

Establishment Licensing and Good Manufacturing Practices (GMP) of Active Pharmaceutical Ingredients (API)

Lorraine Van Loon and Andrei Baume
Health Canada
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Context: Requirements for APIs

- On November 8, 2013, amended *Food and Drug Regulations* (FDR) came into force, extending the Good Manufacturing Practises (GMPs) and Drug Establishment Licensing (DEL) requirements to Active Pharmaceutical Ingredients (APIs) used in drugs for human use.
- As stated in the Regulatory Impact Analysis Statement, Health Canada has taken a phased implementation plan over three years, ending on November 8, 2016 (see Annex A).
- RORB has focussed on progressive compliance promotion; working closely with importers to gather intelligence on foreign suppliers; and preparing to conduct / working with trusted partners to plan foreign inspections.

*Certain APIs are subject to reduced requirements under the ongoing **Pilot Project for Selected Consumer Health Products** – e.g. acne therapy, anti-dandruff, athlete's foot treatments, sunscreens, etc., selected based on their safety and efficacy profiles.*

Annex A: Phased Implementation Approach

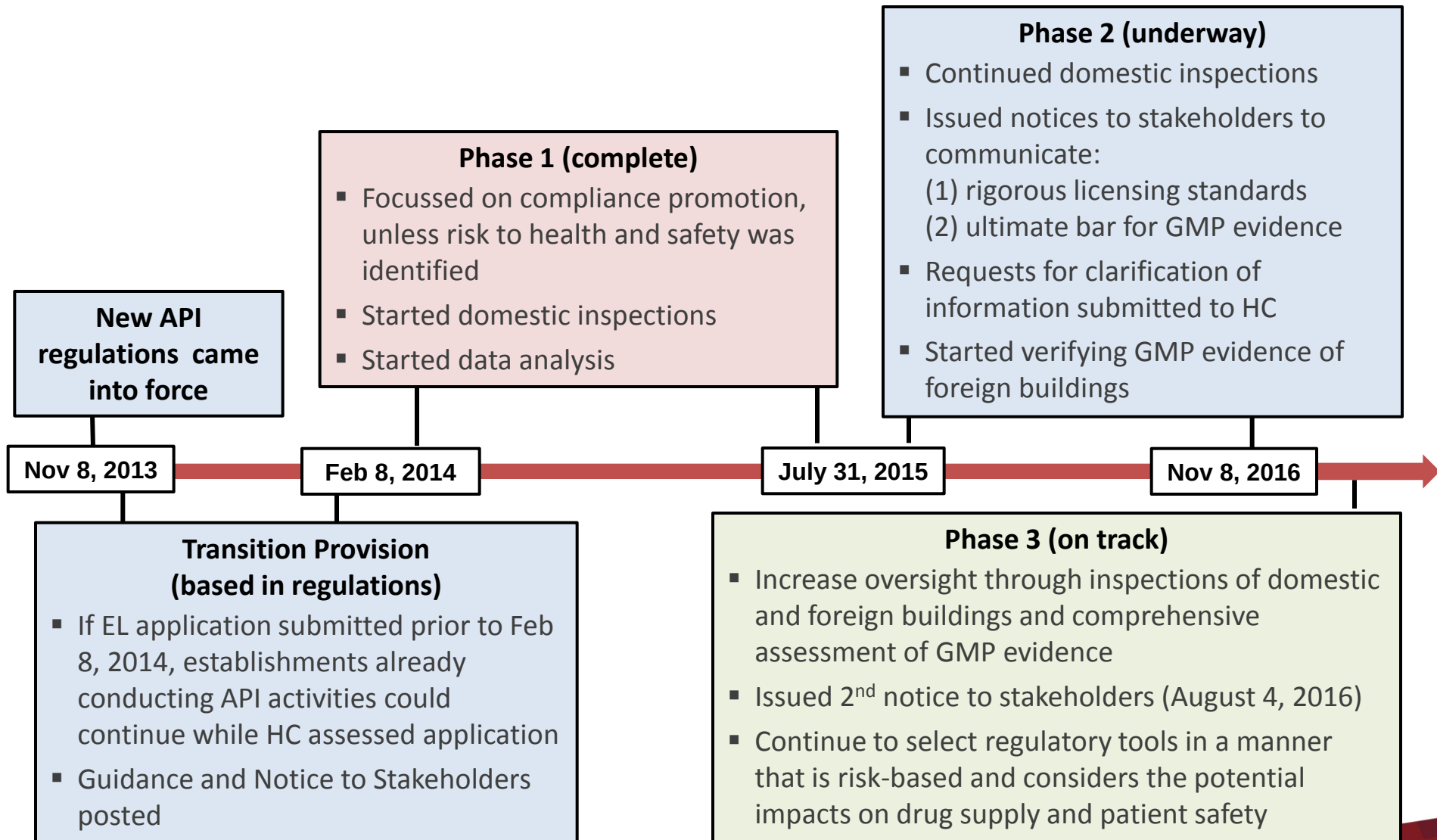


Table A

- A Table A is required for all importers of drugs in a finished dosage form and for APIs
- Veterinary drugs, medical gases, medical devices, natural health products, cosmetics, should NOT be included on Table A
- Biologics and sterile APIs should be submitted using Section 5.0 of FRM-0033 rather than on the Table A.
- A Table A is always required at Annual Licence Review regardless of whether it has changed from your last submitted Table A. If nothing has changed from your last submitted Table A, indicate as such.

Table A (continued)

- Once the Table A is reviewed and deemed complete, an acknowledgement acceptance notice will be sent along with either an API Foreign Building Annex or a copy of the Table A
- If the Table A is not filled out correctly or is incomplete, the 20 day performance standard referred to in the Notice to Stakeholders of July 31, 2015, no longer applies and a deficiency notice will be sent requesting the missing information.

