Please note that the following document is NOT a new Therapeutic Products Programme guideline. Hard copies of this guideline are no longer available. For the convenience of clients and stakeholders we are making this guideline available electronically.

Health Canada Santé Canada

THERAPEUTIC PRODUCTS PROGRAMME QUESTIONS AND ANSWERS

Published by authority of the Minister
of National Health and Welfare

Health and Welfare Canada
January 1991

Disclaimer

The material herein was prepared under the direction of the Therapeutic Products Programme, Health Canada. No changes are permitted.

Avertissement

Le document ci-joint a été préparé sous la direction de la Programme des produits thérapeutiques, Santé Canada. Aucune modification n'est permise.

DD-91-2

Canada

Catalogue No. H42-2/47-1991IN
ISBN 0-662-58022-2

TABLE OF CONTENTS

Introduction

This Questions and Answers publication has been prepared by the Drugs Directorate, Health Protection Branch (HPB), Health and Welfare Canada. Its purpose is to assist drug manufacturers, distributors, and importers in quickly obtaining answers to those questions most often directed to Directorate staff.

The topics run the gamut of federal drug regulations and practices. The publication contains information on the interpretation of the *Food and Drugs Act and Regulations*, the *Cosmetic Regulations*, and the *Narcotic Control Act and Regulations*, the manufacture of both prescription and nonprescription drugs, the import and export of drug products, and the submission of samples for branch approval.

Readers are advised to use this publication as a general reference only. Detailed information must be obtained from the published acts and regulations, and from the pertinent volume of the Drugs Directorate Guidelines.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

SECTION A

THE ACTS AND REGULATIONS

1

Q. Where can I obtain a copy of the *Food and Drugs Act and Regulations* or the *Narcotic Control Act and Regulations?*

A. They can be purchased from the Canadian Government Publishing Centre, Ottawa, Canada, K1A 0S9 (Telephone (819) 956-4800), or from an authorized bookstore agent or local bookseller.

2

Q. What substances are classified as drugs?

A. Section 2 of the *Food and Drugs Act* defines a drug as:

"any substance or mixture of substances manufactured, sold or represented for use in

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof, in man or animal,

(b) restoring, correcting or modifying organic functions in man or animal, or

(c) disinfection in premises in which food is manufactured, prepared or kept. "

3

Q. What steps must be taken before a manufacturer is permitted to market a drug?

A.

Before a drug can be sold in Canada, a manufacturer or importer must apply for and obtain a Drug Identification Number (DIN) from the Drugs Directorate. Should the drug product be classified as a new drug, a new drug submission must also be filed. Before marketing a new drug, a manufacturer must receive a Notice of Compliance (NOC) and a DIN from the Drugs Directorate.

4

Q.

What is a Drug Identification Number (DIN)?

A.

A Drug Identification Number (DIN) is a number assigned to each drug product sold in Canada. All drug products sold in Canada must be assigned a DIN prior to any marketing of the drug product. The eight-digit DIN must be displayed on the main panel of the label.

5

Q.

How does a Drug Identification Number (DIN) differ from a General Public (GP) number?

A.

DINs apply to all classes of drug products, while GPs (also known as Proprietary Medicines) are issued only for a narrow range of products that are intended for use in humans and that are suitable for self-medication without the assistance of a health professional. A manufacturer has the option, for certain products, to apply to market a drug product under either a DIN or GP number.

6

Q.

Can a product have a dual classification?

A.

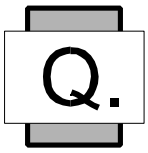
Yes. Some combinations of products can be considered as drugs, medical devices, or foods. Where requirements differ, all pertinent legislation must be met.

7

What is a Drug Notification form?

A Drug Notification form is a computerized form bearing the Drug Identification Number (DIN). The form must be signed, dated, and returned to the Bureau of Pharmaceutical Surveillance by the applicant or an authorized person within 30 days of the marketing (first sale) of the product.

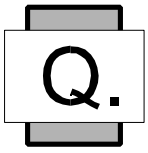
8



When are Drug Notification data renewed?

Drug Notification forms are mailed annually to manufacturers who have drug-related products on the Canadian market. The manufacturers are required to complete, verify, sign, and return the form to the Drugs Directorate before the first of October.

9



Can the formulations of a drug be changed without reregistration?

