Canada Gazette
- About Us
- Mandate
- Service Standards
- History since 1841
- Learn more about the *Canada Gazette*

Consultation
- What is the consultation process?
- Current Consultations

Archives
- Part : Notices and Proposed Regulations
- Part : Official Regulations
- Part : Acts of Parliament
- Quarterly Index and Consolidated Index
- 1841–1997

Publishing Information
- Publishing Requirements
- Deadline Schedule
- Request for Insertion Forms
- Insertion Rates
- Subscription Information
- Publication of Extra Editions (Part and Part)

Resources
- News and Announcements
- FAQ

Vol. 147, No. 10 — May 8, 2013

Registration

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FOOD AND DRUGS ACT

Regulations Amending the Food and Drug Regulations (1475 — Good Manufacturing Practices)

P.C. 2013-420 April 25, 2013

His Excellency the Governor General in Council, on the recommendation of the Minister of Health, pursuant to section 30 (see footnote a) of the *Food and Drugs Act* (see footnote b), makes the annexed *Regulations Amending the Food and Drug Regulations (1475 — Good Manufacturing Practices)*.

REGULATIONS AMENDING THE FOOD AND DRUG REGULATIONS (1475 — GOOD MANUFACTURING PRACTICES)

AMENDMENTS

1. The definition "expiration date" in subsection C.01.001(1) of the *Food and Drug Regulations* (see footnote 1) is replaced by the following:

"expiration date" means

(*a*) in the case of a drug in dosage form, the earlier of the following dates, expressed at minimum as a year and month:

(i) the date up to and including which the drug maintains its labelled potency, purity and physical characteristics, and

(ii) the date after which the manufacturer recommends that the drug not be used; and

(*b*) in the case of an active ingredient, whichever of the following dates is applicable, expressed at minimum as a year and month:

(i) the retest date, or

(ii) the date after which the manufacturer recommends that the active ingredient not be used. (*date limite d'utilisation*)

2. (1) The definition "wholesale" in subsection C.01A.001(1) of the Regulations is repealed.

(2) Subsection C.01A.001(1) of the Regulations is amended by adding the following in alphabetical order:

"active ingredient" means a drug that, when used as a raw material in the fabrication of a drug in dosage form, provides its intended effect. (*ingrédient actif*)

"active pharmaceutical ingredient" means an active ingredient that is used in the fabrication of a pharmaceutical. (*ingrédient actif pharmaceutique*)

"bulk process intermediate" means an active ingredient that is used in the fabrication of either a drug of biological origin that is listed in Schedule C to the Act or a drug that is listed in Schedule D to the Act. (*produit intermédiaire en vrac*)

"wholesaler" means a person who is not a distributor described in section C.01A.003 and who sells any of the following drugs other than at retail sale:

(*a*) a drug in dosage form that is listed in Schedule C or D to the Act or in Schedule F to these Regulations, or a controlled drug as defined in subsection G.01.001(1);

(*b*) an active ingredient; or

(*c*) a narcotic as defined in the *Narcotic Control Regulations*. (*grossiste*)

(3) Subsection C.01A.001(2) of the Regulations is replaced by the following:

(2) In this Division and in Division 2, "drug" does not include a dilute drug premix, a medicated feed as defined in subsection 2(1) of the *Feeds Regulations, 1983*, an active ingredient that is for veterinary use or a drug that is used only for the purposes of an experimental study in accordance with a certificate issued under section C.08.015.

3. Section C.01A.003 of the Regulations is replaced by the following:

C.01A.003. This Division and Divisions 2 to 4 apply to the following distributors:

(*a*) a distributor of an active ingredient or a drug in dosage form that is listed in Schedule C to the Act; and

(*b*) a distributor of a drug for which the distributor holds the drug identification number.

4. Subsection C.01A.004(1) of the Regulations is replaced by the following:

C.01A.004. (1) Subject to subsection (2), no person shall, except in accordance with an establishment licence,

(*a*) fabricate, package/label or import a drug;

(*b*) perform the tests, including examinations, required under Division 2;

(*c*) distribute a drug as set out in section C.01A.003 that is not an active pharmaceutical ingredient; or

(*d*) wholesale a drug that is not an active pharmaceutical ingredient.

5. (1) Paragraphs C.01A.005(*f*) and (*g*) of the Regulations are replaced by the following:

(*f*) whether the applicant proposes to carry out a licensed activity in respect of an active ingredient;

(*g*) the address of each building in Canada in which the applicant proposes to fabricate, package/label, test as required under Division 2 or store drugs, specifying for each building the activities and the categories of drugs and, for each category, the dosage form classes, if any, and whether any drug will be in a sterile form;

(2) Subparagraph C.01A.005(*m*)(i) of the Regulations is replaced by the following:

(i) the name and address of each fabricator, packager/labeller and tester of the drug and the address of each building in which the drug is fabricated, packaged/labelled or tested, specifying for each building the activities and the categories of drugs and, for each category, the dosage form classes, if any, and whether any drug will be in a sterile form,

(3) Paragraph C.01A.005(*n*) of the Regulations is replaced by the following:

(*n*) in the case of any other importer, the name and address of each fabricator, packager/labeller and tester of the drugs proposed to be imported and the address of each building in which the drugs will be fabricated, packaged/labelled and tested, specifying for each building the activities and the categories of drugs and, for each category, the dosage form classes, if any, and whether any drug will be in a sterile form; and

6. (1) Item 4 of Table I to section C.01A.008 of the Regulations is replaced by the following:

Item	Activities
4.	Distribute as set out in paragraph C.01A.003(*a*) a drug that is not an active pharmaceutical ingredient

(2) Item 7 of Table I to section C.01A.008 of the Regulations is replaced by the following:

Item	Activities
7.	Wholesale a drug that is not an active pharmaceutical ingredient

(3) Table II to section C.01A.008 of the Regulations is amended by adding the following after item 1:

Item	Categories of drugs
1.1	Active ingredients

7. The Regulations are amended by adding the following after section C.02.003:

C.02.003.1 No person shall sell a drug that they have fabricated, packaged/labelled, tested or stored unless they have fabricated, packaged/labelled, tested or stored it in accordance with the requirements of this Division.

C.02.003.2 (1) No person shall import an active ingredient into Canada for the purpose of sale unless they have in Canada a person who is responsible for its sale.

(2) No person who imports an active ingredient into Canada shall sell any lot or batch of it unless the following appear on its label:

(*a*) the name and civic address of the person who imports it; and

(*b*) the name and address of the principal place of business in Canada of the person who is responsible for its sale.

Use in Fabrication

C.02.003.3 No person shall use an active ingredient in the fabrication of a drug unless it is fabricated, packaged/labelled, tested and stored in accordance with the requirements of this Division.

8. Subsections C.02.012(2) to (4) of the Regulations are replaced by the

following:

(2) Every fabricator and packager/labeller and, subject to subsections (3) and (4), every distributor referred to in paragraph C.01A.003(*b*) and importer of a drug shall maintain a system to ensure that any lot or batch of the drug fabricated and packaged/labelled on premises other than their own is fabricated and packaged/labelled in accordance with the requirements of this Division.

(3) Subsection (2) does not apply to a distributor if the drug is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes those activities in respect of that drug.

(4) Subsection (2) does not apply to a distributor or importer if the drug is fabricated or packaged/labelled in an MRA country at a recognized building and both of the following requirements are met:

(*a*) the address of the building is set out in their establishment licence; and

(*b*) they retain a copy of the batch certificate for each lot or batch of the drug that they receive.

9. Sections C.02.013 and C.02.014 of the Regulations are replaced by the following:

C.02.013. (1) Every fabricator, packager/labeller, wholesaler, distributor referred to in section C.01A.003 and importer of a drug shall have on their premises in Canada a quality control department that is supervised by personnel described in section C.02.006.

