Canada

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In Canada drugs are regulated under the statutory authority of the Food and Drugs Act and its Drugs Regulations. The Act was passed by Parliament on December 8, 1954 and was extensively modified in 1961 following the thalidomide fiasco. The regulations are drafted by the bureaucracy and are promulgated by order-in-council by the Privy Council. Amendments are added to it from time to time to keep it current.

Health Canada is the responsible Ministry for the enforcement of the Food and Drugs Act and for the formulation of and amendments to the Drugs Regulations. The former Drugs Directorate and the Medical Devices Bureau of the Health Protection Branch (HPB) have been combined to form a new agency, the Therapeutic Products Programme (TPP).

The six programmes that constitute the TTP are: the Pharmaceutical Assessment responsible for premarket evaluation of drugs; the Medical Devices Programme responsible for the administration and enforcement of the new medical devices regulations; the Biologics and Radiopharmaceuticals Bureau; Drug Surveillance; Compliance and Enforcement; and the Policy and Coordination Division.

The five supporting divisions are the Strategic Planning, Communications and Quality; Continuing Education; Drug Analysis Service; Management Services; and Executive Services.

The TTP has streamlined the regulatory process among the various programmes (foods, drugs, devices, radiopharmaceuticals and biotechnology) and the respective regulations it administers, thereby achieving a uniform philosophy of regulation and control.

Canada is an active participant in the Working Groups of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The Conference meets biannually and its stated objective is to reduce or obviate redundancy of preclinical and clinical testing. Participants identify areas for improvement and recommend ways to achieve harmonisation in the interpretation and application of technical guidelines and requirements for approval. The ICH has three branches: the European Union (EU), Japan and the United States, and observers from the World Health Organisation (WHO), European Free Trade Association (EFTA), and the TPP of Canada. The International Federation of Pharmaceutical Manufacturers Association maintains an informative website for the ICH. Its Internet address is: http://www.ifpma.org/ich1.html.

Canada also initialed a Mutual Recognition Agreement with the EU covering good manufacturing practice (GMP) audits. Accordingly, once the equivalency of the Canadian and European GMP audit procedures have been established, products can enter the respective markets without the need of mutual inspections of the producing facilities in each other's territories.

Canada has a cost recovery programme in place for pharmaceutical products. The fees are negotiated between Pharmaceutical Assessment and the manufacturer. Costs vary but are substantial.

FOOD AND DRUGS ACT

Although the Food and Drugs Act is not part of the Criminal Code, its provisions and prohibitions are criminal law and the Act itself often refers to the Criminal Code. Consequently, violations of the law result in gaining a criminal record, imprisonment, fines or all of the above.

I will explain the structure of the regulations in this section. Each of the various sections and divisions are presented in the same order that they appear in the regulations.

Starting with Part I, Section 8 of the Act sets out the prohibited activities in respect to the sale, manufacturing, packaging, labelling and advertising of drugs. It specifies that a drug must comply with a standard if a standard has been established for that drug (Schedule B). If no standard exists, the drug cannot resemble another drug for which a standard has been written. Section 8 prohibits unsanitary manufacturing or retail conditions.

Part II pertains to the administration and enforcement of the Act, setting out the powers of inspectors in seizure and forfeiture of offending drugs. Offences and their respective punishments (ranging from three months to three years of imprisonment and fines from $500 to $5,000) are described in Sections 31–36. Section 37 exempts exports from the provisions of the Act as long as the products are manufactured for consumption outside of Canada.

Part III deals with the administration of the law regarding controlled drugs. A controlled drug is defined as a drug listed in Schedule G of the Act. Punishments for trafficking or other violations of Part III can be up to ten years imprisonment.

Part IV discusses restricted drugs, defined as listed in Schedule H of the Act.

PART C IN DRUG REGULATIONS—DIVISION 1

The general section of Part C contains the definitions applicable to the regulations. Of interest is the definition and description of child-resistant packaging and the associated test methodology.

Section C.01.004 contains the labelling proscriptions. These are extensive and require careful design.