API – Do's and Don'ts

Do:

- Do use the most recent Table A from September 11, 2015. Failure to do so will result in the application being rejected.
- Do respond to deficiency notices within 14 calendar days, as requested. All deficiencies should be addressed or the application will be rejected.
- Do contact the Drug Establishment Licensing Unit (DELU) if you are unsure of what needs to be fixed on your Table A in response to a deficiency notice.
- Do send applications in a more consolidated fashion (ie. send Table A amendments such as additions/removals of foreign buildings less frequently, if possible); this will allow for more efficient processing of applications by DELU.

API – Do's and Don'ts

Do (continued):

- Do enable macros each time you are modifying Table A and add to the table starting in row 7, below the orange bar. This will apply validation rules to your entries and minimize deficiency notices.
- Do send a comprehensive Table A listing both FDF and API with every application outlining changes from the last version, as per the July 31, 2015, Notice to Stakeholders. If no changes to Table A have been made, a new Table A does not need to be submitted along with your application, but it should be clear in the cover letter that this is the case.
- Do use the pick lists for columns D (API name) and J (country).

API – Do's and Don'ts

Don't:

- Don't follow the instructions included in FRM-0033 for filling out Table A, since these refer to the old Table A. These will be updated with the next release of FRM-0033.
- Don't start importing newly added APIs until you have received an acknowledgement acceptance notice informing you that your Table A has been reviewed, and that you are able to import APIs. Importation can continue from buildings listed on your previously issued API Foreign Building Annex unless otherwise informed by HC.
- Don't send in a Table A with "N/A" or blanks in required fields. This will result in a deficiency notice and the 20 day performance standard will no longer apply.
- Don't send applications with a Table A indicating "D-Other" in Column N (inspection type).