(2) Except in the case of a wholesaler or a distributor referred to in paragraph C.01A.003(*a*), the quality control department shall be a distinct organizational unit that functions and reports to management independently of any other functional unit, including the manufacturing, processing, packaging or sales unit.

C.02.014. (1) Except in the case of a wholesaler or a distributor referred to in paragraph C.01A.003(*a*), no lot or batch of a drug shall be made available for further use in fabrication or for sale unless the person in charge of the quality control department approves the sale or the further use.

(2) A drug that is returned to its fabricator, packager/labeller, wholesaler, distributor referred to in section C.01A.003 or importer shall not be made available for further use in fabrication or for further sale unless the person in charge of the quality control department approves the further sale or further use.

(3) No lot or batch of a raw material or packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug unless the person in charge of the quality control department approves the use.

(4) No lot or batch of a drug shall be reprocessed unless the person in charge of the quality control department approves the reprocessing.

10. Subsections C.02.018(1) and (2) of the Regulations are replaced by the following:

C.02.018. (1) Each lot or batch of a drug shall, before it is made available for further use in fabrication or for sale, be tested against the specifications for that drug.

(2) No lot or batch of a drug shall be made available for further use in fabrication or for sale unless it complies with the specifications for that drug.

11. Sections C.02.019 to C.02.023 of the Regulations are replaced by the following:

C.02.019. (1) A packager/labeller of a drug, a distributor referred to in paragraph C.01A.003(*b*) and an importer of a drug other than an active ingredient shall perform the finished product testing on a sample of the drug that is taken either

(*a*) after receipt of each lot or batch of the drug on their premises in Canada; or

(*b*) before receipt of each lot or batch of the drug on their premises in Canada if the following conditions are met:

(i) the packager/labeller, distributor or importer

(A) has evidence satisfactory to the Director to demonstrate that drugs sold to them by the vendor of that lot or batch are consistently manufactured in accordance with and consistently comply with the specifications for those drugs, and

(B) undertakes periodic complete confirmatory testing, with a frequency satisfactory to the Director, and

(ii) the drug has not been transported or stored under conditions that may affect its compliance with the specifications for that drug.

(2) If the packager/labeller, distributor or importer receives a lot or batch of a drug on their premises in Canada the useful life of which is more than 30 days, the lot or batch shall be tested for identity and the packager/labeller shall confirm the identity after the lot or batch is packaged/labelled.

(3) Subsections (1) and (2) do not apply to a distributor if the drug is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes that activity.

(4) Subsections (1) and (2) do not apply to a distributor or importer if the drug is fabricated, packaged/labelled and tested in an MRA country at a recognized building and both of the following requirements are met:

(*a*) the address of the building is set out in their establishment licence; and

(*b*) they retain a copy of the batch certificate for each lot or batch of the drug that they receive.

Records

C.02.020. (1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(*b*) and importer shall maintain all of the following records on their premises in Canada for each drug that they fabricate, package/label, distribute or import:

(*a*) except in the case of an importer of an active pharmaceutical ingredient, master production documents for the drug;

(*b*) evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents;

(*c*) evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and stored are in compliance with the requirements of this Division;

(*d*) evidence that establishes the period during which the drug in the container in which it is sold or made available for further use in fabrication will meet the specifications for that drug; and

(*e*) evidence that the finished product testing referred to in section C.02.018 was carried out and the results of that testing.

(2) Every distributor referred to in paragraph C.01A.003(*b*) and importer shall make available to the Director, on request, the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of a drug that it distributes or imports.

(3) Every fabricator shall maintain on their premises written specifications for all raw materials and adequate evidence of the testing of those raw materials referred to in section C.02.009 and of the test results.

(4) Every person who packages a drug shall maintain on their premises written

specifications for all packaging materials and adequate evidence of the examination or testing of those materials referred to in section C.02.016 and of any test results.

(5) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada detailed plans and specifications of each building in Canada where they fabricate, package/label or test drugs and a description of the design and construction of those buildings.

(6) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada personnel records in respect of each person who is employed to supervise the fabrication, packaging/labelling and testing of drugs, including the person's title, responsibilities, qualifications, experience and training.

C.02.021. (1) All records and evidence of the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage of a drug in dosage form that are required to be maintained under this Division shall be retained for one year after the expiration date of the drug unless the person's establishment licence specifies some other period.

(2) Subject to subsection (4), all records and evidence of the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage of an active ingredient that are required to be maintained under this Division shall be retained in respect of each lot or batch of the active ingredient for the following period unless the person holds an establishment licence that specifies some other period:

(*a*) in the case of an active ingredient that has a retest date, three years after the lot or batch has been completely distributed; or

(*b*) in any other case, one year after the expiration date of the lot or batch.

(3) Subject to subsection (4), all records and evidence of the raw material testing referred to in section C.02.009 and of the testing of packaging/labelling materials that are required to be maintained under this Division shall be retained for five years after the raw materials and packaging/labelling materials were last used in the fabrication or packaging/labelling of a drug unless the person's establishment licence specifies some other period.

(4) If a fabricator is required to maintain records and evidence in respect of the same active ingredient under subsections (2) and (3), they shall maintain them for the longest period that is applicable.

C.02.022. (1) Every wholesaler, distributor referred to in section C.01A.003 and importer of a drug in dosage form shall retain records of sale of each lot or batch of the drug, which enable them to recall the lot or batch from the market, for one year after the expiration date of that lot or batch unless their establishment licence specifies some other period.

(2) Every distributor of an active ingredient referred to in paragraph C.01A.003(*a*) and every wholesaler and importer of an active ingredient shall retain records of sale of each lot or batch of the active ingredient, which enable them to recall the lot or batch from the market, for the following period unless the person holds an establishment licence that specifies some other period:

(*a*) in the case of an active ingredient that has a retest date, three years after the lot or batch has been completely distributed; or

(*b*) in any other case, one year after the expiration date of the lot or batch.

C.02.023. (1) On receipt of a complaint or any information respecting the quality of a drug or its deficiencies or hazards, every fabricator, packager/labeller, wholesaler, distributor referred to in section C.01A.003 and importer of the drug shall make a record of the complaint or information that contains the following:

(*a*) the results of any investigation carried out under subsection C.02.015(2) and, if applicable, the corrective action taken; or

(*b*) the name and business address of the person in charge of the quality control department to whom the complaint or information was forwarded under subsection C.02.015(2.1) and the date on which it was forwarded.

(2) Records referred to in subsection (1) shall be retained for the following period unless the person holds an establishment licence that specifies some other period:

(*a*) in the case of a drug in dosage form, one year after the expiration date of the lot or batch of the drug; and

(*b*) in the case of an active ingredient,

(i) if the active ingredient has a retest date, three years after the lot or batch has been completely distributed, or

(ii) in any other case, one year after the expiration date of the lot or batch of the active ingredient.

12. The Regulations are amended by adding the following after section C.02.024:

C.02.024.1 Every distributor of an active ingredient referred to in paragraph C.01A.003(*a*) and every fabricator, packager/labeller, wholesaler and importer of an active ingredient shall add all of the following information to the documentation that accompanies the active ingredient, immediately after any like information that has been added by another person:

(*a*) their establishment licence number, or if there is none, their name, address, telephone number, fax number and email address;

(*b*) an indication whether they have fabricated, packaged/labelled, wholesaled, distributed or imported the active ingredient and the date on which that activity was carried out;

(*c*) the expiration date; and

(*d*) the lot number.

13. Section C.02.025 of the Regulations is replaced by the following:

C.02.025. (1) Every distributor referred to in paragraph C.01A.003(*b*) and importer of a drug in dosage form shall retain in Canada a sample of each lot or batch of the packaged/labelled drug for one year after the expiration date of the drug unless their establishment licence specifies some other period.

(2) Subject to subsection (4), the fabricator of a drug in dosage form shall retain a sample of each lot or batch of raw materials used in the fabrication for two years after the materials were last used in the fabrication unless their establishment licence specifies some other period.

