Drug GMP Inspection Program

CAPRA Education Day
June 9, 2015




Canada

Presentation Outline

- Drug GMP Inspection Trends
- Active Pharmaceutical Ingredients (API) Inspections
- Transparency Initiatives

Canadian Good Manufacturing Practices (GMP)

What are GMPs?

Part of **quality assurance** and help in:

- ensuring that drugs are consistently produced,
- controlling the quality standards appropriate to the intended use, and
- meeting specifications required by the marketing authorization.

GUI-0001: Good Manufacturing Practices (GMP) Guidelines

- Our main guidance document is GUI-0001 Good Manufacturing Practices Guidelines
- Revisions made internally
- Posted for 75 days for external consultation
- Each comment received is reviewed and considered
- Current edition came into force March 4, 2011

Health Canada References

- Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)
- GMP Questions and Answers
- Risk classification of GMP observations (GUI-0023)
- Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)
- Good Manufacturing Practices for Medical Gases (GUI-0031)
- Product Recall Procedures (POL-0016)
- Cleaning Validation Guidelines (GUI-0028)
- Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)
- Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers

Annexes to GUI-0001

- Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines - Selected Category IV Monograph Drugs (GUI-0066)
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule D Drugs, Biological Drugs (GUI-0027)
- Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule C Drugs (GUI-0026)
- Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines - Veterinary Drugs (GUI-0012)
- Annex 5 to the Current Edition of the Good Manufacturing Practices Guidelines - Positron Emitting Radiopharmaceuticals (PER's) (GUI-0071)
- PIC/S Annex 11: Computerised Systems
- Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines - Drugs Used in Clinical Trials (GUI-0036)
- Annex 14 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule D Drugs, Human Blood and Blood Components (GUI-0032)
- PIC/S Annex 17: Parametric Release

International References

- PIC/S Annex 17: Parametric Release
- PIC/S Annex 11: Computerised Systems
- ICH Q1A(R2): Stability Testing of New Drug Substances and Products
- ICH Q1C: Stability Testing for New Dosage Forms
- ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology
- ICH Q7: Good Manufacturing Practice Guide for APIs
- ICH Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products
- Stability Requirements for Changes to Marketed New Drugs
- Stability Testing of Existing Drug Substances and Products

Regulatory Sections

- Part C of the Food and Drug Regulations (FDR)
  - Division 1A – Establishment Licences Requirements
  - Division 2 – Good Manufacturing Practices Requirements

DEL requirements

As per Division 1A of the FDR, a **Drug Establishment Licence (DEL) is required** to perform the following drug activities…however **GMP compliance is required for all**.

Activity	Finished Dosage Forms (FDF)	Active Pharmaceutical Ingredients (API)
Fabrication	X	X
Packaging/Labeling	X	X
Testing	X	X
Importation	X	X
Distribution	X	
Wholesale	X	

Scope of Division 2

The GMPs described in Division 2 of the FDR apply to…

- Pharmaceuticals
  - Medical gases
  - Prescription drugs
  - Over-the-counter drugs
  - Veterinary drugs
- Biologics
- Radiopharmaceuticals
- Active Pharmaceutical Ingredients (APIs)
- NHPs exported to MRA jurisdictions

Finished dosage forms (FDF)

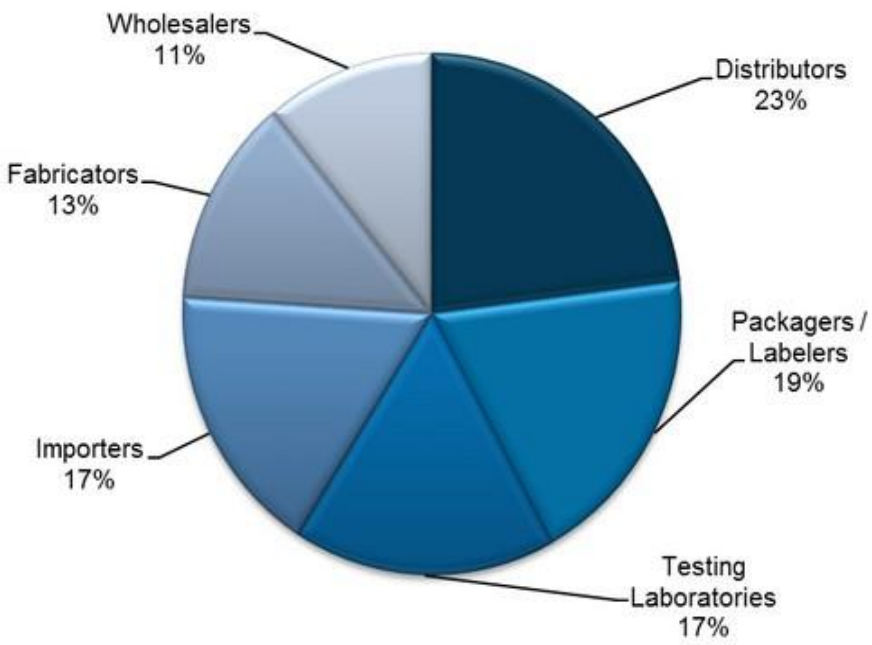
Who do we inspect?