Both the inner and outer labels of a drug shall contain the brand name of the drug followed immediately by the proper name in not less than half the type size of the brand name, or the common name if there is no proper name for the drug. If there is a standard for the drug (Schedule 6), the abbreviation CSD (Canadian Standard Drug) has to be applied. For prescription drugs (Part D), a vertical black rectangle containing an upper case white letter "P" and a lower case letter "r" has to be placed in the upper left quarter of the main panel. This symbol cannot be displayed for any other drugs. For controlled drugs, the symbol of a square standing on its point containing a lower case letter "c" shall be displayed, for narcotic drugs, the letter "N" in a sharply contrasting colour shall be displayed. The name of the manufacturer, the lot number of the drug, directions for use, a quantitative list of ingredients indicated by their proper names and the expiration date of the drug should also be indicated on the panel. In addition, the net amount of the drug in terms of weight, measure or number, and in special cases (for example, for parenteral drugs) the list of any preservative by proper names (or common names) shall be given. There is an exemption for small containers that cannot accommodate an inner label of sufficient size for all of the prescribed information.

Sale of a drug in dosage form is prohibited unless there is a responsible person for the drug in Canada. The responsible person's name and address must appear on the inner and outer labels. If the drug is imported into Canada, the importer's name shall appear on the labels also. The Drug Identification Number (DIN) and in the case of proprietary drugs, general product (GP) followed by the number must be printed on the labels.

A manufacturer may use his own standard instead of an official standard but in this case there are requirements that have to be met such as the submission of the details of the standard and method of analysis used. The standard must meet two criteria: it must ensure the highest degree of drug purity and the least variation on potency.

As mentioned earlier, no drug may be sold in dosage form without a DIN. The DIN application has to contain the following data: the name of manufacturer as it appears on the label; the pharmaceutical form in which the drug is sold; the recommended route of administration; a quantitative list of medicinal ingredients by

the proper (common) names; the brand name of the drug; the indication whether the drug is for human, veterinary or disinfection use. (In this case, the grounds for use are recommended); name and quantity of each colouring agent; use or purpose for which the drug is recommended (indications for use); the recommended dosage; address of manufacturer off-shore; the name and address of the importer; any other name and address that may appear on the label; written text of all labels; package insert that will be used in connection with the drug or any further prescribing information stated to be available on request; and the name and position of the person who signed and dated the application.

The Drug Programme will issue a DIN or GP when the review of the submitted data is completed. This document is the licence under which the drug can be sold for one, or a portion, of a year terminating on October 1. Within 30 days of the first sale of the drug, the applicant has to sign and date the DIN or GP authorising document, return it with the confirmation that the data on it is correct and provide the date of first sale. The document has to be accompanied by the copies of labels, the package insert and any further prescribing information.

Each year before October 1, the applicant has to notify the TPP on a prescribed form that the data submitted for a particular drug are still valid and correct. The DIN can be cancelled if the drug is no longer sold if it is determined that the product is not a drug or if the drug is recalled for a number of reasons, listed later.

Drugs sold in tablet form must comply with limits set on tablet disintegration times: for uncoated tablets the maximum disintegration time is 45 minutes, for coated ones, 60 minutes. Enteric coated tablets will not disintegrate in simulated gastric fluid for 60 minutes but when they are placed immediately afterwards in simulated intestinal fluid, they will disintegrate within 60 minutes. The test methodology is given in Division 6.

Manufacturers are obligated to report to the TPP any serious adverse drug reactions occurring in Canada and any serious unexpected adverse reactions occurring anywhere in the world within 15 days. Annually a concise, critical analysis of these events in a summary report shall be submitted to the TPP.

The regulations provide a table on limits and maximum adult and children dosage levels of some drugs and the respective cautionary labelling requirements. These limits should be consulted by the manufacturers before submitting their products for review to the manufacturer, another table of acceptable colouring agents is given in Section C.01.040.2.

ESTABLISHMENT LICENCES—DIVISION 1A

Establishments subject to licensing are defined as premises of distributors, manufacturers (including those who package and label), wholesalers, importers and testers. Pharmacists, medical practitioners and veterinary drug handlers are

exempted. An applicant has to fill out the appropriate form and supply the following information:

- applicant's name and address, telephone, fax numbers and e-mail address
- name, address, telephone, fax numbers and e-mail addresses for the person who is to be contacted in an emergency
- each activity for which a licence is requested (fabrication, packaging/labelling, performing tests including examinations, distribution, importing and wholesaling)
- each category of drug for which the licence is requested (pharmaceuticals, vaccines, whole blood and its components, drugs listed in Schedules D, C and G)
- each dosage form class, if is it a bulk process intermediate drug, address of each building in Canada where any of the activities will be carried out
- address of building where records are kept
- the DIN, if any of the buildings have been inspected
- date and evidence of GMP compliance if buildings were inspected
- with import drugs, the name and address of each manufacturer with proof of compliance of the home country's requirements

Establishment licences can be amended when any information provided is altered, for example, when a new drug is added to the portfolio, a new dosage form and so on. Changes to any information provided in the original or the amending application has to be reported within 15 days.