(3) Subject to subsection (4), the fabricator of an active ingredient shall retain a sample of each lot or batch of it for the following period unless their establishment licence specifies some other period:

(*a*) in the case of an active ingredient that has a retest date, three years after the lot or batch has been completely distributed; or

(*b*) in any other case, one year after the expiration date of the lot or batch.

(4) If a fabricator is required to maintain samples in respect of the same active ingredient under subsections (2) and (3), they shall maintain them for the longest period that is applicable.

14. Sections C.02.027 and C.02.028 of the Regulations are replaced by the following:

C.02.027. (1) Every distributor referred to in paragraph C.01A.003(*b*) and importer of a drug in dosage form shall establish the period during which each drug in the package in which it is sold will comply with the specifications for that drug.

(2) Every fabricator and importer of an active ingredient shall establish the period during which each drug in the package in which it is sold will comply with the specifications for that drug.

C.02.028. (1) Every distributor referred to in paragraph C.01A.003(*b*) and importer of a drug in dosage form shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

(2) Every fabricator and importer of an active ingredient shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

15. The definition "drug" in section C.03.001 of the Regulations is replaced by the following:

"drug" means a drug that is listed in Schedule C to the Act that is in dosage form or a drug that is an active ingredient of biological origin that can be used in the preparation of a drug listed in that Schedule; (*drogue*)

16. The definition "drug" in section C.04.001 of the Regulations is replaced by the following:

"drug" means a drug that is listed in Schedule D to the Act that is in dosage form or a drug that is an active ingredient that can be used in the preparation of a drug listed in that Schedule; (*drogue*)

TRANSITIONAL PROVISIONS

17. (1) Every person who, on the day on which these Regulations come into force, fabricates, packages/labels, tests or imports an active pharmaceutical ingredient may continue to do so without an establishment licence if they submit an application for a licence under section C.01A.005 of the *Food and Drug Regulations* within three months after that day.

(2) Subsection (1) applies until the determination of the licence application under section C.01A.008 or C.01A.010 of the *Food and Drug Regulations*.

18. The *Food and Drug Regulations*, as they read immediately before the coming into force of these Regulations, continue to apply in respect of whole blood and blood components for a period of one year after the day on which these Regulations come into force.

COMING INTO FORCE

19. These Regulations come into force six months after the day on which they are published in the *Canada Gazette*, Part II.

REGULATORY IMPACT ANALYSIS STATEMENT

(*This statement is not part of the Regulations*.)

Executive summary

Issues: The quality of active ingredients (AI) in a drug has a direct effect on the safety and efficacy of that drug. Poorly manufactured and contaminated AI have been associated with negative health outcomes, including death, in a number of incidents over the past decades. Worldwide, there has been growing concern over the quality of AI as the manufacturing of AI and dosage-form drugs has been increasingly outsourced to developing countries.

In 2000, the international community of pharmaceutical regulators and manufacturers developed and adopted a guideline concerning good manufacturing practices (GMP) for AI. In the years since the guideline was finalized, most of the industrialized world has implemented the guideline in

law. These Regulations will make GMP for AI a regulatory requirement in Canada as well, helping to ensure the quality of AI in drugs available to Canadians and bringing Canada into line with its international regulatory counterparts.

Description: These Regulations will extend the drug GMP requirements set out in the *Food and Drug Regulations* such that they apply to all AI; extend the drug establishment licensing (EL) requirements set out in the *Food and Drug Regulations* such that they apply to all AI fabricators, packagers/labellers, testers and importers; and create a new record-keeping requirement to foster the traceability of AI from the original fabricator to the dosage-form drug manufacturer.

Cost-benefit statement: These Regulations will provide a net benefit to Canadians, with a net present value (NPV) of about $33.4 million over 10 years. The quantified benefits relate primarily to cost savings to industry due to removal of poor-quality drug products at the AI stage instead of recalls at the dosage-form stage. The qualitative benefits relate primarily to better protection for Canadians from poor-quality drug products.

"One-for-One" Rule and small business lens: The "One-for-One" Rule applies to these Regulations. Specifically, the administrative burden is estimated to have an annualized "IN" value of $58,500. The small business lens requirements do not apply to these Regulations as the annual average regulatory burden (compliance and administrative costs) to industry of the Regulations is estimated to be $196,000, well below the threshold of $1 million.

Domestic and international coordination and cooperation: These Regulations will allow Canada to establish regulatory equivalence in respect of AI with other industrialized countries, particularly those with which Canada has a Mutual Recognition Agreement (MRA). This will reduce duplicative regulatory oversight, facilitate participation by Canadian manufacturers in the international pharmaceutical market, and allow Health Canada to reciprocate in international regulatory work-sharing to ensure the safety of the global AI supply.

Issue

Active ingredients (AI) are substances or mixture of substances that, when used as a raw material in the fabrication of a drug in dosage form, provide the intended effect. The AI contained in most pharmaceuticals are chemical in origin and are often referred to as active pharmaceutical ingredients (API). Examples would include the acetaminophen contained in a pain relief tablet, or the sildenafil citrate contained in an erectile dysfunction drug. AI of biological origin are often referred to as bulk process intermediates (BPI). One example would be the insulin contained in an insulin pen cartridge, for use by diabetics.

The quality of the AI in a drug has a direct effect on the safety and efficacy of that drug. Poorly manufactured and contaminated AI have been associated with negative health outcomes, including death, in a number of incidents over the past decades. A recent example is the 2008 international crisis regarding contaminated heparin, a blood-thinning drug. An investigation by the U.S. Food and Drug Administration (FDA) revealed that bulk heparin sodium (an AI) purchased from an Asian supplier by the U.S. drug manufacturer was contaminated with oversulfated chondroitin sulphate (OSCS). As of April 29, 2008, the FDA associated 81 deaths and 785 serious injuries in the United States with tainted doses of heparin. (see footnote 2) Worldwide, there has been growing concern over the quality of AI as the manufacturing of AI and dosage-form drugs has been increasingly outsourced to developing countries.

In Canada, the quality of drugs in dosage form and higher-risk AI (namely, BPI) is

ensured through, among other things, the imposition of good manufacturing practices (GMP). GMP ensure that products are consistently produced and controlled according to quality standards. However, there are no GMP requirements for API, the AI used in most pharmaceuticals. Current regulatory requirements pertaining to such AI mostly involve testing before use in a dosage-form drug, which cannot eliminate all risks. (see footnote 3) Testing is also incapable of retroactively improving the quality of a product — an AI which has failed testing must either be destroyed without recovery of the cost of manufacture, or sold into a market which will accept substandard AI (e.g. a country with poor or no regulatory control over drugs, or a counterfeit drug ring).

In 2000, in recognition of the risks posed by poorly manufactured AI in a globalized pharmaceutical market, the international community of pharmaceutical regulators and manufacturers developed and adopted a guideline concerning GMP for AI, known as International Conference on Harmonisation (ICH) guideline Q7. In the years since ICH guideline Q7 was finalized, most of the industrialized world, including the United States, the European Union, Japan, Singapore and Australia, has implemented the guideline in law.

These Regulations will make GMP for all AI a regulatory requirement in Canada as well, helping to ensure the quality of AI that are used in drugs available to Canadians, whether imported or domestically manufactured.

By bringing Canada into line with its international regulatory counterparts, the Regulations will also allow Canada to establish regulatory equivalence in respect of AI with other industrialized countries, particularly those with which it has a Mutual Recognition Agreement (MRA). (see footnote 4) In evaluating the safety of AI manufactured outside of Canada, Health Canada will be able to take advantage of GMP inspections by trusted international partners. Conversely, Canadian manufacturers will be able to leverage their compliance with Canadian requirements and inspection results from Health Canada to participate in the international drug market. Finally, Health Canada will be able to reciprocate in international regulatory work-sharing, joining ongoing programs (see footnote 5) with other regulators to inspect AI manufacturing sites located in developing countries, and otherwise doing its part to ensure the safety of the global AI supply.