All DEL holders are inspected against GMPs

- FDF: F, P/L, T, I, D and W
- API: F, P/L, T and I
- **API distributors and wholesalers** are not inspected by the Inspectorate and do not hold a DEL but they are required to comply with GMP.

- **672** FDF DEL holders for **941** buildings to inspect
- **428** inspections conducted in FY 2013-2014

Numbers from Fiscal Year 2013-2014



When do we inspect?

Activities	Inspection Cycle
Fabricators, packagers/labellers, and testing laboratories	2 years
Importers, distributors, wholesalers, and lower risk labelling activities (e.g. secondary labelling and outer labelling activities).	3 years
Medical gas establishments (engaged in medical gas fabrication, packaging/labelling, importation, and distribution) that have a good compliance history.	4 years
Establishments with significant deficiencies to regulatory obligations or circumstances where an increased inspection oversight is required for risk mitigation strategies.	2 years or less

Types of Inspections

Initial (new establishment)

- Should be conducted 3 months following date of receipt of EL application
- Followed by Regular inspection within **1 year generally**

Regular (establishment holding a DEL)

- All of the applicable requirements of the FDA and its associated Regulations are assessed.
- Notice of upcoming inspection **may or may not** be provided

Partial

- Subset of the applicable requirements of the FDA and its associated Regulations are assessed.

Re-assessment

- Follow-up inspection to an inspection which has resulted in a C rating and which is carried out for the purpose of ensuring that corrective actions have been implemented.

Re-inspection

- Follow-up inspection 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.

In FY 2013-2014…

Types of inspection	% of inspections
Initial	15%
Regular	**74%**
Partial	2%
Re-assessment	7%
Re-inspection	2%

GUI-0023: Risk Classification of GMP Observations

Guide 0023 presents our Risk Classification of GMP Observations.

The risk assigned to each observation is based on the nature of the deviation as well as the number of occurrences.

The overall inspection rating assigned is based on the risk involved taking into account the nature and extent of the deviations with the category of products evaluated.

Generally, a Non Compliant rating is assigned when a Risk 1 observation is noted during an inspection.

Where in the opinion of the inspector the resulting products present a significant health hazard, appropriate enforcement actions may be initiated.

GUI-0023: Risk Classification of GMP Observations

All observations are discussed with the firm during the exit interview and confirmed to the establishment in the Exit Notice.

When a NC rating is assigned, the inspector will issue a draft inspection Exit Notice during the exit meeting. The draft inspection Exit Notice will be reviewed for quality assurance purposes before the final report is issued to an establishment.

When observation(s) leading to a NC rating are made, the inspection Exit Notice could be issued with a C rating if, during the inspection:

- the establishment immediately implements all necessary actions to resolve the cause(s) of the observation(s) leading to the NC rating and,
- sufficient assurance can be provided to prevent a recurrence.

Risk attribution - observations

	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2012-2013	2013-2014
Risk 1	0.2%	0.2%	0.3%	0.9%	0.9%	1%	1%
Risk 2	59%	57%	57%	54%	54%	50%	51%
Risk 3	41%	42%	42%	45%	45%	49%	48%

The percentage of observations noted in each risk category by fiscal year.

****the 2011- 2012 fiscal is omitted as no annual report was published that year.**

Most often cited Regulatory Sections

The majority of **observations** are cited against the following regulatory sections:

- C.02.013-15 Quality Control Department
- C.02.011-12 Manufacturing Control
- C.02.020-24 Records

The majority of **risk ones** are attributed to observations cited against the following two regulatory sections:

- C.02.013-15 Quality Control Department
- C.02.029 Sterile products

Most Common Observations Cited

Regulation	Example of observations
C.02.013 - 15 Quality control department	• Not all the Batch Release Notes and Batch Release Checklists were filled out and signed by the quality control department. • A change control procedure had not been established. • During the release of a lot, the firm had not received or reviewed the Certificate of Analysis prepared by the manufacturer. • During the temperature verification of the shipping of drug products, the firm was not recording the location the drug products were shipped to or what calibrated temperature monitoring device had been used for this activity.
C.02.011 -12 Manufacturing control	• Manufacturing operations are not performed in such a way as to prevent cross-contamination of products. • Temperature mapping and temperature monitoring of the warehouse was not performed. • Quality Agreement between Company A and Company B did not include requirements to notify Company A of any rework, reprocessing and deviations. • The water system sampling and testing program was deficient.
C.02.020 - 24 Records	• The record retention timeframes stated in the written procedure, were not in compliance with GMP requirements outlined in C.02.021, C.02.022 and C.02.023. • Not all the master production documents for product A were available on the premises. • There is no written procedure on proper documentation practices and no evidence that personnel are trained in documentation practices. • Proper documentation practices were not being used in the Cleaning Log (i.e. Dates were observed to be scratched out in the Cleaning Log, rather than crossed out and initialed).

Inspection Outcomes

Two possible outcomes:

C / Compliant : At the time of the inspection, the regulated party has demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations. A C rating does not mean that there are no observations or corrective actions required.

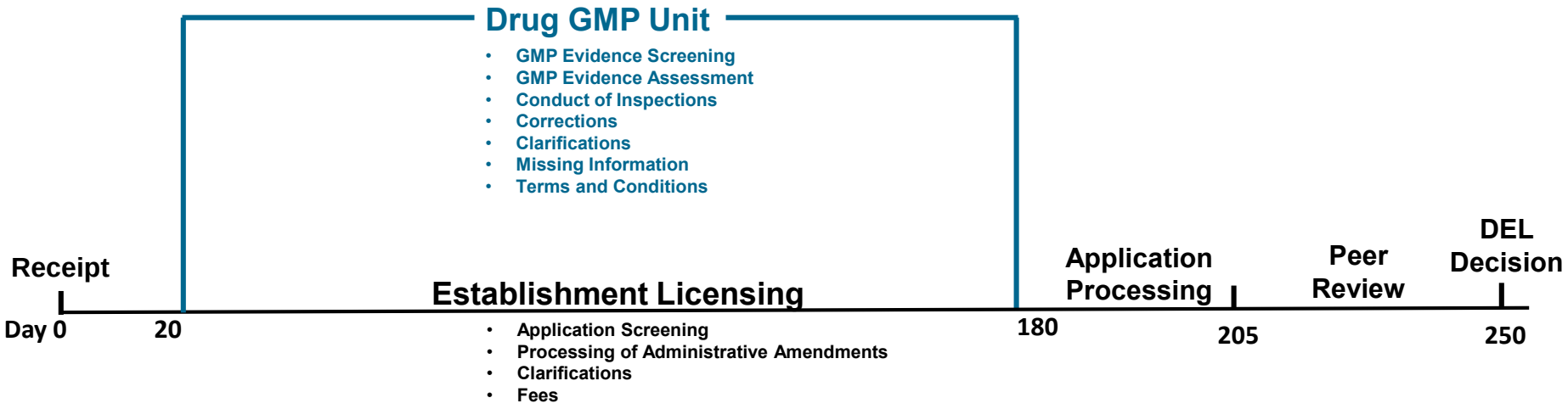
NC / **Non-compliant :** At the time of the inspection, the regulated party has not demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations.

	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2012-2013	2013-2014
C	98%	98%	98%	96%	94%	95%	96%
NC	2%	2%	2%	4%	6%	5%	4%
Total number of inspections	303	383	447	393	440	416	428

We have heard from industry…

- Improvement needed regarding communication with industry
- Improvement needed in timing of electronic acknowledg receipt of applications
- Queuing by application type instead of 1st in 1st out
- Agreement on screening out incomplete applications
- Provide extensions of validity period where new GMP evidence is not available
- Industry prefers face to face meetings

250 Days Performance Standard



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What have we done so far?

Intake and Screening: Internal operational processes improved for efficiency gains and higher performance targets

Implemented

- Increase in Notice to Stakeholders to improve communication
- Since Oct 2013: Tracking numbers provided on acknowledgement notices
- Since Jan 2015: Acknowledgement of applications within 15 business days
- Express queues: cancellations, contact and company updates
- Expedited reviews: medically necessary with no alternative, Blood, TPD priority reviews
- Time-sensitive reviews: mergers and acquisitions
- Application Screening: improved tracking of work in progress

Ongoing implementation

- More express queues: adding a warehouse, removals/deletions,
- Officially launch the express queues externally (notice to stakeholders and guidance)
- Screening earlier in the process (at intake)
- Improved form and guidance for API foreign sites

What have we done so far?