Section C.01.014.4 of the *Food and Drug Regulations* requires that the Drugs Directorate be informed of any changes that a manufacturer proposes to make to a drug product. Changes in the formulation of a drug may also cause it to become subject to Division 8 of the *Food and Drug Regulations.*

10

Q. What drugs are included in Schedule D?

A. Drugs included in Schedule D to the *Food and Drugs Act* are prepared from animal and human tissues or secretions, or from micro-organisms. The manufacturing of these drugs is complex due to impurities in the source material. Chemical impurities and microbial contaminants must be eliminated from these products, thus reducing the potential for hazards to human health. The safety and efficacy can only be assured by a combination of rigid in-process controls and biological tests. Schedule D drugs include vaccines, blood derivatives, certain hormones and enzymes extracted from animal tissue or cultures of micro-organisms, and drugs produced by modern biotechnology. A licence is required for Schedule D drugs, not only by the manufacturer of the final dosage form, but also by the manufacturers of any significant, intermediate, or raw material.

11

Q. Why are licences required for Schedule D drugs?

A. Because Schedule D drugs are manufactured by complex processes, the premises in which they are manufactured must be inspected and licenced by the Bureau of Biologics, Drugs Directorate. Each product and manufactured lot is released following the evaluation of test results and samples by the Bureau.

12

Q. What is Schedule F and why does it have two parts?

A.

Schedule F lists drugs that must be sold by prescription.

Part I of Schedule F to the *Food and Drug Regulations* contains a list of drugs for human and veterinary use that must be sold by prescription.

Part II of Schedule F lists drugs that require a prescription for human use but not when labelled for veterinary use. The symbol "Pr" must appear on the label of all Schedule F drugs.

There are more than 350 drug substances listed in Schedule F. This list represents such widely diverse drugs as antibiotics, hormones, and tranquillizers. Schedule F often changes as a result of the discovery and introduction to the market of new drug substances, the identification of hazards of certain nonprescription drugs, information on changing abuse and misuse patterns, and changes from prescription to nonprescription status.

13

Q.

How can a prescription drug become a non-prescription over-the-counter (OTC) drug?

A.

A proposal to deschedule a prescription drug is generally initiated by the manufacturer. The proposal will be evaluated by the Bureau of Nonprescription Drugs in conjunction with the Bureau of Human Prescription Drugs. The recommendations of the bureaus will be forwarded to the Drugs Directorate's Subcommittee on Prescription Drug Status for a decision on the prescription drug status. If the manufacturer provides information deemed sufficient to support the claim that the product can be adequately regulated as a non-prescription drug, the drug will be removed from prescription drug status. Within this regulatory process, manufacturers of the drug product involved will be consulted and informed of the subcommittee's decision. Should the submission fail to support a change from prescription to non-prescription status, the manufacturer will be advised of the reason and given an opportunity to appeal the decision or to supply additional information.

14

Q.

What is the difference between human and veterinary biological drugs?

A.

The definition of a drug under the *Food and Drugs Act* includes substances of biological origin (agents referred to as biologics) that are used to diagnose and induce immunity to disease in both humans and animals. Diagnostic and immunological agents of biological origin labelled for use in animals are regulated by Agriculture Canada, while their counterparts, intended for use in humans, are regulated by HPB. This division of responsibility stems from Agriculture Canada's responsibility to prevent the entry into Canada of foreign animal disease, to control and eradicate indigenous animal disease, and to ensure that veterinary biologics used in Canada are pure, potent, safe, and effective.

Because veterinary drugs are regulated by HPB, a joint agreement has been established on roles respecting the control of the sale of veterinary drugs and veterinary biologics in order to minimize dual regulation and maintain a balance between the interests of drug manufacturers, animal owners, and consumers.

15

Q.

What is the procedure for the emergency release of a drug?

A.

An emergency release of a drug occurs only under specific conditions. In an emergency, the sale or supply of any drug, except for narcotic drugs, can be exempted from all provisions of the *Food and Drugs Ac*t and Regulations, but not from any other relevant act or regulations. This provides for the sale of a new drug for use in a medical emergency without contravening any regulations.

The release of a drug under the emergency drug release program must be made only to a named medical, dental, or veterinary practitioner for the treatment of a medical emergency involving a patient under the practitioner's care. The practitioner must provide information about the use, safety, and efficacy of the drug, the names of the institutions where the drug will be used, and any other required information.