Objectives

The main objective of the Regulations is to protect the health and safety of Canadians by implementing into regulation internationally accepted GMP for AI requirements. A secondary objective is to ensure that the associated regulatory burden is mitigated by compensating efficiencies or minimized to the extent possible.

Description

The enabling legislation is the *Food and Drugs Act*. These Regulations will amend the *Food and Drug Regulations* as follows.

Good manufacturing practices requirements

The Regulations will generally impose on the fabrication, packaging/labelling, testing, storing and transport of all AI the GMP requirements which currently apply to dosage-form drugs and the subset of AI known as BPI. This will be accomplished through the amendment of the definition of “drug” for the purposes of Division 2 of Part C of the *Food and Drug Regulations*. The Regulations will also amend or add provisions tailored to AI in accordance with ICH guideline Q7 where necessary (e.g. adding AI-specific record retention periods).

Under the Regulations, no person who has fabricated, packaged/labelled, tested or stored a drug will be permitted to sell the drug unless they have performed their activity in accordance with GMP requirements. Dosage-form fabricators will be required to use only GMP-compliant AI in their drugs. A Drug Identification Number (DIN)-holding

distributor or importer of a dosage-form drug will be prohibited from selling the drug unless it — including any AI used in it — are GMP-compliant.

The Regulations will carry out the main objective of improving the quality of AI used in drugs in Canada by implementing into regulation internationally accepted GMP for AI requirements.

Establishment licensing requirements

The Regulations will extend EL requirements to all AI fabricators, packagers/labellers, testers and importers. As with current EL holders, an EL will not be issued until the applicant has been assessed by Health Canada and found to be in compliance with GMP requirements.

Distributors and wholesalers of the subset of AI known as API, which only store and transport already-packaged and -labelled API, will be subject to the applicable GMP requirements but will not be required to apply for an EL, as the risks do not warrant the imposition of an EL requirement and accompanying inspection program. (see footnote 6) Dosage-form and BPI distributors and wholesalers will continue to be subject to EL requirements.

The Regulations will thus provide Health Canada with oversight and enforcement authorities regarding the riskiest activities in the AI supply chain, while ensuring the regulatory burden is not extended unnecessarily.

Traceability requirement

Every fabricator, packager/labeller, distributor, wholesaler and importer of an AI, whether an API or a BPI, will be required to include, on the container label or on other documentation accompanying the drug, directly following the information provided by any previous party (*a*) the regulated party's name, contact details, and EL number, if applicable; (*b*) whether it has fabricated, packaged/labelled, distributed, wholesaled or imported the drug; (*c*) the date of that activity; (*d*) the expiration or re-test date of the drug; and (*e*) the lot number of the drug.

This record-keeping amendment fostering the traceability of AI will help to protect the health and safety of Canadians in several ways. It will allow for more rapid and targeted investigation and recall of problematic AI. It will also make the introduction of illegitimate, substandard AI into the supply chain more difficult as verification of an AI's provenance will be simplified.

The anticipated burden of this new requirement will be minimized to the extent possible by requiring only basic, easily available information from each regulated party, and by being nonprescriptive in terms of the format of the documentation. The burden will also be offset by the greater efficiency it will lend to both Health Canada when carrying out regulatory actions, and other regulated parties in complying with their obligations (such as the dosage-form manufacturer's obligation to verify the GMP compliance of the AI they use). Such transparency in the Canadian AI supply chain will also help to foster international confidence in the Canadian drug industry generally.

Transition period

The Regulations will come into force six months after the day on which they are published in the *Canada Gazette*, Part II. This delay in the coming into force of the Regulations will allow all regulated parties to adjust to the new requirements. Furthermore, on the day the Regulations come into force, any person who fabricates, packages/labels, tests or imports an API will be allowed to continue to do so without an EL provided they submit an EL application within three months after the coming into force of the Regulations. This transition provision will ensure that regulated parties do not find themselves in a state of non-compliance solely due to any Health Canada

administrative delays.

Miscellaneous

Veterinary drugs: AI included solely in drug products for veterinary use are not within the scope of the Regulations.

Natural health products: As with veterinary drugs, AI included solely in natural health products are not within the scope of the Regulations.

Whole blood and blood components: Until the new *Blood Regulations* are made, existing requirements, as they read immediately before the coming into force of the *Regulations Amending the Food and Drug Regulations (1475 — Good Manufacturing Practices)*, will continue to apply to whole blood and blood components.

Regulatory and non-regulatory options considered

The following regulatory and non-regulatory options were considered.

Option 1: Status quo

Currently, API (a subset of AI) are not subject to any direct regulatory requirements other than the requirement for dosage-form fabricators to test a sample of each lot or batch of raw material against its specifications. The only assessment by Health Canada of API quality takes place during the pre-market drug submission review. The pre-market assessment provides an evaluation of the quality of the proposed API at the time of the application to market the dosage-form drug, but the evaluation is focused on the API's chemical properties and method of manufacture, and does not cover critical GMP areas such as quality management, facilities, and materials management (among others). This approach does not provide for oversight once manufacturing is underway.

A benefit of this option is that no additional financial costs for Health Canada or for regulated parties would be incurred. However, it constitutes an ongoing risk to the health and safety of Canadians. Also, under this option, Canada continues to be unable to participate in international regulatory cooperation to ensure the safety of the global AI supply, and Canadian industry continues to face barriers to entry into the global drug market.

Option 2: More active and ongoing promotion of the voluntary implementation of GMP for AI

Health Canada guidance documents currently recommend voluntary implementation of ICH guideline Q7. Option 2 differs from Option 1 (status quo) in that it would involve more active and ongoing promotion by Health Canada of GMP for AI on a voluntary basis.

Knowledge of the benefits of GMP for AI is currently well disseminated throughout industry. Most Canadian companies which voluntarily comply with ICH guideline Q7 do so for the purposes of fulfilling the requirements of foreign regulatory authorities and business partners. These companies have some difficulty being inspected or audited for compliance, sometimes needing to arrange and pay for "foreign" inspections from their target markets, which puts them at a disadvantage compared to companies based in jurisdictions which have implemented requirements for, and inspect against, GMP for AI. Companies which sell only in Canada and which have voluntarily adopted ICH guideline Q7 as a best practice, to the benefit of Canadians, may be at a competitive disadvantage compared to other non-exporting companies which have chosen not to incur the additional cost of following ICH guideline Q7.

It is doubtful that further promotion by Health Canada at this point would motivate more of the Canadian AI industry to voluntarily adopt GMP. Under Option 2, Canadian companies which do not undertake foreign inspections would continue to be unable to

participate in the international pharmaceutical market, and Canada would continue to be unable to participate in international regulatory cooperation to ensure the safety of the global AI supply.

Option 3: Regulatory amendment

Under this recommended option, following GMP for AI will become mandatory for Canadian industry and enforceable by Health Canada. Such a regulatory approach is consistent with Canada's current regulatory framework, which imposes GMP requirements for dosage-form drugs and BPI (AI of biological origin). The approach is also consistent with the approach taken by many of Canada's international regulatory counterparts, including the European Union, the United States, Japan, Singapore and Australia. A regulatory approach will allow for the extension of existing MRA arrangement to apply also to AI, and permit Health Canada to engage in international regulatory work-sharing in respect of GMP for AI inspections.

At some point in the future, Health Canada may consider the merits of developing a regulatory amendment to recover from industry some of the cost of conducting inspections by imposing EL fees similar to those currently in place for dosage-form drugs and BPI.

Benefits and costs

Cost-benefit statement

As AI of biological origin (BPI) are already regulated in Canada due to their higher-risk nature, the focus of the cost-benefit analysis is primarily on API. As indicated in the cost-benefit analysis, the Regulations will provide a net benefit to Canadians, with a net present value (NPV) of about $33.4 million over 10 years. The complete cost-benefit analysis is available upon request.