GMP Review: Internal operational processes improved for efficiency gains and higher performance targets

Implemented

- Proactive request of CoCs from MRA partners
- Conduct of abbreviated assessments (MRA inspection reports and FDA EIR with no 483)
- Assignment of validity period risk-based extensions to foreign sites
- Phase II of the Regulatory Cooperation Initiative (RCI) with the Therapeutic Good Administration (alignment of GMP compliance assessment programs)

Ongoing implementation

- Streamlining processing of applications and screening of GMP evidence
- Triaging DEL applications in 6 categories based on risk
  - Expedited requests, Inspections, Full Assessments, Abbreviated Assessments, CoC requests, and Cross-references and extensions

What have we done so far?

Licensing and issuance: Internal operational processes improved for efficiency gains and higher performance targets

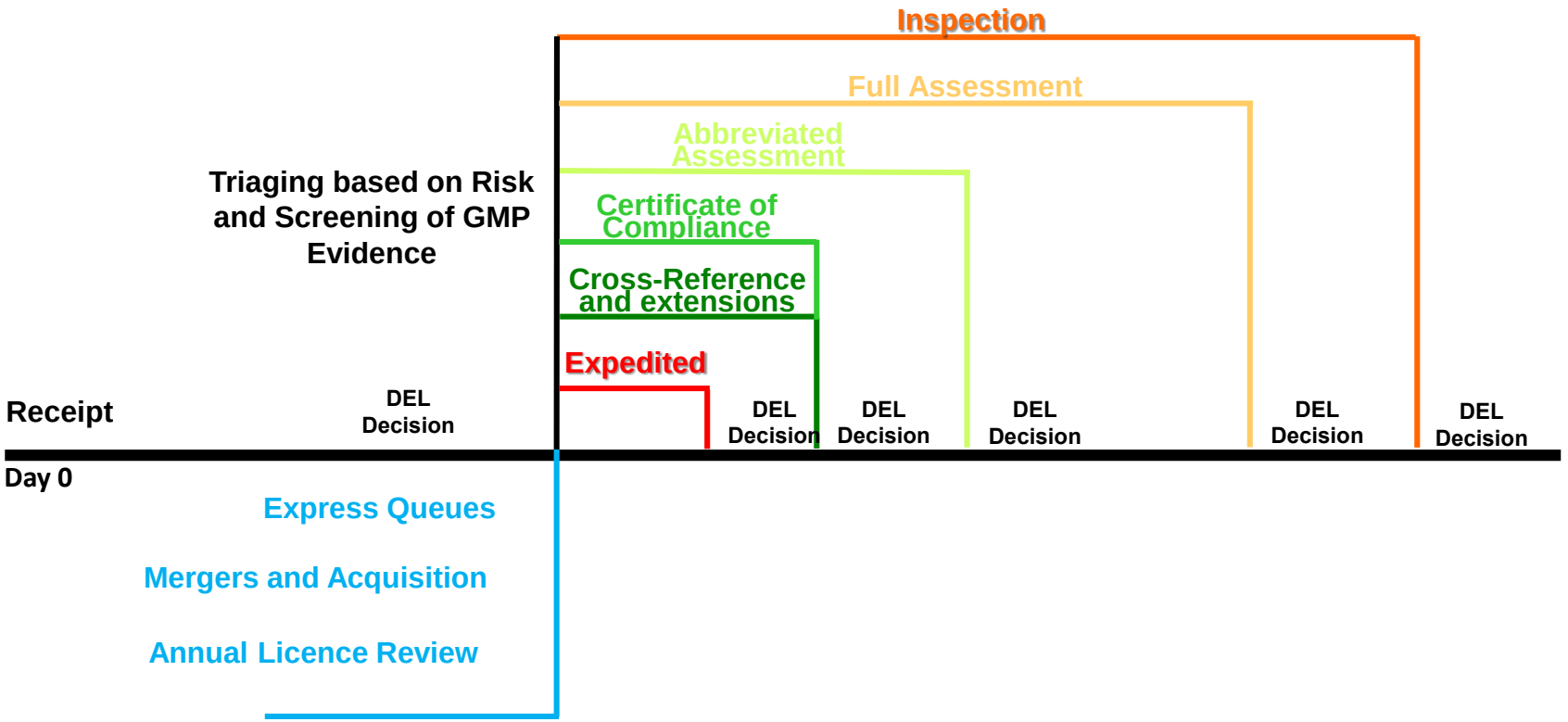
Implemented

- PDF of licences emailed
- Priority licensing for new DELs
- No backlogs for issuance once the licence is signed
- Foreign site supplements are issued instead of full annexes
- Licences are not issued for ALR applications in most cases

Ongoing implementation

- Queuing by application type (different targets for different application types)
- Improved licensing as soon as the review is complete by considering alternatives to the paper licence (email, supplement, web)
- New Establishment Licence numbers (coming with the new IT solution)
- Improve reporting of performance and in-process workload

What will you see?