GOOD MANUFACTURING PRACTICE (GMP)

The good manufacturing practice (GMP) requirements pertain to the manufacture, packaging/labelling, testing and storing of pharmaceutical products. The provisions cover the premises, equipment, personnel, sanitation, raw material testing, manufacturing control, quality control, packaging material testing, finished product testing, record keeping, samples, stability and sterile products.

Premises have to be so designed, constructed, maintained and organised so that operations performed are in clean, sanitary and orderly surfaces that can be effectively sanitised to prevent the contamination of the drugs. Equipment used in operations should be able to be easily and effectively cleaned to prevent contamination of the drugs.

Supervisory personnel should have adequate technical, academic and other kinds of training that render them suitable for their duties.

The company should have a written sanitation programme implemented under the supervision of a qualified manager. The programme should include cleaning procedures for the premises and the equipment in addition to procedures for the sanitary handling of materials and products. Policies should be in force regarding minimum requirements for health, hygienic behaviour and clothing of personnel. Personnel with a communicable disease or open lesions are prohibited from entering areas of manufacturing operations.

Written specifications should be in place for the testing of each lot of incoming raw material and segregation of nonconforming lots will be made with to ensure safe disposal. Manufacturing control is achieved by having written operating procedures prepared by qualified personnel to ensure that the drug meets its specifications. It is the responsibility of each person required to obtain these procedures and adhere to them. A programme of self-inspection has to be designed and implemented, accompanied by a traceability system which can enable the complete and rapid recall of nonconforming products from the market.

The Quality Control Department must function and report independently to the company management. This department must be independent from manufacturing, processing and sales. The manager of quality control has to be qualified by technical expertise, academic achievement or other acceptable ways of training. The manager in charge of quality control has among his responsibilities: the approval of each lot of incoming raw material, labelling, and so on prior to its release to manufacturing; approval of each lot or batch of the drug released for sale; the approval of release for sale of returned products after each returned lot or batch of the drug has met required specifications; complaint recording, handling, investigation and resolution; approval of all manufacturing, packaging, testing, storage, transportation methods and procedures that may affect quality of the drug; supervising and approving the testing; and examining laboratories.

Each lot of packaging material has to be tested against the specifications of that material or label prior to its use. Each lot or batch of finished product has to be tested against the specifications of that drug and a written report, approved by the manager of quality control, must be kept for inspection. Importers and distributors have to test samples from each lot or batch received at their premises before the drug can be sold in Canada. The manufacturer may provide the testing data to the importer or distributor, however, even in the case where periodic complete confirmatory testing is required.

For each drug sold in Canada, the manufacturer, importer or distributor must keep the following records on their premises in Canada: master production documents for the drug; proof that each lot, batch manufactured, packaged/labelled, tested and stored are in compliance with the procedures described in the master production documents; evidence that the drug is manufactured in compliance with regulations; evidence that the drug is within specifications until the indicated use-before-date; and adequate evidence of testing. Records that each manufacturer has to keep and provide upon request are as follows: written specifications for each raw material and adequate evidence of testing against them; detailed plans and specifications, description of design and construction for each building

involved in manufacturing, testing, packaging/labelling; details of supervisory personnel, including title, responsibilities, qualifications, experience and training; reports of self-audits; and records of the sanitation programme.

Each distributor must furnish the results of raw material and packaging material testing for each lot or batch sold; distribution records for each lot and batch of a drug; and complaint records including the result of its investigation.

All records must be kept for at least one year after the expiration date on the label of the drug with the exception of raw material and packaging/labelling materials testing which must be kept for five years. Internal audit and sanitation inspection records must be kept for three years.

Manufacturers shall retain a sample of each batch of raw material used for two years after its last use. A sample of each lot or batch of the packaged/labelled drug has to be kept in Canada for one year after the expiration date on its label.

Each distributor has to establish the time period during which the packaged drug will be within its specifications. Stability has to be continuously monitored and the time period adjusted accordingly.