A. Quantified impacts ($)

		Base Year	Final Year (see footnote 7)	Total (PV) (see footnote 8)	Annual Average
Benefits	Industry — "Foreign" inspection fees savings for Canadian manufacturers selling abroad. (see footnote 9)	$0.7M	$1.6M (see footnote 10)	$8.9M	$1.3M
	Industry — Cost savings due to removal of poor quality drug products at API stage instead of dosage-form stage. (see footnote 11)	$2.4M (see footnote 12)	$5.6M	$34.4M	$4.9M
	Total benefits	**$3.1M**	**$7.2M**	**$43.3M**	**$6.2M**

Costs	Industry — Training and administration costs for API fabricators, packagers/labellers, testers, importers, distributors and wholesalers.	$1.0M (see footnote 13)	<$0.1M	$1.4M	<$0.2M
	Health Canada — Administration of new requirements.	$0.1M	$1.7M	$8.5M	$1.2M
	Total costs	**$1.1M**	**$1.8M**	**$9.9M**	
Net present value (NPV)				**$33.4M**	

B. Positive qualitative impacts

- Potential reduction in the number of recall incidents due to API quality issues.
- Reduced impact of recalls should they occur by helping to narrow down the scope of the recall, through problem identification and record-keeping requirements that allows the isolation of problem lots.
- Consumers and patients, as well as Canada's international regulatory counterparts, are assured explicitly that API in dosage-form drugs sold in Canada are meeting the international safeguard standard (GMP).
- As the number of jurisdictions requiring API to meet the international standard continues to expand, the implementation of the Regulations will protect Canada against the increased risk of becoming a destination to divert non-GMP-compliant products to, which in turn could translate into health costs to Canadians, and sales and economic costs to business.
- The Regulations will allow Health Canada to establish regulatory equivalence with its international counterparts, enabling Health Canada to reciprocate in international regulatory work-sharing to ensure the safety of the global AI supply.
- Establishing regulatory equivalence will also result in the reduction of duplicative oversight by various regulators internationally, and the reduction of Canadian manufacturers' worldwide compliance costs, consistent with the Government of Canada's Red Tape Reduction Initiative.

Benefits

Canadian consumers and patients

Although no Canadian data is currently available, the GMP requirements should reduce the future risk of pharmaceuticals for human use with substandard AI being on the Canadian market, given the experience of the World Health Organization (WHO), (see footnote 14) the European Union (see footnote 15) and countries that have implemented

similar regulations. This in turn could reduce the health hazards for consumers and patients. Also, the increased ability of the system to trace problematic API will allow removal of such products from circulation more rapidly, which in turn could reduce the risk of their use and consumption by consumers and patients.

Furthermore, as the number of jurisdictions requiring API to meet the international Q7 standard continues to expand, without the Regulations, Canada would increasingly run the risk of becoming a destination to divert non-compliant products to, which in turn could translate into health costs to Canadians and sales and economic costs to business.

At a minimum, the Regulations will provide additional assurance that patients and consumers are "getting what they pay for," i.e. drug products with the expected quality, safety and efficacy. Given that Canadians spent about $31.1 billion on drugs outside hospital settings in 2010, (see footnote 16) the prevention of the entry of a miniscule percentage of drugs with substandard AI into the market could translate into a significant amount in dollar terms.

Industry

Once the GMP for AI requirements are in place, they should reduce wastage, save costs and minimize negative impacts by allowing for timelier discovery and better pinpointing of the specific troubling areas, rather than later during the dosage-form manufacturing process or after the drugs have been on the market, when additional investment has been made. This additional investment could range from a minimum of 50%–60% for a generic oral solid (see footnote 17) to a possible higher percentage for those products still under patent protection, where the API represent a lesser percentage in total cost.

Because Canada does not regulate API directly at present, there are no specific Canadian data available. Nevertheless, there is evidence to support API-related problems being responsible for an estimated 2%–8% of dosage-form recalls in this country. There were between 135 and 241 recalls in Canada during the last four years with an annual average of 193 recalls. In the past, industry has suggested informally that it costs the sector about $1 million per recall in Canada. If the GMP requirements prevent the need for 2%–8% of recalls, the savings could range between $3.8 million and $15.4 million annually. At the very least, the savings could be worth between $1.9 million and $7.7 million if the recalls are triggered at the API stage rather than at the dosage-form stage.

The traceability requirement in the Regulations will help drug manufacturers in Canada to identify API problems specifically and possibly earlier in the supply chain — a process that should already be considered best business practice. The benefits of traceability are best illustrated by a recent case in which the AI of two biologics for the treatments of a couple of rare maladies were found by the U.S. FDA to be contaminated. (see footnote 18)

According to the American manufacturing company, the supply constraint due to the manufacturing problems adversely impacted its bottom line by about $451 million. (see footnote 19) However, the situation could have been much worse if the entire production had had to be shut down and the inventory had been deemed contaminated — one AI alone could have reduced the company's revenue by an additional $793 million. (see footnote 20), (see footnote 21) As it was, the ability to trace allowed the company to identify the problem lots, and salvage the rest. Because the drugs are for rare diseases and the production from the only facility of the U.S. firm is small to begin with, there could have been significant health consequences to patients if the supply of AI from the whole plant had had to be disposed of.

The alignment of domestic GMP requirements with international standards will facilitate participation by Canadian manufacturers in the international market, and level the playing field between domestic-only and international manufacturers in the Canadian market. Currently, some companies pay for inspections in order to sell into jurisdictions where ICH guideline Q7 has already been implemented. The European Directorate for the

Quality of Medicines and HealthCare (EDQM) charges EUR 9,000 or CAN$13,050 in such cases. In the United States, there are 310 Canadian companies identified by the U.S. FDA (see footnote 22) as subject to its inspections. The Regulations will allow such companies to rely on inspection by Health Canada instead. Also, the Regulations will reduce the domestic and international compliance obligations of Canadian manufacturers by harmonizing rules, which is consistent with the Government's Red Tape Reduction Initiative.

Health Canada

Implementation of the Regulations will allow Health Canada to establish regulatory equivalence with its international counterparts. It will allow Health Canada to take advantage of GMP inspections by trusted international partners in ensuring higher quality drugs for Canadians, reducing duplicative oversight. It will also allow Health Canada to reciprocate in international regulatory work-sharing to ensure the safety of the global AI supply. From this perspective, Canada will help protect its credibility as a regulator in the global environment by playing an active role in enforcing the standards of this important commodity, where WHO and EDQM GMP inspections have revealed high failure rates.

The traceability requirement will allow Health Canada to carry out more rapid and targeted investigation of problematic AI. It will also make the introduction of illegitimate, substandard AI into the supply chain more difficult as verification of an AI's provenance will be simplified.

Costs

Canadian consumers and patients

It is not expected that Canadian consumers and patients will bear any significant cost as a result of the Regulations.

Industry

Canada is among the last industrialized countries to formalize GMP for AI in accordance with the international guideline. Because the Canadian pharmaceutical industry exports a significant proportion of its products to jurisdictions which have already implemented such requirements, it is expected to incur minimal incremental costs to comply. There will be miscellaneous administrative and clerical time spent by the affected parties for filing EL applications. This is estimated to be about $58,500 annually, assuming it is less than five hours of work per EL application. A one-time training cost, including employee time, may also be required for a minority of companies that are not currently following ICH guideline Q7, particularly those under the category of API packagers/labellers, distributors or wholesalers. Using ISO and on-line FDA cGMP training as proxies, it is estimated the cost will be in the $966,000 range under certain assumptions. (see footnote 23)

Health Canada

Health Canada estimates that there will be approximately 400 prospective licensable parties in Canada and its administrative cost will start at about $95,000 during the transition year. The cost will increase continuously for the next three years until it reaches $1.5 million when the program is fully implemented. Anticipated increases after that reflect the cost of inflation or other similar items.