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Next Steps

- Finalise streamlining of the processing of applications and screening of GMP evidence
- Finalise implementation of triaging DEL applications based on risk
- Ongoing exploration of:
  - Expiry dates of foreign sites
  - Cross-reference of foreign sites
- Establish and operationalise new performance targets
- Implement new IT solution
- Continual improvements to licensing process

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

Amended Food and Drug Regulations Part C, Div. 1A, Div. 2

Overview

1. Amended Food and Drug Regulations (FDR)

2. Update on Establishment Licensing

3. Domestic
   I. Inspections
   II. Path Forward

4. Foreign Sites
   I. Landscape / Challenges
   II. Path Forward

5. Summary

Amended FDR

- **Health Canada's regulatory GMP requirements for API destined for human use is aligned internationally.**
- **Divisions 1A and 2 of the *Food and Drug Regulations (FDR)* were amended to apply to Active Pharmaceutical Ingredients (APIs)**
- **The amended *FDR* came into force on November 8, 2013 extending Establishment Licensing and GMP requirements to APIs**
- **Establishment License applications were to be submitted by February 8, 2014**
- **GUI-0104 - Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (APIs) is the 'GUI-0001' for APIs.**

Who Does It Apply To?

Canadian Establishments impacted by API regulations:

- **API fabricators, packagers/labellers, testers, importers**
- **Finished dosage form (FDF) establishments also conducting API-related activities**
- **Finished dosage form importers**
- **Distributors and Wholesalers**

Excluded:

- **Veterinary drugs and Natural Health Products (NHPs) are excluded from the amended FDR for APIs**

Regulated prior to Amended FDR

Regulated Prior to Amended FDR:

- **Foreign Sites conducting activities related to sterile APIs and non-sterile API Testers testing on behalf of the Canadian manufacturer have had to follow Guide 0080, undergo paper assessment and have the sites conducting these activities on their behalf, added to the Foreign Site Annex of the Establishment Licence (EL).**

Establishment Licensing

Establishment License Application Form (FRM-0033)

- **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 on site and to submit to Health Canada, as required**
- **The data gathered to date gave us information to aid in the development of our inspection strategy, compliance and enforcement efforts and tracking/tracing of API foreign sites**

TABLE A: FOREIGN BUILDINGS CONDUCTING API-RELATED LICENSABLE ACTIVITIES

Note: Ensure that macros are enabled before proceeding. Enabling macros will unlock the complete functionality of Table A.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X
Import Information			API Foreign Building Information					API Foreign Building GMP Status								API Product Information			API Activity Information				
DEL #	Imported As A- API F- Dosage Form	API name	Foreign Building Name	Street, City, Postal code	Province/ State	Country	GPS # Latitude/Longitude	Building complies with applicable GMP requirements set out in Part C Div. 2, FDR?	Date first used as Foreign API Source Site	Date of Last Inspection	Inspection Type A- PIC/S B- EDQM C- Corporate / Consultant D- Other	Specify Other	Date of renovations (if applicable)	Has this building been issued a Non-compliant rating in the last 5 years?	Years conducting API-related activities?	Final API Form Class A- Powder B- Crystal C- Liquid D- Suspension E- Sterile Powder F- Sterile Crystal G- Sterile Liquid H- Sterile Suspension I- Other	Specify Other	DIN associated with API	Activity A- Fabrication B-Packaging/ Labelling C-Testing	Manufacturing process (for fabricators only) A- Chemical Synthesis B- Extraction C- Cell Culture/Fermentation D- Isolation/Recovery from natural sources E- Other	Specify Other	Testing process (for testers only) A- Chemical B- Microbial C- Sterility D- Other	Specify Other

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Pilot Project

Pilot Project for Selected Consumer Health Products

- **Notice to Stakeholders published on the Health Canada website on December 9, 2013.**

- **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.**

DEL Applicants for APIs

Status Update

150 establishments conducting API-related activities applied for a Drug Establishment License (DEL)