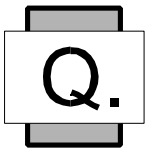
Requests for emergency drug releases may be made in writing, by telephone, or by facsimile to the Drugs Directorate in Ottawa. Authorizations are usually provided to the manufacturer by telephone immediately following the request. (Manufacturers' after-hours telephone numbers are used when available.) The manufacturer may then ship the drug to the practitioner; this can normally be done within 24 hours. Copies of the formal written authorization are sent to the practitioner, the Deputy Minister of Health for the province concerned, and the company.

16

Do Good Manufacturing Practices (GMP) apply to all classes of drugs?

The GMP Regulations (Division 2, Part C of the *Food and Drug Regulations*) apply to all classes of drugs in dosage form except radiopharmaceuticals (Schedule C to the *Food and Drugs Act*) and biologicals (Schedule D to the *Food and Drugs Act*).

17



When is a New Drug Committee established?

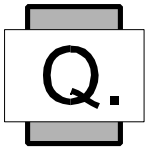
Section C.08.009 of the *Food and Drug Regulations* pertains to the establishment of a New Drug Committee. A manufacturer can ask the Minister to refer a decision to a New Drug Committee if:

a) the manufacturer is advised that the Notice of Compliance for their New Drug Submission or supplement is being suspended; or

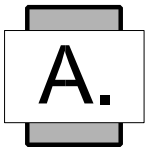
(b) the sale of the new drug to qualified investigators is prohibited.

The New Drug Committee is composed of one member appointed by the Minister, one member appointed by the dissenting manufacturer, and one member appointed jointly by the two appointees. This New Drug Committee considers the reasons for the Minister's decision, the reasons for the manufacturer's dissatisfaction, and any other relevant information. The committee reports its findings and recommendations to the Minister, who renders a decision.

18

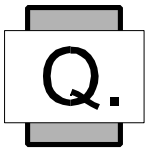


What is an Expert Advisory Committee?

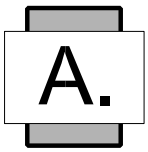


An Expert Advisory Committee (EAC) is set up by HPB when the assistance of individuals who possess expert knowledge and judgement in a specific scientific or medical field is required to evaluate and interpret complex questions respecting a particular drug, class of drugs, or group of drugs. Guidelines for EACs are available from the Drugs Directorate.

19

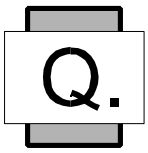


What is the policy concerning contact with the Drugs Directorate to discuss the status of a submission?

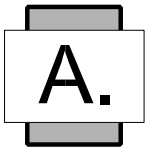


Each bureau has established a contact person to receive telephone inquiries regarding the status of a submission that has been accepted for review by the Drugs Directorate. (See *For More Information* at the back of this publication.) Personal visits to the Directorate offices are to be made by appointment only and should take place in meeting rooms separate from review offices.

20



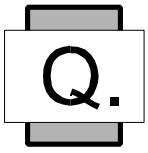
How legal and binding is the government's interpretation of the *Food and Drug Regulations*?



The government's interpretation of the Regulations is binding to all parties concerned until it is challenged in the courts. The validity of any regulation is open to challenge in the courts, either on its constitutionality or interpretation.

Related Concerns

1



How can a manufacturer appeal the government's interpretation respecting safety and efficacy of drugs?

A.

If a manufacturer objects to the government's interpretation respecting safety and efficacy of a drug, a defined appeal procedure is instituted. The first step is a discussion of the problem with the proper officials. If the issue is not resolved to the satisfaction of the manufacturer, the manufacturer should submit a written request to the Director of the appropriate Bureau. The Director is then responsible for a review, the results of which are reported to the manufacturer. If the manufacturer determines that an appeal is necessary, a written request must be made to the Director General, Drugs Directorate. An Appeal Committee is then formed, with membership determined by the Director General and including an officer of the Drugs Directorate not previously involved in the review of the data. The manufacturer can make a further appeal on the decision of the Director General to more senior levels within the Department. This procedure is described in detail in Information Letter No. 740, which is available from the Drug Regulatory Affairs Division.

2

Q.

How does the Drug Quality Assessment Program (QUAD) function?

A.

QUAD provides information about the quality of drugs available on the Canadian market. This information is provided on a regular basis to purchasing groups in provincial and territorial departments of health. The information is based on inspection reports and analyses performed in regional laboratories of the Health Protection Branch.

