Implementation of the Canadian Regulatory Framework for Active Pharmaceutical Ingredients (APIs)

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Canada

Outline

- Canadian API regulatory framework
- Updates on Implementation
- Key Guidance Documents
- References

Amended *Food and Drug Regulations*

- Amendments to the *Food and Drug Regulations* (FDR) published in *Canada Gazette, Part II* on May 8, 2013
- Amended regulations for APIs came into force on November 8, 2013
- Amendments extend scope of FDR to include APIs used in the manufacture of pharmaceutical drugs for human use:
  - Establishment Licensing requirements of Division 1A
  - GMP requirements of Division 2

Why Regulate APIs?

- Harmonization with recognized international standards – ICH Q7
- Ensure the overall quality and consistency of drugs in Canada

Scope of amended FDR for APIs

- APIs used in the manufacture of drugs for human use
  - Over-the-counter drugs
  - Prescription drugs
  - APIs produced using blood or plasma as raw material

- Establishment License required for **Fabrication, Packaging/Labelling, Testing, and Importation** of APIs

  * *Fabrication, packaging/labeling and testing of sterile APIs is considered finished dosage form fabrication.*

- Inclusion of additional documentation requirements to foster traceability from the original fabricator to the finished dosage from manufacturer

Excluded from amended FDR for APIs

- APIs for veterinary drugs and Natural Health Products (NHPs)
- Medical gases
- Vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), gene therapy APIs
- Bulk-packed drug (medicinal) products

Excluded from amended FDR for APIs

- Manufacturing/control aspects specific to radiopharmaceuticals

- Active Ingredients used in the fabrication of hard surface disinfectants are excluded from the requirements of Division 1A (Establishment Licensing) and Division 2 (Good Manufacturing Practices)

- Medical devices classified as combination products where the primary mode of action is a medical device.

Excluded from amended FDR for APIs

- APIs are not yet included in the Mutual Recognition Agreements (MRAs): European Community, Switzerland, Australia

Who will these changes affect?

Canadian Establishments impacted by API regulations

- API fabricators, packagers/labellers, testers, importers
- Finished dosage form fabricators who import APIs for use in manufacturing their own product(s)
- Finished dosage form importers
- API distributors and wholesalers
- Establishments that begin to conduct licensable activities related to APIs on or after November 8, 2013

Canadian API Regulations

- Canadian amended FDR for active ingredients (AIs) in line with ICH Q7
- GMP guidelines for APIs (GUI-0104) incorporates ICH Q7 but with Canadian regulatory context applied
- AIs includes APIs and Bulk Process Intermediates (Biologicals)
- Scope: Fabrication, Packaging/Labelling, Testing, Importation, Distribution & Wholesale
- Additional documentation requirements (records)

Implementation of API Regulatory Framework

- The amended Food and Drug Regulations came into force on November 8, 2013
- Establishment License applications were to be submitted by February 8, 2014

Updates on Implementation

Notice to stakeholders

- Published on the Health Canada website on November 8, 2013

- Non-sterile Active Pharmaceutical Ingredients
  - API Fabricators, Packagers/Labellers, Testers and Importers
  - Finished dosage form fabricators who import API for use in manufacturing of own drug
  - Importers of finished dosage forms

- Submission of Establishment License application form (FRM-0033) by February 8, 2014

Updates on Implementation

Establishment License Application Form (FRM-0033)

- Activity, product category, API form class
- **Attestation to Division 2, *Food and Drug Regulations* of foreign buildings where APIs are fabricated, packaged/labeled and tested**
- GMP evidence not required at submission of application but must be available upon request by Health Canada
- **API Foreign Building Information Table (Table A): name, address, etc.**

DEL Applications – Helpful tips

Quality of Application

- Introduction of a screening step
  - Respond in a timely manner

- Overall Applications are acceptable

DEL Applications – Helpful tips

Common Errors

- FRM-0033
  - Missing tombstone information
  - Incomplete section 5.1

- Table A
  - Wrong DEL number
  - Last inspection date
  - Enable macro
  - Pilot participant (exemption)

Table A – Helpful tips

API Foreign Building Information Table (Table A)

API GMP Q&A – Importation / Foreign Buildings / Table A

4. After February 8, 2014, if a company changes API foreign suppliers or if a company starts using a new API foreign supplier, must the Foreign Building Information Table be completed and submitted to Health Canada? If yes, is the company required to wait for the approval from Health Canada prior to using the new API foreign supplier?