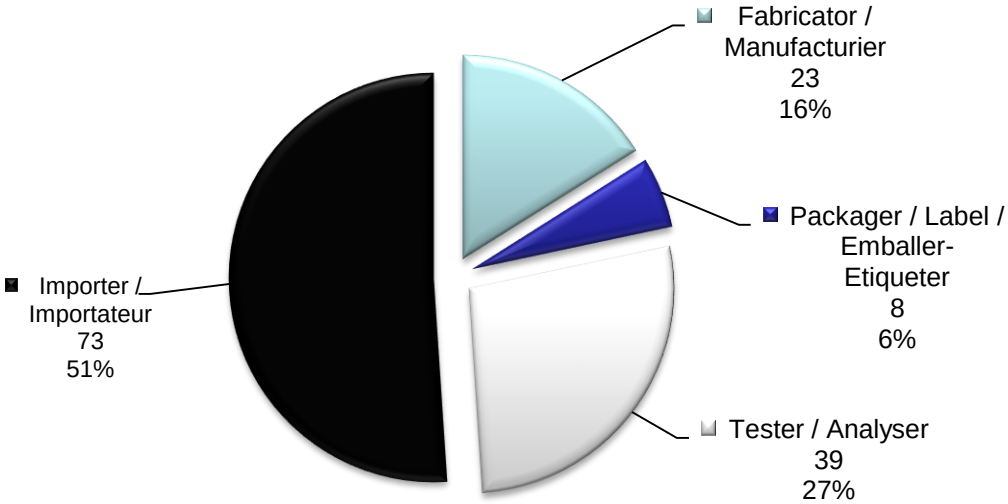
New DELs
- **52 API only**
- **14 Finished Dosage Form (FDF) and API**

Amended DELs
- **84 amended the existing DEL to add an API activity**

FDF Importers

348 FDF importers needed to complete and submit Table A with regards to the API foreign sites

API Activity Distribution



NOTE:
- **To avoid duplication, all the counts are performed by highest level of risk of activity F>P>T>I.**
- **Snapshot data as of February 20, 2015**

Compliance and Enforcement

Adopted phased approach:

- **Education and other compliance promotion activities**
- **Managing risk at the border (interim approach between April 1, 2014 and August 31, 2014: API importers without an EL application were notified to apply immediately)**
- **Escalating actions depending on the seriousness of the violation and risk to health and safety (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)

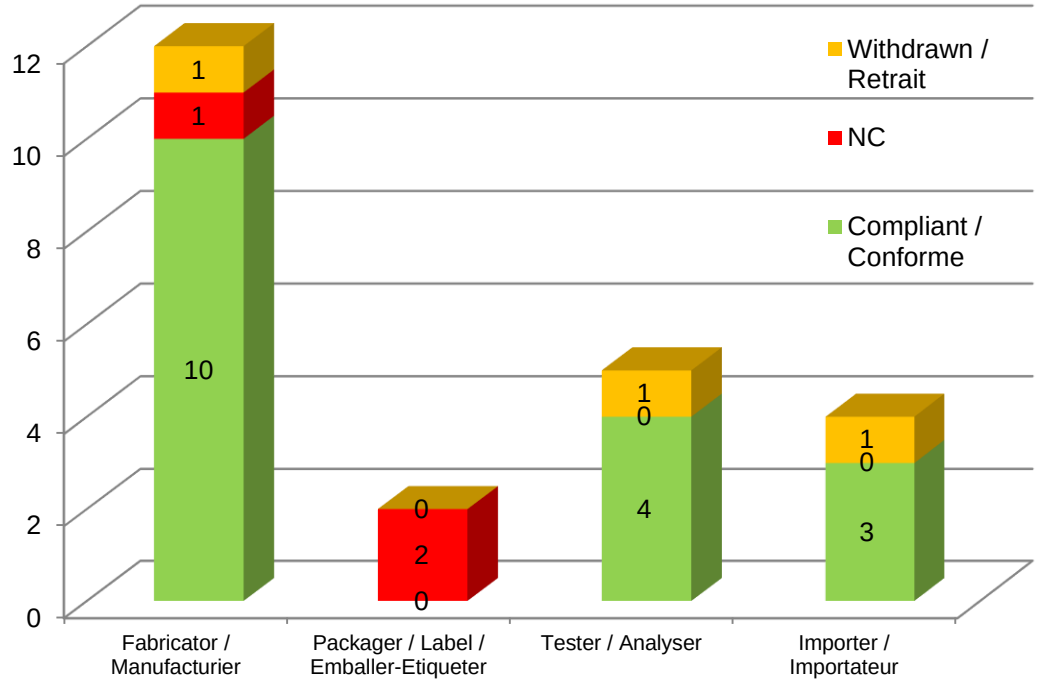
Domestic API Inspections

Inspection results as of March 2015

23 sites have been inspected

- **17 were deemed Compliant (C)**
  - **14 have been issued a DEL**
  - **3 awaiting License**
- **3 were deemed Non-Compliant (NCs)**
  - **2 received a Non-Issuance letter**
  - **1 withdrew after the inspection, but prior to Non-Issuance letter**
- **3 Withdrew before a rating was issued**