API – Do's and Don'ts

Don't (continued):

- Don't copy information from columns D (API name) and J (country) from old Table A and paste into new Table A. The API names have been standardized and will prevent multiple versions of the same API, and the countries are displayed in both English and French. Enter the information using row 7, below the orange bar.
- Don't submit Table A's directly to inspectors; only Table A's sent with an up to date Section 5.1 of FRM-0033 directly to DELU using the ELapplicationLE@hc-sc.gc.ca account will be processed and acknowledged. You may cc. the Inspector on your application.
- Don't respond to an acknowledgement notice with specific questions related to an application. Any questions following receipt of an acknowledgement notice should be sent to the DEL_questions_LEPPP@hc-sc.gc.ca account.

Changes to Table A Screening

As of November 8, 2016:

- Any application with a Table A indicating “D-Other” in Column N (inspection type), will be rejected, since this evidence is insufficient to demonstrate compliance to GMPs.
- When applications and Table A’s are deemed incomplete, and are sent a deficiency notice, if a response addressing all of the requested information is not received within **14 calendar** days, the application will be rejected.
- Applications with Table A’s sent in the old format (prior to September, 2015) will be rejected.
- Applications for which an up to date Section 5.1 is not received will be rejected.

Changes to Table A Screening (continued)

- Importers who have remaining stock from a foreign site, where it is determined that as of November 8, 2016, the evidence is insufficient to demonstrate compliance to GMPs, may continue to sell until such time that the stock is depleted.
- In these instances, importers should clearly indicate any remaining stock in Table B, and should specify the timeframe for the stock to be depleted.
- We encourage companies to start sending these applications in well in advance of November 8, 2016, so as to minimize any delays in processing.

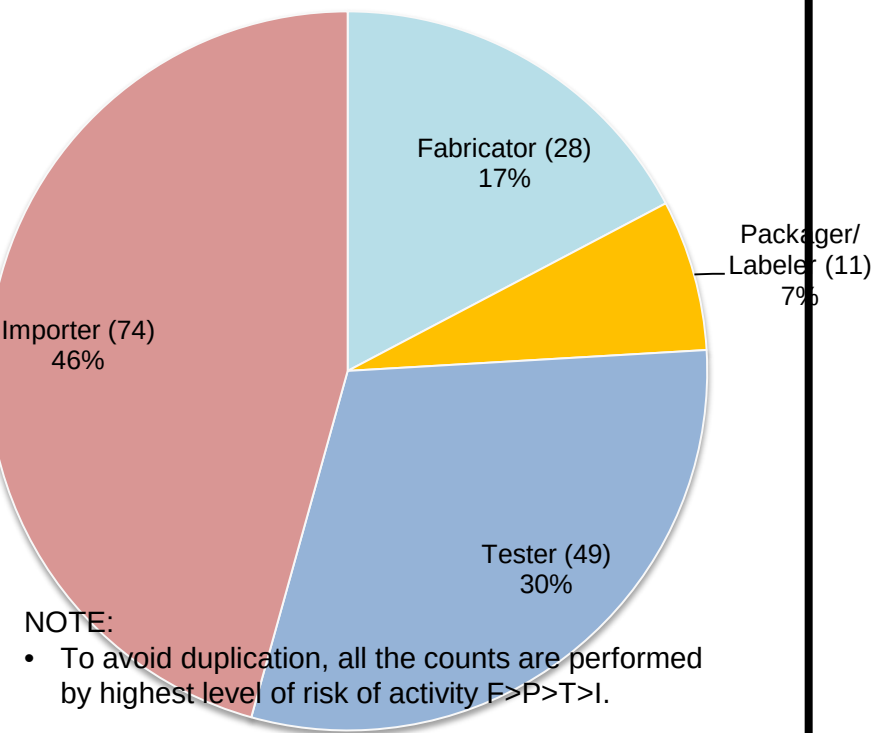
How to facilitate the process?

The quality of your application has an impact on timelines for processing.

