier that has the required GMP evidence. It is the importer's responsibility to advise the DIN holder of any change in suppliers, so that the DIN holder may obtain Health Canada approval, as applicable;
2. Arrange for a corporate or consultant audit to be conducted as noted in the "Next phase – Beginning November 8, 2016" section of the July 2015 Notice; or
3. Request a Health Canada inspection using *Good Manufacturing Practices – Request for Inspection of a Foreign Site Form (FRM-0213)*.

   Health Canada takes a risk-based approach to inspections. Importers should prioritize inspection requests for foreign buildings listed on their Table A to Health Canada based on a combination of the following factors:
   - category of the drug products (e.g., prescription, controlled drugs)
   - number of different APIs sourced from the foreign building
   - availability of alternate suppliers
   - medical necessity of the drug (a medically necessary drug is defined as a market-authorized drug in Canada which is used to prevent, treat or diagnose a serious or life-threatening disease or medical condition, for which there is no available alternative. Other criteria such as label indications, market share, unique characteristics, on-going shortage of any of the approved alternatives and possible off-label use can also be used to determine if a drug product is medically necessary)

   An inspection should be requested as soon as possible for API foreign buildings involved in activities related to prescription and controlled drugs that the importer would deem medically necessary and/or for which there are no alternate suppliers. Following the inspection request and until the inspection is conducted, establishments should have measures in place (such as a corporate audit) to mitigate the potential risks to the health and safety of Canadians.

Contact us

Should you have any questions related to GMP evidence requirements for API foreign buildings, please contact the GMP Inspection Headquarters at:

E-mail: api_questions_ipa@hc-sc.gc.ca