Domestic Inspections



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Domestic API Inspections

Sample Observations

Risk 1
- **Incomplete Batch records for fabricators**
- **Not all batches are tested prior to release**

Risk 2
Quality Control
- **Deficiencies with Vendor Qualification Program and Quality Agreements**
- **Independent role responsible for QC**
- **Lack of control over storage conditions**
- **OOS and deviation handling**
- **No change controls in place**

Manuf. Control
- **Labeling issues and product Identification issues**

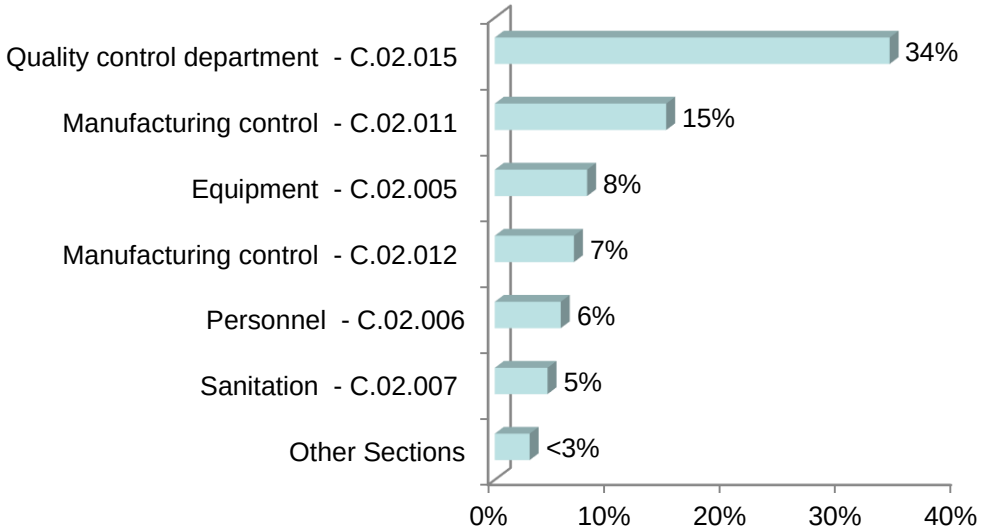
Premises
- **Issues with potential cross-contamination**
- **Un-cleanable areas and cleaning validation**

Records
- **Issues with data integrity**

Stability
- **Inadequate stability program**

Samples
- **Issues with sampling and sample retention**

This list is not exhaustive and is solely intended to provide examples of observations noted during an inspection. These same observations may be assigned a higher or lower rating depending on the nature and extent of the deficiency.



Sections of the Food and Drug Regulations against which observations were cited during 21 API inspections.

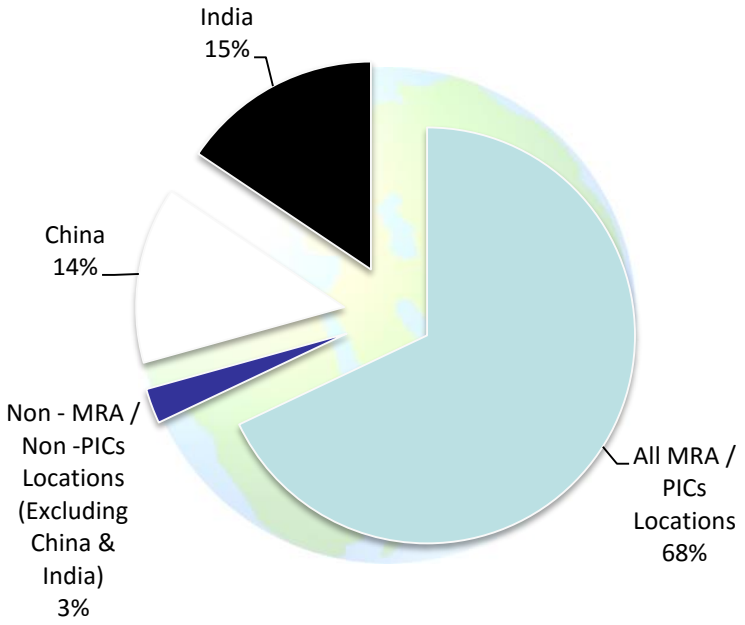
Foreign Sites

Foreign Data (Table A)