"One-for-One" Rule

Subsequent to the development and submission to the Minister of Health of the regulatory proposal pertaining to these Regulations, a number of regulatory reform initiatives, including the “One-for-One” Rule and the small business lens, came into effect. A supplemental analysis was prepared to address the new requirements in accordance with the draft guidance then available. There was no public consultation requirement at that time, but, in the interests of transparency, the supplemental analysis was posted on Health Canada’s Web site along with the original cost-benefit analysis for the Regulations, concurrent with the publication for comment of the Regulations in the *Canada Gazette*, Part I. Health Canada has received no comments on the supplemental analysis.

The “One-for-One” Rule applies to the Regulations. Administrative costs are time and resources required to demonstrate compliance with government regulatory requirements in terms of (1) planning, collecting, processing and reporting of information; and (2) completing forms and retaining data required by governments. They include filling out licence applications, various forms, finding and compiling data for audits, and learning about requirements. There is a distinction between administrative costs related to regulations, and “business as usual” administrative costs, which would occur regardless of whether a regulation is in place or not. “Business as usual” administrative costs are excluded from the calculations.

Health Canada has encouraged compliance with ICH guideline Q7 on a voluntary basis since 2002. Stakeholders have informed the department during public consultation that many of them have done so, and that many dosage-form manufacturers institute physical audits of their Canadian suppliers to ascertain the obligations have been met.

In addition, Canada is one of the last industrialized countries to implement GMP for API. The United States and the European Union, which constitute at least 60% of the market for API, (see footnote 24) already have an equivalent regulatory requirement. Other developed countries such as Australia, Singapore and Japan also have a similar legal framework in place. The Pre-Qualification program of API for the World Trade Organization (WTO) is based on the same model as well. Thus, there are few if any developed countries in the world that will allow API without meeting the GMP requirements, including the need for record-keeping and inspections by competent regulatory authorities of either the country of origin where the API are produced, or the country into which the API are imported. It is estimated that only about 15% of API for the Canadian market are produced domestically while the rest are imported. As Canada is a small market, (see footnote 25) Canadian manufacturers are unlikely to rely solely on sales within Canada to survive, nor would any foreign manufacturers. It is assumed that the Regulations will add Health Canada as a regulator with the appropriate authority to carry out API inspection but will not change the frequency of inspection for Canadian companies, due to the business environment and the likelihood of MRAs with our international counterparts.

For these reasons, the incremental administrative costs associated with inspection are estimated to be nil, (see footnote 26) and only those expenditures relating to the regulatory requirement for annual filing for EL renewal are included as administrative costs for the purposes of the “One-for-One” Rule. Health Canada’s best estimate of the number of regulated parties requiring an API EL is 390. (see footnote 27) The clerical and administrative time required to prepare an annual filing is estimated at five hours. The average Canadian hourly wage is $30/hour. (see footnote 28) The total annualized administrative costs increase associated with the Regulations in 2012 dollars (i.e. the “IN” for the purposes of the “One-for-One” Rule) is approximately $58,500. (see footnote 29) The average administrative cost per business is $150. The present value of the administrative costs over 10 years, using a 7% discount rate, is estimated to be about $410,880.

Small business lens

The small business lens applies to regulatory proposals that impact small business and have nation-wide cost impacts over $1 million annually. According to Statistics Canada,

90% or more of the pharmaceutical industry would be considered micro- or small businesses. (see footnote 30) The Regulations will therefore undoubtedly impact small business.

The total regulatory burden of the Regulations, comprising administrative costs at $58,500 annually and compliance costs for those companies in need of one-time GMP training at $966,000 in year one, (see footnote 31) on a present value basis with a discount rate of 7% over 10 years, would be approximately $1.4 million. The annual average regulatory cost, with compliance cost amortized over a 10-year period, is estimated to be approximately $196,000, (see footnote 32) well below the $1 million threshold for triggering the small business lens.

Although the small business lens does not apply to the Regulations, a small business lens checklist was completed for the Regulations and appended to the supplemental analysis, which is available on Health Canada's Web site. (see footnote 33)

Consultation

Development of regulatory proposal

On December 7, 2002, Health Canada published in *Canada Gazette*, Part I, a notice of intent to proceed with the development of a regulatory framework for AI. Various stakeholder consultations were conducted by way of mail surveys, mixed stakeholder sessions and bilateral association meetings in 2002, 2003, 2004, 2009 and 2011. The stakeholders consulted included dosage-form and AI manufacturers, distributors and importers; drug industry associations; health professional associations (including pharmacy associations); veterinary associations; consumer and public interest groups; academia; and other government departments. Stakeholders also submitted unsolicited correspondence inquiring after the status of the regulatory proposal over the years.

Overall, stakeholders were supportive of the regulatory proposal. Stakeholders involved with drugs for human use indicated that they were generally prepared for the proposed requirements. Stakeholders involved with the veterinary drug industry gave strongly opposing views on the desirability of the regulatory proposal (i.e. some strongly for, some strongly against). Stakeholders involved with drugs traditionally accorded some flexibility in the interpretation of GMP requirements, such as Category IV monograph products, clinical trial drugs and radiopharmaceuticals, wanted some assurance that flexibility would also be accorded to AI for such drugs.

Health Canada gave consideration to all the comments. In particular, in response to feedback received from veterinary stakeholders in 2009, Health Canada decided to include only AI for human drugs within the scope of this regulatory proposal. The concerns of stakeholders involved with drugs traditionally accorded some flexibility will be addressed in guidance documents, as is currently the case with these drugs.

Comments received following publication of the Regulations in the *Canada Gazette*, Part I

The Regulations were published in the *Canada Gazette*, Part I, on September 29, 2012, followed by a 75-day comment period. Stakeholders notified by email of the publication and invited to submit written comments regarding the proposal included dosage-form and AI manufacturers, distributors and importers; drug industry associations; health professional associations (including pharmacy associations); veterinary associations; consumer and public interest groups; and academia.

Comments were received from approximately 30 stakeholders, including dosage-form and AI manufacturers, distributors, and importers; drug industry associations; drug industry consultants; a veterinary association; and a federal government department. Overall, stakeholders were supportive of the Regulations, but expressed some concerns over their administration. The comments received were organized according to themes and are summarized below, along with Health Canada's responses.

EL requirement for API companies

Two stakeholders objected to the imposition of an API-related licensing requirement as overly burdensome on both industry and Health Canada. Two stakeholders expressed support for an API-related licensing requirement.

Health Canada maintains that EL requirements are necessary to provide adequate oversight over and enforcement of the GMP requirements. Concerns over the administrative burden have been taken into account in designing the operational program, as set out in departmental guidance. The existing guidance on establishment licensing will be updated to incorporate changes related to the API program by September 2013.

AI foreign site annex for dosage-form importer EL

Four stakeholders expressed concern over consequential changes to the administration of the licensing of dosage-form importers, namely, the anticipated requirement to submit AI foreign site information. Stakeholders made several suggestions to reduce the associated burden.

These concerns and suggestions have been taken into account, as set out in departmental guidance. The existing guidance on establishment licensing will be updated to incorporate changes related to the API program by September 2013.

International equivalence

Four stakeholders expressed support for the international harmonization achieved by the Regulations. Three expressed concern that the Regulations are not equivalent to other jurisdictions' requirements.

Health Canada has been in regular communication with its international regulatory counterparts, including its MRA partners, for the purpose of ensuring that the Regulations will be recognized as equivalent.

Category IV monograph products

Two stakeholders requested that API used solely in Category IV monograph products be exempted from the Regulations, stating that these are low-risk products which are generally accorded special consideration commensurate with their nature, and which do not warrant additional regulatory scrutiny. One of the stakeholders also noted that some of the API used in these products are manufactured primarily for other industries, such as food or cosmetics; that it will be difficult to find suppliers able to manufacture them under drug GMP conditions; and that this will lead to shortages or considerable increases in cost which will ultimately be passed to consumers.

Category IV monographs have been developed for drugs that have well-characterized safety and efficacy profiles under specific conditions of use, allowing manufacturers to reference such monographs in their drug submissions. They are an administrative tool which helps to reduce duplicative work during the review process.