Sterile products must be manufactured in separate enclosed areas under the supervision of a microbiologist. The sterilisation method has to be scientifically proven, validated and qualified.

SCHEDULE C DRUGS—DIVISION 3

Schedule C contains radiopharmaceuticals. The manufacturing premises of these drugs need an annual licence which expires on June 30 of each year.

The labelling requirements for radiopharmaceuticals are extensive. Both the inner and outer labels should indicate the proper name of the drug, the name of distributor and the lot number.

The outer label should carry the following information:

- address of the distributor
- the standard the drug is claimed to meet
- route of administration
- recommended use and radioactivity to be administered
- the Establishment Licence Number
- the radiation warning symbol and the words
- "Caution—Radioactive Material"
- names and amounts of stabilising agents in the drug
- names and amounts of non-radioactive components in the drug
- total radioactivity content of the drug including overfill

- total volume of drug including overfill (except where contents are entirely in gaseous, capsule or lyophilised form)
- concentration of radioactive material expressed as units of radioactivity per capsule or per unit volume
- specific activity of the drug in units of radioactivity per unit weight of carrier, or the statement "carrier-free"
- reference time in respect of the radioactivity, the name of month written or abbreviated
- expiration date
- special storage conditions

If the radiopharmaceutical is to be used in a clinical study the words "Investigational Drug" and "Only For Qualified Investigator Use" must appear.

The inner label should contain the following information:

- proper name of radionuclide generator
- name and address of distributor
- lot number
- the standard the radionuclide generator claims to meet
- the "Establishment Licence Number"
- radiation warning symbol and the words "Caution—Radioactive Material"
- total parent radioactivity contained in radionuclide generator
- the hour and date at which the radioactivity value is valid
- expiration date
- recommended useful life of drug after removal from the radionuclide generator
- special storage requirements
- caution against dismantling of the radionuclide generator

In the case of kits the same information should be indicated on the labelling.

Technetium-99m containing drugs are prohibited from sale if these contain a radionuclide impurity mentioned in the monograph for Sodium Pertechnetate Tc-99m injection.

SCHEDULE D DRUGS—DIVISION 4

Schedule D contains drugs of biological (animal or human) origin. Products covered by this division are vaccines, bacteriophages, toxins and toxoids, antitoxins, antisera, human plasma components, insulin, anterior pituitary extracts and anticoagulants.

Instead of providing the testing methodologies, harvesting conditions required for each product, I shall restrict this description to the common elements in labelling and licensing. Expiration dates are established according to the following formula: the expiration date will not be later than the set time period after the date of manufacture for a drug that has been kept constantly at a temperature not exceeding:

- 10° C: 6 months;
- 5° C: 12 months;
- 0° C: 24 months.

The manufacturer who processes spore-bearing, pathogenic microorganisms and other infectious agents, must take special precautions, care of equipment and supervisory arrangements to prevent the contamination of other drugs. Diagnostic laboratory procedures conducted at the same premises must be segregated from all activities pertaining to the manufacturing of the drug. All animals used as source subjects must be under the supervision of a veterinary or medical doctor and kept in quarantine for at least seven days prior to their use to ensure they are healthy and free from infectious diseases. Necropsy records shall be kept of all animals that have died or have been killed after having been used in the production of the drug. The manufacturer must quarantine and segregate, then report immediately to the TPP any animal that has or is suspected to have vesicular stomatitis, foot and mouth disease, encephalomyelitis, infectious anaemia, glanders, anthrax, tetanus or any other serious infectious diseases.

The labelling requirements for Schedule D products are required to contain the following information on both the inner and outer labels:

- the proper name of the drug followed by the brand name
- name of distributor
- potency of the drug
- recommended dose
- lot number
- expiration date and the directions for use

The outer label should contain:

- the address of the distributor;
- the Establishment Licence number for whole blood and its components;
- proper name of the preservative;
- instruction of storage between 2° C and 10° C;
- net contents in terms of number, weight or measure.

The symbol for prescription has to be on the upper left corner of the label.

CANADIAN STANDARD DRUGS—DIVISION 6

This division defines and enumerates those drugs that are defined by a Standard in Canada including:

- conjugated estrogens;
- conjugated estrogens for injection;
- conjugated estrogen tablets;
- digitoxin;
- digitoxin tablets;
- digoxin;
- digoxin elixir;
- digoxin injection;
- digoxin tablets;
- esterified estrogens;
- esterified estrogen tablets; and
- gelatin and thyroid.