Challenges for Health Canada:

- **Limited IT/IM capabilities**
- **Processing duplication caused by large number of amendments**
- **Identifying unique foreign sites due to**
  - **Incorrect information**
  - **Incomplete information**
  - **Inconsistent information (declared by multiple importers using the same foreign site)**

Foreign Site Location Breakdown



Total Countries	MRA / PICs Countries	Non-MRA / Non-PICs Countries	Approx. # Foreign Buildings
50	35	15	2000

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Path Forward

During our inspections of Importers

Inspectors:

- **Verify completeness of Table A**
- **Verify that the type of GMP evidence supporting each foreign API site matches what the importer has on site, and depending on the evidence**
- **Verify that the GMP Evidence of all Foreign API sites indicate: a Compliant rating, the issuance date, the signing authority, the scope of the inspection and corrective actions**

International Collaboration

- **At this time, APIs are not included in the Mutual Recognition Agreements (MRAs) Canada has with the European Community, Switzerland, Australia**

- **Discussions are ongoing to establish Regulatory equivalency with our MRA partners in order to include API in our existing MRAs**

- **We will continue to collaborate with trusted regulatory partners on joint inspections and leverage inspections conducted by these regulatory partners wherever possible**

Going Forward

Going forward we will be:

- **Continuing with API inspections**
- **Further integrating API inspections into domestic FDF inspections**
- **Strengthening our oversight of foreign sites**
- **Implementing a new IT/IM System**
- **Addressing challenges with data management**

Transparency

Objectives of Transparency

- Help Canadians to better understand how and why our decisions are made. They can use this information to make well-informed decisions on their health and the health of their families.

- Assist industry to be better positioned to comply with current regulatory requirements and plan for upcoming regulatory changes.

New Initiatives

- Inspection Tracker
- Initial Inspection Deficiencies
- Inspection Report Card Summaries
- Domestic GMP Inspection List
- Foreign GMP Inspection List

Inspection Tracker

Inspection Tracker:

- Publishes information regarding emerging issues identified through Health Canada's drug inspection program
- Provides a snapshot of *potential* health and safety issues that Health Canada is tracking with drug companies
- Highlights actions Health Canada is taking such as:
    - requests for voluntary quarantine
    - stop sales
    - import restrictions
    - product recalls
- The tracker is updated regularly

Initial Inspection Deficiencies

The Initial Inspection Deficiencies (IID):

- Posted on www.healthycandians.gc.ca
- Linked to Inspection Listings
- Posted within 3 days of an inspector leaving the site of an inspection.
- High level Standard lines describing Regulatory Sections where deficiencies were noted

Inspection Report Cards

The Inspection Report Cards (IRC):

- Posted on www.healthycanadians.gc.ca
- Linked to Inspection Listings
- Posted after Exit Notice/Inspection Report is finalised.
- Standard lines describing nature of the observations noted, more specific than the IID standard lines.

Transparency Timelines

2013 & 2014 - Published 1st and 2nd Annual Reports

Dec 2014 – Posted NC Report Cards

Dec 2014 – Posted Domestic Inspection List

Feb 2015 – Launched Inspection Tracker

April 2015 – Begin posting Report Cards for all Drug GMP inspections

Spring 2015 – Launch Inspection Web Application and List of Foreign Sites

Spring 2015 – 3rd Annual Report

2015-2016 – Expand Inspection Report Cards to all Inspection Programs

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Inspection Transparency Timelines

- Inspectorate Annual Reports published in 2013 & 2014
- December 2014 – posted Non-Compliant Inspection Report Card Summaries for any NC ratings issued from 2012 - 2014
- December 2014 – posted Domestic GMP Inspection List with all ratings for all inspections from 2012 - 2014
- February 2015– Launched Inspection Tracker, to be updated weekly
- April 1, 2015 – Report Card Summaries created for all Drug GMP Inspections
- Spring 2015 – Planned launch of Inspection web application and List of Foreign Sites
- 2015 / 2016 (On-going) – Expand Inspection Report Card Summaries to other inspection programs (Medical Devices, Good Clinical Practices, Good Vigilance Practices, etc)

QUESTIONS?

Email: gmp_questions_bpf@hc-sc.gc.ca
APIs: api_questions_ipa@hc-sc.gc.ca

Please remember, the clearer and more specific your question is, the higher the likelihood we will be able to provide a helpful response!

Thank you!