The quality-related risks of Category IV monograph products — the kinds of risks which are addressed by GMP requirements — are not uniform. Some Category IV monograph products in dosage form are subject to the same GMP requirements as any other drug (e.g. diaper rash products, contact lens disinfectants). Some are subject to the same regulatory requirements but have specialized GMP guidance applicable only to them (e.g. antiseptic skin cleansers, sunburn protectants, throat lozenges). Some are exempt from GMP requirements (e.g. toilet bowl disinfectant cleaners). It is Health Canada's

experience that Category IV monograph products are not at lower risk than other products in the area of quality defects such as heavy metal contamination or mould growth. For these reasons, it is Health Canada's position that an exemption for Category IV monograph products would not be appropriate.

Under the Regulations, AI used solely in Category IV monograph products which are currently exempt from regulatory GMP requirements will also be exempt. AI used in Category IV monograph products which are currently subject to regulatory GMP requirements will be subject to the Regulations. Consideration has been given to the specific circumstances affecting such AI, where applicable, as set out in departmental guidance. Health Canada is committed to ongoing dialogue to ensure that the administrative and compliance burden of the Regulations is proportional to the quality risks applicable to these products.

Natural health products

Two stakeholders requested that the Regulations not proceed unless similar requirements are put in place for the AI used in natural health products, on the grounds that non-prescription drugs and natural health products are viewed by consumers as similar products, have similar risk profiles, are subject to the same types of quality risks and should be subject to the same level of regulatory scrutiny in order to create a level playing field.

Natural health products are governed under a separate regulatory framework, subject to the requirements of the *Natural Health Products Regulations* rather than the *Food and Drug Regulations*, and also subject to a different compliance and enforcement model (e.g. no inspection program). Although there are some similarities between non-prescription drugs and natural health products, any change to the natural health product regulatory framework would need to be considered in a separate regulatory package.

Veterinary drugs

One stakeholder expressed concern over the omission of AI used solely in veterinary drugs, stating that the use of poor quality AI could have significant impact on the value of breeding stock.

Active ingredients used solely in veterinary drugs were removed from the scope of the Regulations following stakeholder consultations in 2009. Health Canada is currently reviewing its oversight of veterinary health products generally and will be addressing quality-related issues as part of that review.

Cost-benefit analysis

Three stakeholders commented on the cost-benefit analysis for the Regulations. One commented that the cost savings to industry set out in the cost-benefit analysis appeared to be significantly on the high side. One stated that the assumptions set out in the cost-benefit analysis do not apply to "cosmetic-like" drugs (i.e. Category IV monograph products) as they do not generally require the arrangement of foreign inspections, and their recalls tend to be smaller (and therefore less expensive). One commented that the assumption of five hours of administrative and clerical time in filing an EL application is unreasonably low, and that the estimated cost of recalls ($1 million) is not realistic for non-prescription drugs, stating that non-prescription drug recalls are more typically under $150,000.

All assumptions in the cost-benefit analysis necessarily reflect an average rather than the situation of any given stakeholder. Efforts were made to ensure that the cost-benefit analysis, which includes both quantified and qualitative impacts, is a reasonable approximation of the anticipated impact of the Regulations on affected stakeholders as a

whole. With respect to Category IV monograph products in particular, it is expected that importers and exporters of such products will benefit from the regulatory equivalence established by the Regulations in the same manner as other drugs. It is also expected that Category IV monograph product stakeholders will receive proportional benefit from reduced rate of recalls, as it is Health Canada's experience that the recall rate of these products is similar to that of other drugs.

Transitional provisions

Three stakeholders commented that the six-month delay of the coming into force of the Regulations will be insufficient to come into compliance with the GMP requirements. Five stakeholders commented that the six-month delay will be insufficient to gather AI foreign site information for the EL.

The ICH guideline Q7 has been recommended as a voluntary guidance, and stakeholders have been aware of the development of the Regulations, since 2002. Many stakeholders have indicated that they are already in compliance. Private sector GMP for API services, including online training and consultancy services, exist for stakeholders who do not feel able to implement the new requirements on their own. Departmental guidance is also available.

Concerns and suggestions relating to AI foreign site information have been taken into account, as set out in departmental guidance.

Cost recovery/resource allocation

Two stakeholders urged Health Canada to adequately resource the department's new licensing and inspection responsibilities in order to avoid negatively impacting Health Canada's existing responsibilities. One of these recommended that foreign pre-approval and ongoing domestic inspections be financed via cost recovery. A third stakeholder expressed concern over whether the new responsibilities are adequately resourced, and stated that cost-recovering for API-related work would be financially burdensome to industry.

Ongoing funding for this regulatory program has been granted under the Food and Consumer Safety Action Plan. In the future, Health Canada may consider developing a regulatory amendment to recover from industry some of the cost of conducting inspections, through EL fees similar to those currently in place for dosage-form drugs. Any such regulatory package would involve public consultation in compliance with Treasury Board policy and applicable legislation, such as the *User Fees Act*.

Master production documents

Two stakeholders commented that AI importers would be unable to comply with a requirement to maintain on their premises master production documents for the drugs they import, as these documents contain confidential and trade secret information normally provided only to Health Canada in the restricted part of the Drug Master File. One stakeholder commented that the existing requirement for dosage-form importers to have master production documents on their premises should remain unchanged, in order to enable them to continue to ensure compliance of each lot or batch of drug to the master production documents and the marketing authorization. This stakeholder suggested that API importers should be exempted from this requirement only to the extent of removing the trade secret portion of the master production documents.

Health Canada has amended the Regulations to provide that API importers will not be required to maintain master production documents on their premises in Canada. The existing requirement for dosage-form and BPI importers to maintain master production documents on their premises in Canada is unchanged.

Traceability requirement

One stakeholder stated that Health Canada already has submission information concerning the AI contained in drug products in Canada and that no additional tracking should be required. One stakeholder commented that listing the EL number on imported API is unnecessary because the API is traceable back to the manufacturer based on the lot number.

Current challenges in the traceability of AI are internationally recognized as problematic, as they can permit the introduction of counterfeit AI into legitimate supply chains. Many of Health Canada's international regulatory counterparts, including the European Union and the United States, have or are putting in place requirements for better tracking and tracing. The traceability requirement in the Regulations, including the requirement to list the EL number of each regulated party interacting with the AI, will allow for faster and more targeted investigation of problematic AI in Canada and increased accountability from the responsible regulated parties.

Miscellaneous

Health Canada received various requests for clarification and editorial comments during the comment period. These have been taken into consideration and incorporated into the Regulations, this Regulatory Impact Analysis Statement or departmental guidance, where appropriate.

Regulatory cooperation

The Regulations will implement into law internationally accepted GMP for AI requirements. Canada is a party to several MRAs relating to the parties' respective GMP compliance programs for drug products. (see footnote 34) The MRAs allow each regulator party to the agreement to accept the others' GMP inspection results as equivalent to its own. It is expected that equivalence with Canada's MRA partners in respect of AI will be established prior to the coming into force of the Regulations after an equivalency exercise following existing MRA procedures (e.g. a documentary review by the other MRA regulators).

Also, some regulators (see footnote 35) which have already implemented GMP for AI have entered into a regulatory work-sharing pilot program, sharing inspection reports and carrying out joint inspections of foreign AI manufacturers. It is expected that Canada will be able to participate in such a program following the coming into force of the Regulations.

Rationale

The selected option is Option 3 (regulatory amendment). It best fulfills the primary objective of protecting the health and safety of Canadians by implementing GMP for AI requirements equivalent to those of Canada's international partners. Due to the high level of voluntary compliance which already exists and measures taken to minimize the regulatory burden where possible, the costs of regulatory implementation will be low relative to the expected benefits, thus fulfilling the secondary objective.