- Read instructions and notices.
- Send complete applications:
 - o FDF applications- FRM-0033 + GMP evidence in accordance with GUI-0080 must be submitted together from either the importer or the foreign site.
 - ☐ If the GMP evidence is insufficient or requires additional information, this evidence/information can be sent to the requestor directly from the foreign site, provided the application# is referenced.
 - o API applications- Up to date Section 5.1 of FRM-0033 + Table A must come from the importer.
- Ensure that FRM-0033 is completed and signed.
- Ensure that your contact person is up to date in our systems.
- Respond to Health Canada inquiries (deficiency notices/clarifications via email or phone) in a timely manner.
- Do not submit evidence with your table A, unless requested.
- Have your evidence available on-site (could be requested at anytime).

Domestic API Buildings

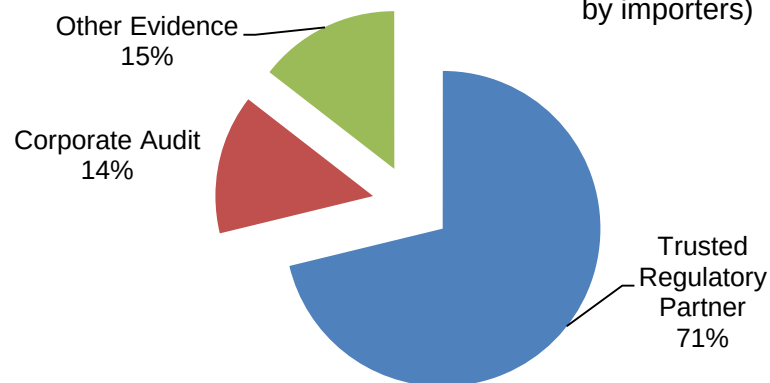
Domestic API Activity Distribution



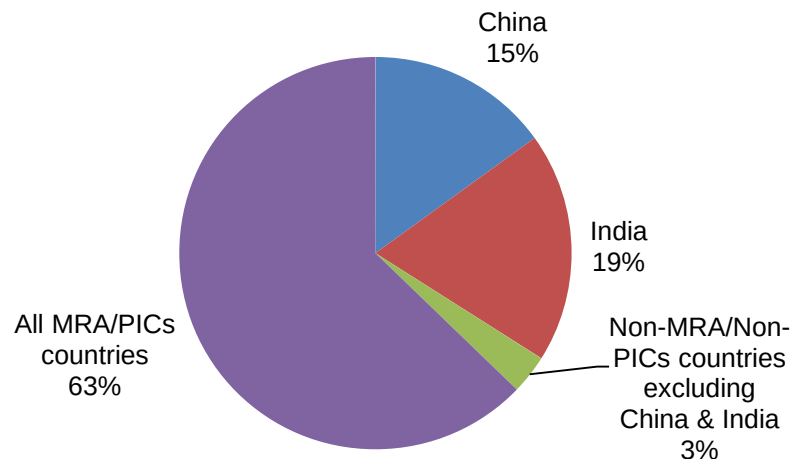
Domestic API Buildings: 155

Foreign API Buildings

Inspection Type (Self-reported by importers)



Foreign API Building Location



Foreign API Buildings: ~1900

Inspections to Date

127 buildings were inspected

- 121 were Compliant (C)
- 2 Non-Compliant (NCs)
- 4 have Withdrawn before a rating was issued
- A re-inspection may be carried out when unacceptable practices have been identified which resulted in an NC rating and for which the purpose is to ensure that corrective actions have been implemented.



NOTE:

- To avoid duplication, all the counts are performed by highest level of risk of activity F>P>T>I.
- Snapshot data as of August 31, 2016

Communication to Industry

DEL Bulletin # 2 : GMP Practices requirements for foreign buildings conducting activities in relation to API destined for Canada or used to fabricate FDF destined for Canada (August 4, 2016)

- Reminder of the the July 2015, Notice to Stakeholders
- Specifies to all importers the GMP requirements for foreign buildings as of November 8, 2016
- Reiterates the responsibilities of the importers
- Specifies the requirements for the API used in a prescription drug.