NEW DRUGS—DIVISION 8

This division has the greatest interest for the regulatory professional since the submission of new drugs is the most important and most difficult part of the working environment. As a consequence, this division will be dealt with in great detail.

It is important to define what is meant by the term "new drug" in Canada. According to the regulations, a new drug means "a drug that contains or consists

of a substance, whether as an active or inactive ingredient, carrier, coating, menstruum or other component that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish its safety and effectiveness for use as a drug". Also included are drugs that are a combination of two or more drugs, with or without other ingredients, that have not been sold in that combination or in the proportions in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish the safety and effectiveness of that combination or proportion for use as a drug. The last are drugs with respect to those the manufacturer prescribes, recommends, proposes or claims use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use for sufficient time and in sufficient quantity to establish the safety and effectiveness of that drug."

New Drug Submission

A drug cannot be sold in Canada until a new drug submission or an abbreviated drug submission has been evaluated and a Notice of Compliance is issued. The purpose of the submission is to enable the TPP to establish the safety and effectiveness of the new product. The submission should contain a description of the new drug and a statement regarding its proper name or common name, and the proposed brand name or other identifier for the new drug.

A list of ingredients should be provided, stated quantitatively, and accompanied by the specifications for each ingredient. A description of the plant and equipment to be used in the manufacture, preparation and packaging of the drug should include the physical layout and that part of the GMP that pertains to the facility. Details of tests applied to control potency, purity and stability of the new drug have to be provided, as well as detailed test reports establishing the safety and substantial evidence for the clinical effectiveness of the drug "for the purpose and under the conditions of use recommended". The submission has to list the names and qualifications all the investigators who participated in the clinical trial. The sponsor of the new drug has to provide the draft of every label to be used with the drug and a statement delineating the recommended route of administration; the proposed dosage; the claims made for, and the contraindications and side effects of the new drug. The manufacturer is obligated to provide evidence that the drugs used in the clinical trial were manufactured and controlled in the manner that is representative of the market production run. The Drug Directorate may request the names and addresses of the manufacturers of the ingredients as well as of the new drug in the dosage form in which it is to be sold, samples of the ingredients and of the drug in the proposed dosage form and anything else the evaluators may deem necessary.

Abbreviated New Drug Submission

An abbreviated new drug submission may be filed with the Drugs Directorate if the manufacturer uses a "Canadian reference product" for comparison. The definition of the Canadian reference product needs careful consideration. It is defined as:

(a) a drug in respect of which a Notice of Compliance is issued and which is marketed in Canada by the innovator of the drug;

(b) a drug, acceptable to the Minister that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug, in respect of which a Notice of Compliance has been issued cannot be used for that purpose because it is no longer marketed in Canada; or

(c) a drug acceptable to the Minister that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical, and where applicable, bioavailability characteristics, in comparison of a drug referred to paragraph (a).

The submission has to establish that the new drug is the pharmaceutical equivalent and the bioequivalent (based on pharmaceutical and bioavailability data) to the reference product, the new drug has the same route of administration and has the same conditions for use as the reference drug.

The submission body should contain the same data as the new drug submission with the exception of clinical trial results and tests performed establishing the safety and effectiveness of the drug. The submission needs to identify the reference product used in comparative studies in aid of the submission. These comparative studies should demonstrate that the new drug is the pharmaceutical and bioequivalent with the Canadian reference drug. The studies may include bioavailability, pharmacodynamic and/or clinical studies. As with new drugs, evidence has to be presented that all test batches used in the studies are manufactured and controlled in the same manner as the market production runs.

When a notice of compliance or a supplementary notice of compliance has been issued, the manufacturer has to submit all labels, package inserts, brochures and file cards that are intended to be used with the new drug before it can be sold.

The regulations list a number of items that, if changed, will require a supplementary submission. A submission has to be submitted if there is a change in:

- the description of the drug;
- the brand name or identifying code;
- specifications for ingredients;
- plant and equipment used in manufacturing, preparation and packaging;

- method of manufacturing and/or controls;
- tests for purity, potency, stability and safety of the drug;
- recommended route of administration;
- dosage;
- claims;
- contraindications and side effects;
- withdrawal period for the drug.