Pharmaceutical manufacturers located in Canada may participate in this program by signing a QUAD consent form. These forms are available from the Bureau of Pharmaceutical Surveillance.

3

Q.

Can information on medicinal and non-medicinal ingredients be provided under an Access to Information request?

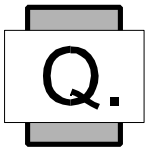
A.

Information released under an Access to Information request must be reviewed in order to remove third party secrets under Section 20(1) (a) of the *Access to Information (ATI) Act*. Financial, commercial, scientific, or technical information of a third party that has been consistently treated in a confidential manner is dealt with

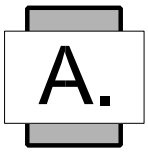
under Section 20(1) (b) of the ATI Act. If such information has been previously disclosed, such as in a Product Monograph (see Section C, below) that has been released by the manufacturer, it no longer qualifies for exemption.

Disclosure requires a careful examination of the current status of the product and evaluation of the eligibility for disclosure of the information.

4



What information is available concerning Adverse Drug Reaction (ADR) reporting?



There are several parts of Division 8 of the *Food and Drug Regulations* that concern ADR reporting. Paragraph C.08.005 (2) (b) requires reporting by manufacturers during clinical trials. Section C.08.007 and paragraph C.08.008 (c) provide for post-marketing reporting by manufacturers. Sale of drugs under the *Emergency Drug Regulations* (C.08.010) requires practitioners to report ADRs encountered during use of a drug authorized under this regulation.

The Product-Related Disease Division (PRDD), Bureau of Pharmaceutical Surveillance, is establishing a link between voluntary reporting and reporting pursuant to regulatory requirements so that all Canadian ADR reports will be sent to this division for entry into a computerized data base.

Computer printouts of suspected ADRs are available to bureaus and program participants upon request. Outside of government, persons making such requests may be provided with computer printouts via Access to Information requests. Most printout material will contain information on voluntary reports only.

PRDD provides information from its data bases to the World Health Organization (WHO) on a quarterly basis.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

SECTION B

INVESTIGATIONAL NEW DRUG (IND) SUBMISSIONS

1

Q. What is an Investigational New Drug (IND) submission?

A. An Investigational New Drug Submission (formerly Preclinical New Drug Submission) is filed for purposes of clinical testing by a manufacturer who wishes to distribute a drug to one or more named, qualified investigators. The investigator is to perform clinical testing in patients in order to determine the drug's tolerated dosage, effectiveness, and safety for humans (or, in the case of veterinary drugs, animals). The basic requirements are outlined in Section C.08.005 of the *Food and Drug Regulations*.

2

Q. Are test samples, results, and protocols required for an IND submission?

A. For drugs that are subject to Schedule D of the *Food and Drugs Act*, test samples should be included with an IND submission. This allows for testing of the individual lots prior to their use in clinical testing, as required by Section C.04.015 of the *Food and Drug Regulations*.

Because an IND submission relates to investigations that support the clinical testing of the new drug, test results are required. If the drug is for clinical testing in food-producing animals, the results of investigations supporting the safety of the new drug in humans are also required.

Protocols are required for IND submissions.

3

Q. Can a responsible clinical investigator (or co-investigator) in a multicentre study transfer from one centre to another without submission of a new IND?

A.

A new IND is not required; however, the manufacturer must submit the names and qualifications of all responsible clinical investigators, as well as the location of the study facilities where the clinical testing will be carried out. Further information can be obtained by referring to the guideline entitled, "Conduct of Clinical Investigations."

4

Q.

Does HPB review situations where the location of a multicentre study changes?

A.

If the site of the investigation changes within Canada, the information must be submitted to the Drugs Directorate by the manufacturer.

5

Q.

Does an IND change or restart with each new protocol, additional data, or packaging change?

A.

<u>New Protocol</u>

A new protocol requires the filing of a new IND submission.

<u>Additional Data</u>

Additional data of a minor nature, such as the addition of a non-intrusive test to the protocol, does not require the filing of a new IND submission. Major changes in the protocol, such as changes in the eligibility criteria for patients, dosage, and so on, require a new IND submission.

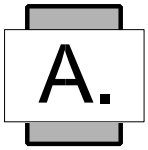
It is a requirement of an IND submission that all serious or unexpected adverse experiences should be reported immediately to HPB by the manufacturer.