Nov. 2016 – onward

Compliance and Enforcement

- Foreign API sites will be selected for paper assessments or inspections based on risk
- Multi-approach compliance verification to phase out reliance on attestation as GMP evidence.
- Quality of drugs will be overseen by HC from API manufacture to finished dosage form drug manufacture.
- Starting November 2016, full inspection reports, including CAPA, Quality Agreements and SMF will be expected to be available for review for all foreign API buildings, which are not part of the Atypical or Pilot Project.

Acceptable GMP Evidence

Prior to November 8 th 2016	After November 8 th 2016
<u>Certificate from Canadian Inspector:</u> - GMP inspection report with a 'compliant' rating issued by Health Canada <u>Recognised Regulatory Authorities:</u> GMP Inspection Reports and Certificates issued : - Regulatory partners under the MRA Regulatory partners under PIC/s - Organizations inspecting under ICH Q7 such as EDQM and WHO <u>Consultant or Corporate Audits:</u> Corporate and consultant audits for non-prescription and prescription drugs. <u>Non-PIC/s and non-MRA agencies:</u> GMP Inspection Reports and Certificates issued by other agencies	<u>Certificate from Canadian Inspector:</u> - GMP inspection report with a 'compliant' rating issued by Health Canada <u>Recognised Regulatory Authorities:</u> Full GMP Inspection Reports issued by : - Regulatory partners under the MRA - Regulatory partners under PIC/s - Organizations inspecting under ICH Q7 such as EDQM and WHO <u>Consultant or Corporate Audits:</u> Corporate and consultant audits for non-prescription, non-controlled drugs.

* Red text indicates change, no longer acceptable as of Nov 2016

Documents that will enable HC to assess conformity of the FB

Recognised Regulatory Authority	Corporate Audit
• Most recent available signed inspection report issued by a recognized regulatory authority • Copy of the GMP certificate issued by the recognized regulatory authority stating the outcome of the inspection above (if available) • Corrective actions taken, signed by a responsible official of the foreign building, if applicable • Copy of the Site Master File, or a similar document such as a quality manual • Copy of the quality / written agreement between the foreign building and the Canadian establishment	• Most recent (within the last 3 years) corporate or consultant audit, signed and dated by the Lead Auditor • Justification for the use of a consultant or corporate audit report (e.g. sole available GMP compliance evidence) • Outline of the qualifications and experience of the auditor(s) • The scope of the inspection including the activities being performed, the drugs / APIs covered and the specific building address • Conducted, section by section, against the Part C, Division 2 of the Food and Drug Regulations • Corrective actions taken, signed by a responsible official of the foreign building and assessed by the auditor for adequacy, if applicable • Copy of the Site Master File, or a similar document such as a quality manual • Copy of the quality/written agreement between the foreign site and the Canadian site

Atypical APIs

Atypical APIs are subject to Divisions 1A and 2 of the FDR; however...

Health Canada **is considering** a more flexible, risk-based approach to reduce regulatory burden for APIs* that meet some of the following criteria:

- Low Risk – OTCs and/or topical
- Physical effect - no significant pharmacological effect
- Limited market size – limited exposure
- Used primarily in other industries such as food, chemical, etc...
- Classified as excipients, foods, medical devices, natural health products in other PIC/S jurisdictions

Notice of Intent to Reclassify Disinfectants and Sterilants for Use on Medical Devices
published on September 14, 2016

It is the responsibility of:

- API and FDF importers to ensure the quality of atypical APIs imported from abroad
- FDF manufacturer to ensure the quality, safety and efficacy of the drug product

* Until atypical APIs are transferred to a different regulatory framework, Health Canada would apply a lower priority for enforcement actions.

QUESTIONS?