When a manufacturer submits a new drug submission containing reference data from the innovator of a substance without a notice of compliance, a waiting period of five years is specified before the new drug can have its notice of compliance. The five years can be waived if the innovator of the substance gives his written approval to another manufacturer to use his test data as reference.

Clinical Trials

Clinical trials may not commence without a letter providing investigational drug status to the investigational new drug.

When a manufacturer wishes to conduct a clinical trial he needs to submit a preclinical drug submission containing the following information: brand name; chemical structure of the drug and its source; investigational protocol; results of previous investigations in support of clinical use; known contraindications and side effects as well as treatment of overdosage; quantitative listing of all ingredients; methods, equipment, plant and controls used in manufacture; names and qualifications of investigators; names of institutions where the trial will take place; labels stating "Investigational Drug" and "To Be Used By Qualified Investigator Only"; written statements by the investigators that they will not use or permit the drug to be used outside of the investigation; only the investigator or personnel under his supervision can use the drug; any serious adverse effect will be immediately reported to the manufacturer; and that the investigator will account for all quantities of the drug to the manufacturer. The manufacturer must keep detailed distribution records of drugs shipped to the investigators and is obliged to immediately report all serious adverse effects to the Drug Directorate.

Additional information required in any submission should include:

- a copy of all clinical case reports of patient who have died, suffered a serious or unexpected adverse effect;
- a sectional and a comprehensive report on each human, animal or in vitro study which are included or referenced in the submission (sectional reports include a summary of each included study;

- summary of any additional information in amendments;
- where raw data is available, a summary of the data;
- cross-referencing the data to the relevant portion of the submission;
- description of the experimental conditions;
- details of data treatment and the results and conclusions of the study.

The comprehensive reports include a summary of the methods used, results obtained and the conclusions arrived at in all submitted studies. The manufacturer shall include in the submission a "submission certificate" certifying that all information contained in the submission are accurate and complete and that the sectional and comprehensive reports correctly represent the data in the submission. The certificate has to be signed by the senior executive officer (CAE or COO) and the senior medical or scientific officer of the manufacturer in Canada.

The regulations list the following causes for the suspension of the notice of compliance issued for a new drug:

- evidence that the drug is not safe deemed from clinical studies or from new tests and methodologies not available at time of submission; lack of effectiveness as learned from market experience;
- the submission contained untrue data;
- the manufacturer failed to keep records; manufacturing facilities are inadequate to ensure the drug produced will be safe and effective;
- the labelling is false or misleading.

An appeal-handling mechanism is established in the form of the New Drug Committee. A manufacturer may appeal to it if his submission has been rejected or the notice of compliance has been suspended. Members of the Committee are obligated to keep confidential the proceedings of the meetings and all information presented to them. The Committee is comprised of one member from the Drugs Directorate and one member appointed by the manufacturer (full-time employees of the Directorate or of the manufacturer are disqualified). The two appointed members then elect a third one who will act as chairman.

Experimental Studies

Experimental studies are defined as "limited tests of a new drug in animals, carried out by an experimental studies investigator". The investigator needs to obtain a certificate called the "experimental studies certificate" in order to participate in the tests.

The manufacturer of the drug has to apply for permission to conduct the tests by submitting the following information:

- the brand name of the drug (or identifier if does not have a brand name as yet);
- the protocol for the study including its objectives;
- the species, number and "production type" of the animals planned to be used in the tests;
- name and address of the manufacturer of the drug;
- address and description of the premises where the testing is being conducted;
- name, address and qualifications of proposed investigator;
- chemical structure and relevant compositional characteristics of the drug;
- proposed quantity of the drug;
- and the results of previous toxicological and pharmaceutical studies.

When permission is received after review of the application, a determined amount of the drug can be given to the investigator for the test.

The labelling of the experimental drug should indicate the brand name: a warning statement to the effect the drug is to be used only for animal experiments; lot number of the drug; name and address of manufacturer; and name and address of the investigator.

The experimental study investigator is under obligation to use the drug only according to the protocol, report immediately any serious adverse reactions, provide a report of the study, return all unused drugs still in his procession, maintain all records for at least two years after the conclusion of the tests, report on the disposition of the experimental animals and account for all quantities of the drug received by him.