Table A – Helpful tips

API Foreign Building Information Table (Table A) *(…continued)*

Answer

- Canadian importers are required to provide current, accurate and complete information related to foreign buildings by submitting Tables 1 to 5 of FRM-0033 and an updated Table A (include only new or modified information relating to amendment) before implementing the change.

Table A – Helpful tips

API Foreign Building Information Table (Table A) *(…continued)*

Answer *(…continued)*

- Importation from new API foreign building can begin as long as appropriate paperwork is submitted to Health Canada.

- If the amendment is to add a new licensable activity, category or dosage form (for example, starts importing APIs) the company is required to submit the application and have the EL issued by Health Canada prior to starting this new licensable activity.

Table A – Helpful tips

API Foreign Building Information Table (Table A) *(…continued)*

Clarifications

- During interim measure - updated Table A should only be submitted if an existing API foreign building is no longer being used, a new API foreign building will be used or the GMP status of the API foreign building has changed.

- Table A only includes information related to foreign buildings.

Table A – Helpful tips

API Foreign Building Information Table (Table A) *(…continued)*

Clarifications *(…continued)*

- If foreign building conducts API release testing and Canadian dosage form fabricator relies on these test results, submit Table A to indicate fabricate, package/label and testing (all other tests under Division 2, FDR) and GMP evidence for API release testing.

Importation from a foreign building

- Listing addresses of foreign API building on Establishment License:
  - API Importers – addresses will be listed
  - Importers of finished dosage forms – addresses will not be listed
- No validity periods or expiry dates will be assigned to foreign API building
- API Importers required to maintain current information related to the foreign API building
- Sterile APIs + Testers of non-sterile APIs: GMP evidence required at submission (GUI-0080) + Attestation + Foreign API Building Information

Updates on Implementation

Pilot Project for Selected Consumer Health Products

- Notice to Stakeholders published on the Health Canada website on December 9, 2014.

- Pilot affects:
  - importers of finished dosage form products, and
  - importers of API intended for use in the finished dosage form products.

- Products selected based on their respective safety and efficacy profiles.

Updates on Implementation

Pilot Project for Selected Consumer Health Products
(…continued)

- Modified version of Table A to complete, along with DEL application (FRM-0033).

- Ultimate goal is to implement the new regulatory requirements in a manner which ensures that the administrative and compliance burden of the requirements is proportional to the quality risks presented by such products.

- Health Canada will communicate the risk-based Compliance and Enforcement strategy moving forward in the fall of 2014.

Updates on Implementation

Compliance and Enforcement

- Adopted phased approach:
  - Encouraging compliance through education and other compliance promotion activities
  - Managing risk at the border (interim approach between April 1, 2014 and August 31, 2014)
  - Encouraging compliance through a series of escalating actions depending on the seriousness of the violation (post August 31, 2014)

- If at any time a risk to the health and safety of Canadians is identified Health Canada will take immediate action according to the Inspectorate's Compliance and Enforcement Policy (POL-0001)

Key Documents

Number	Title	Status
POL-0108	*API Inspection Strategy*	Under development
GUI-0104	*GMP Guidelines for APIs*	Final
GUI-0112	*Annex 18 to GUI-0001 – APIs and finished dosage form importers and dosage form fabricators*	Under development
GUI-0080	*Guidance on Evidence to Demonstrate GMP Compliance of Foreign Sites*	Being revised
GUI-0111	*Guidance on Evidence to Demonstrate GMP Compliance of API Foreign Sites*	Under development

POL-0108 – API Inspection Strategy

Inspection Strategy for Canadian API establishments

- DEL applications are risk-ranked and prioritized for inspections based on factors such as complexity of the activities conducted and oversight by other regulatory bodies.
  - API fabricators, packagers/labellers, testers and importers will be inspected in accordance with POL-0108.
  - API distributors and wholesalers will be inspected if a GMP non-compliance issue arises.
  - Finished dosage form importers and finished dosage form fabricators that import APIs for use in their own manufacturing will be assessed for compliance with API requirements during their GMP inspection of finished dosage form related activities in accordance with POL-0011 – *GMP Inspection Policy for Canadian Drug Establishments*.