Implementation, enforcement and service standards

Upon publication of the Regulations in the *Canada Gazette*, Part II, there will be a six-month period before the Regulations come into force, giving all regulated parties an opportunity to adjust to the new requirements. Guidance documents created by Health Canada will be available to aid regulated parties in coming into compliance.

In addition, API fabricators, packagers/labellers, testers and importers already active as of the day of the coming into force will be permitted to continue conducting their activities without an EL, provided that they have applied for an EL within three months after that day. This transition provision will ensure that regulated parties do not find themselves in a state of non-compliance solely due to any Health Canada administrative delays. No service standards will be applicable to the EL application process as no user fee will be charged, but Health Canada expects the AI process timeline will be comparable to the process timeline for drugs.

Enforcement of the new regulatory requirements will commence once the Regulations come into force. Enforcement mechanisms will be based on the current system for dosage-form drugs (i.e. EL requirements, GMP inspections, compliance verifications, and required follow-up actions). Ongoing implementation will include setting a schedule for regular inspections of EL holders.

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Footnote a
S.C. 2012, c. 19, ss. 414(2) and 415

Footnote b
R.S., c. F-27

Footnote 1
C.R.C., c. 870

Footnote 2
Four lots of contaminated heparin, manufactured by another company but using AI supplied by the same firm, were also discovered in Canada and recalled in March 2008. No increase in heparin-related adverse reactions were reported to Health Canada. It is possible that the recalled Canadian products had lower levels of contamination, reached fewer patients, or were formulated differently from the recalled U.S. products. There may also be different practices or tendencies relating to adverse reaction reporting in the two countries.

Footnote 3
For example, there was no test for OSCS prior to the 2008 heparin crisis.

Footnote 4
Canada currently has MRAs with the regulatory authorities of Austria, Belgium, Cypress, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Malta, Netherlands, Portugal, Slovak Republic, Spain, Sweden, United Kingdom, Switzerland, Iceland, Liechtenstein, Norway, and Australia. The MRAs relate to the parties' respective GMP compliance programs for drug products, allowing each regulator party to the agreement to accept the others' GMP inspection results as equivalent to its own. It is expected that equivalence in respect of AI could be established fairly rapidly, using existing MRA procedures, once the Regulations are implemented.

Footnote 5
The United States, the European Union and Australia are currently carrying out a pilot program, sharing inspection reports and carrying out joint inspections of foreign AI manufacturers.

Footnote 6

Currently, distributors and wholesalers of BPI are subject to EL requirements because the risks incurred by improper storage and transportation are fairly high. BPI tend to be living organisms that can be killed, or have their nature radically changed, by small fluctuations in temperature, humidity, pH level, or stability (e.g. shaking). By contrast, while the storage and transportation of API are not without risk (hence the need for GMP requirements), finished API in sealed containers are able to withstand greater environmental fluctuation without effect.

Footnote 7
Year 2022.

Footnote 8
Discount rate of 7% as recommended by Treasury Board.

Footnote 9
It is a conservative figure based on the assumption that there are a minimum of 310 firms selling aboard (FDA data) and European Directorate for the Quality of Medicines & HealthCare (EDQM) inspections are done at least once every three years (Health Canada estimate); no U.S. fees are taken into account. The amount reflects the transition period, or 50% of the full year cost that could be charged by EDQM.

Footnote 10
Assumption of annual increase 2% in fees.

Footnote 11
It is a conservative figure based on the assumption that there are an average of 193 recalls of drugs in dosage form annually, where 2–8% (5% being the median) of these recalls are API-related. Assuming the recall cost to industry is $1 million per recall, which is likely to be on the low end of the spectrum, there should be savings if the recalls were to be triggered earlier by API inspection or audit, before further investments are made to incorporate the substandard products into the final dosage form. The calculation uses generic oral solids as the baseline, which have a lower rate of saving as API constitute a higher proportion of their total cost (40–50%). Alternatively, one could argue GMP for API could prevent the quality defects leading to recall from occurring in the first place, which would provide a benefit of between $3.8 million and $15.4 million annually.

Footnote 12
The amount reflects the transition period, or 50% of the full year savings.

Footnote 13
Base year includes upgrade cost to some companies as a result of the Regulations. ISO certification and online FDA cGMP trainings are used as proxies, assuming a majority of 400 firms are already in compliance. Subsequent years cover administrative and clerical cost for regulatory filing only. Please see the cost-benefit analysis for further details.

Footnote 14
Before the WHO established the Pre-Qualification program (PQ) for API — a variation of ICH guideline Q7 — in 2008, its PQ program applied only to final formulations and required final formulators to use GMP procedures to acquire API for United Nations tenders, a similar approach to that currently taken by Canada, that theoretically ensured a quality API. The WHO became concerned about API quality following an incident in 1995 and 1996 when more than 100 children died in Haiti following ingestion of cough-and-cold syrup containing counterfeit glycerin — an ingredient used as an excipient in this incident but which is an AI in other medications. Other cases were also identified in Australia, the United States and the United Kingdom. Subsequent to the implementation of the PQ program for API, the WHO conducted GMP inspections of 31 sites, 6 of which failed. The 19% failure rate in this case would need to take into context that the sample represents companies that volunteered for the inspection, and which were therefore likely to have higher confidence in their quality standards that companies that did not volunteer.

Footnote 15
In 2010, the European Directorate for the Quality of Medicines and HealthCare (EDQM) conducted 34 API on-site inspections and reviewed 25 inspection reports of other regulators. As a consequence, there were 16 suspensions (10 reinstated after reinspection) and 8 withdrawals of the sites' Certificates of Suitability (CEPs). The initial

failure rate of 40% is significant.

Footnote 16
Source: Canadian Institute of Health Information (CIHI).

Footnote 17
Based on the HNP Discussion Paper, “Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines” (Bumpas and Betsch, September 2009), which indicated that APIs could represent 40%–50% of the total cost for generic orals.

Footnote 18
It should be noted that some traceability requirements for AI for biologics already exist in Canada.

Footnote 19
Source: the Securities Exchange Commission (SEC).

Footnote 20
Idem.

Footnote 21
$793 million represented the actual 2009 sales. If all of the AI were deemed contaminated, there would be no sales.

Footnote 22
“After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs,” PEW Health Group, retrieved from the Internet on September 13, 2011.

Footnote 23
See the cost-benefit analysis for more details.

Footnote 24
See the cost-benefit analysis.

Footnote 25
According to Industry Canada, Canada represents 3% of the world market in pharmaceuticals.

Footnote 26
If inspection-related costs (estimated at $55,000) were to be included in administrative costs, the total administrative cost would be approximately $113,500. See footnotes 14 through 16 of the supplemental analysis.

Footnote 27
Forty fabricators, 30 to 40 packagers/labellers, 10 testers, 250 to 300 importers. See the cost-benefit analysis for more details.

Footnote 28
This assumption is used in the original cost-benefit analysis. The Regulatory Cost Calculator now referenced by the “One-for-One” Rule and the small business lens stipulates a $24 hourly wage for administrative support, based on Statistics Canada data.

Footnote 29
390 × 5 hours × $30/hour = $58,500.

Footnote 30
See the supplemental analysis for details.

Footnote 31
See the cost-benefit analysis.

Footnote 32
An amount of $155,000 ($96,000 compliance cost plus $58,500 administrative cost) was originally stated in the *Canada Gazette*, Part I. The change is due to a modification in amortizing the initial training cost (a compliance burden) from the straight line method ($96,000) to the formula now provided by the new Treasury Board Secretariat guidance for the “One-for-One” rule ($137,537). See also the supplemental analysis for original calculation details.

Footnote 33
www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingred-cba-aca-suppl-compl-eng.php

Footnote 34

Canada currently has MRAs with the regulatory authorities of Austria, Belgium, Cypress, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Malta, Netherlands, Portugal, Slovak Republic, Spain, Sweden, United Kingdom, Switzerland, Iceland, Liechtenstein, Norway, and Australia.

Footnote 35

The United States, the European Union and Australia.