NON-PRESCRIPTION DRUGS—DIVISION 9

This division deals with analgesics, specifically, acetaminophen and salycilates. Combination of two salycilates or their salts and the combination of acetaminophen and salycilates are prohibited. Cautionary statements are required on the labels to the effect that a physician should be consulted if the condition does not improve in five days, that it is hazardous to exceed the recommended maximum dosage unless so instructed by a physician and during the last trimester of pregnancy and during nursing analgesics should be taken only after consulting a physician.

Acetaminophen

Standard adult dosage of acetaminophen is identified as 325 mg. Children's standard dosage is 80 mg or 160 mg. Standard dosage means the amount of acetaminophen in a tablet or other solid dosage form. The amount of the drug can be increased to 500 mg per tablet or capsule if it is stated on the label that it is not the standard adult dosage form. Liquid forms of acetaminophen intended for adult use shall contain one adult standard dosage form per teaspoon.

Liquid dosage forms of acetaminophen, intended to be taken in drops by children, shall have one standard dosage form per each milliliter. In this case, the bottle in which the liquid is packaged should be accompanied by a measuring device calibrated to accurately deliver 0.5 ml of the product.

Liquid dosage forms not intended to be taken in drops but recommended for children shall have a standard dosage form of acetaminophen per teaspoon.

Salycilates

The adult standard dosage form for acetylsalicylic acid, sodium and magnesium salicylate will be 325 mg, and 435 mg for choline salicylate. The children's standard dosage form will be 80 mg and 110 mg respectively.

Salicylate products are those that contain either one of the salicylates as the only component in the tablet or products in combination with caffeine, buffering agents or antacids.

If the label indicates it is not the standard adult dosage form, the amount of drug in a tablet or capsule may be increased to 500 mg in the case of acetylsalicylic acid and sodium or magnesium salicylates or 670 mg in the case of choline salicylate.

The label should indicate if a tablet or capsule contains one, two or three adult standard dosage forms of the drug. Liquid preparations should indicate similarly if there is one, two or three adult standard dosage forms per teaspoon of the preparation. Buffered salicylate products must have at least 1.9 milliequivalent of acid neutralising capacity per adult dosage unit.

PROPRIETARY MEDICINE—DIVISION 10

In order to sell a proprietary drug, a submission has to be made in triplicate to the TPP for a "numbered certificate" (certificate of registration).

The submission should contain all of the following elements:

- a description of the pharmaceutical dosage form of the drug including the brand name;
- a quantitative list of all ingredients;
- name and address of the company that formulates, compounds or packages the drug;

- specifications for raw materials and for those packaging materials that are in contact with the drug and draft of all labelling. (Samples may be required of the drug or of any component of it.);
- the manufacturing process;
- stability data for the finished product, including the test methodology used to determine it;
- the proposed expiration date;
- description of each active ingredient of the drug identified by their proper names, chemical structure, method of synthesis, isolation and purification and the name and address of the manufacturer of each ingredient.

Reports of all in vivo and in vitro studies performed with and for the drug for determining its action, properties and toxicity are required. Reports of clinical investigations establishing the safety and effectiveness of the drug for the claimed indications should be submitted.

Requests for further information may be sent to the manufacturer and a reply within 90 days is expected. The regulatory decision on these materials is due within an additional 90 days.

Changes in the label, characteristics of the drug or in the method of production must be submitted to the TPP for their approval.

A large number of prohibitions are attached to these drugs. The list is too long to reproduce here. The reader is referred to the actual regulations or to the respective office of the TPP for further elaboration.

A great number of interpretative guidelines have been published by the TPP in aid of manufacturers. These may be obtained by accessing the TPP web site: http://www.hc-sc.gc.ca/hpb-dgps/therapeut.html.

The Departmental Consolidation of the Food and Drugs Act, the Foods and Drugs Regulations and the Guidelines can be obtained for US $90.95 by writing to the following address:

Canada Communications Group
Operations Distribution Logistics Services
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ABOUT THE AUTHOR

John Gams, PhD, has been involved in regulatory affairs and standards for the past 30 years in the pharmaceutical and medical devices industry. He has been the industry representative on Health Canada industry committees and task forces and is also involved in international and national standards regarding healthcare products. Dr. Gams currently chairs 4 international and domestic technical committees in the healthcare field. He has degrees from Concordia University and McGill University, Montreal, and at the Union Graduate School. He is active in international regulatory harmonisation activities and endeavors.