POL-0108 – API Inspection Strategy

Inspection Strategy for Canadian API establishments *(…continued)*

- Actively working on the analysis of the content of the DEL applications to finalise the Inspection Strategy for domestic establishments conducting API activities (POL-0108).
- This policy will provide more details as to how domestic inspections will be prioritised and eventually will include an established inspection cycle.
- POL-0108 is expected to be published on Health Canada's website in the fall 2014.

GMP Guidelines for APIs

- Interpretative document to facilitate compliance to GMP regulations
- Scope: Fabricate, Package/Label, Test, Import, Distribute and Wholesale
- ICH Q7 incorporated but with Canadian regulatory context applied
- Cross-walk between ICH Q7 and GUI-0001

  (Appendix F)
- Posted on the Health Canada website on

  February 3, 2014

Guidance for finished dosage form importers and finished dosage for APIs

- GUI-0112 is an Annex to the main GMP guidelines (GUI-0001).
- It provides guidance for finished dosage form Importers and finished dosage form fabricators who source APIs within Canada on how to meet API requirements for their finished dosage form products.
- Final version is expected to be published on the Health Canada website in the fall 2014.

GMP Evidence for finished dosage form foreign buildings

- GUI-0080 was revised to incorporate API foreign sites. Public consultation period ended on July 7, 2013.
- Due to numerous reasons, a full and in-depth review of Health Canada's GMP compliance assessment program for foreign sites is underway.
- Once the proposed changes are approved, GUI-0080 will be revised accordingly. It is expected to be published on the Health Canada website by the end of 2014.
- Until then, the August 1st, 2009 version of Guide 0080 applies.

GMP Evidence for API foreign buildings

- Interim measure – Attestation process until mid-2015
- Actively analysing data contained in the completed API Foreign Building Tables (Table A), included in the DEL application (FRM-0033). Based on this analysis, Health Canada will determine the risk-based strategy moving forward, including the use of expiry dates.
- GUI-0111 – A separate guidance document to be issued on GMP evidence for API Foreign Buildings. GUI-0111 is expected to be published on the Health Canada website in the fall 2014.

Next Steps

- Implement an inspection strategy (domestic and foreign sites)
- Complete GUI-0111 – Evidence to Demonstrate GMP Compliance of API Foreign Buildings
- Expand scope of Mutual Recognition Agreements (MRAs) to include APIs (European Community, Switzerland, Australia)

References

- Notice to Stakeholders
  - Coming into force of amended FDR

    http://web.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugsdrogues/actingred-eng.php
  - API Pilot

    http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingred-notice-avis-pilot-eng.php
  - EL Deadline

    http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingred-notice-avis-pilot-eng.php

- Canada Gazette, Part II – Final Regulations Amending the FDR

  http://www.gazette.gc.ca/rp-pr/p2/2013/2013-05-08/html/sor-dors74-eng.html

- GUI-0104 – GMP Guidelines for APIs

  http://web.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingre-gui-0104-eng.php

References

- GUI-0080 – Guidance on Evidence to Demonstrate GMP Compliance of Foreign Sites
  http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0080-eng.php

- Active Pharmaceutical Ingredients GMP – Questions & Answers
  http://web.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingre-question-eng.php

Summary – Key messages

- New Canadian amended FDR for APIs are in effect
- Scope of FDR extended to APIs used in the manufacture of drugs for human use
- Interim measures (attestation process, no validity period for API foreign buildings, not listing API foreign buildings on finished dosage form importer's DEL) in place until mid-2015

Summary – Key messages

- Analysis on-going to finalise the Inspection Strategy for domestic establishments conducting API activities and to establish the level of GMP evidence required for API foreign buildings – risk-based approach to be communicated in the fall of 2014 to stakeholders.
- Phased approach to compliance and enforcement
- Submission of high quality and complete DEL applications

Summary – key messages

- GMP guidelines for APIs (GUI-0104) incorporates ICH Q7 but with Canadian regulatory context applied
- API Importers required to maintain on their premises current information related to the foreign API building
- APIs excluded from Mutual Recognition Agreements (MRAs) to include APIs (EC, Switzerland, Australia)
- Inquiries – contact Health Canada

Contact Information

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Thank you !

Health Products and Food Branch Inspectorate

L'Inspectorat de la Direction générale des produits de santé et des aliments