<u>Packaging Changes</u>

Packaging changes of a minor nature do not require a new IND submission. Because the drug is usually intended for short-term use, stability does not have the same emphasis as in a New Drug submission. For major changes, filing of a new IND submission is required.

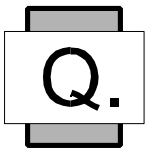
6

Are INDs required for comparative bioavailability studies in healthy volunteers?

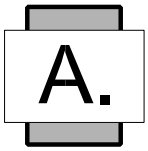


INDs are normally required in all human studies conducted in Canada when a drug product to be administered does not have a valid Notice of Compliance and the study sponsor is a manufacturer according to the definition of the *Food and Drugs Act*. The Health Protection Branch randomly audits INDs for comparative bioavailability studies in healthy volunteers. Regulatory amendments are being considered to exempt manufacturers from the requirement to file this type of IND with the Branch.

7

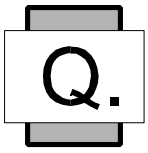


Where would a manufacturer obtain guidance and requirements for testing for toxicology?

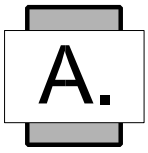


Information pertaining to testing for toxicology can be obtained by referring to the guideline entitled Toxicologic Evaluation (available from the Canadian Publishing Centre (819)956-4800). Other information may be obtained from our website at www.hc-sc.gc.ca/hpb-dgps/therapeut.

8



Is an Experimental Studies Certificate (ESC) needed for a veterinary new drug, even if it is to be used in a pilot project?



An ESC is applicable only to veterinary drugs and is required when:

(a) a clinical investigator wishes to perform limited experimentation in animals (food or non-food) with a drug for which a Notice of Compliance has not been issued in Canada; or

(b) the experimenter wishes to investigate a new indication for use, method of administration, and so on, with a drug that is marketed in Canada.

In the case of an Investigational New Drug (IND), an ESC is not issued when the manufacturer has submitted a protocol and necessary residue data (for food-producing animals) to establish a withdrawal period.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

SECTION C

NEW DRUG SUBMISSIONS (NDS)

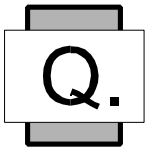
1

What is a New Drug Submission (NDS) and a Supplemental New Drug Submission (S/NDS)?

In order to sell a new drug in Canada, a manufacturer is required to file a New Drug Submission (NDS). The information contained in the NIDS must be in accordance with the *Food and Drug Regulations* Sections C.08.002 and C.08.005.1.

If there is significant change to the information contained in an NDS that has received a Notice of Compliance, the manufacturer is required to file a Supplemental NDS (S/NDS) in accordance with Sections C.08.003 and C.08.005.1 of the *Food and Drug Regulations*.

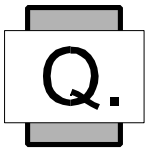
2



What is the difference between a "biological" NDS and a "regular" NDS?

Although the basic components of a "biological" and "regular" NDS are the same, there are differences in content. In a "biological" NDS, purity, identity, and stability are less easily defined than for a "regular" NDS. In addition, manufacturing and testing are more rigidly circumscribed, and toxicological, pharmacological, and pharmacolkinetic requirements receive different emphasis. Clinical trials also differ for such products as vaccines, where the trials for a "biological" NDS are large and complex.

3



Why is a submission for different routes of administration made as a New Drug Submission (NDS) rather than as a Supplemental New Drug Submission (S/NDS)?

A.

The use of a drug by a different route of administration may not be for the same indication for use, have the same mode of action, or have the same metabolic pathway; therefore, the submission requires the detailed evaluation of an NDS. (See also the definition of "new drug submission" in the Drugs Directorate Guideline entitled *Glossary of Terms*.)

4

Q.

What is a Notice of Compliance (NOC) and when can it be revoked?

A.

A Notice of Compliance (NOC) is issued by the Department for a new drug. It states that the NDS or S/NDS complies with the requirements of Sections C.08.002, C.08.003, and C.08.005.1 of the *Food and Drug Regulations*.

An NOC may be suspended when evidence reveals that the drug is shown to be neither safe nor effective for the use represented in the NDS or S/NDS on which the NOC was based.

5

Q.

What is the relationship between the issuance of an NOC, an inspection, and the issuance of a licence for a biological drug?

A.

Different regulations apply for issuance of a licence for a biological drug and the issuance of an NOC. For drugs that are subject to Schedule D of the *Food and Drugs Act*, inspection takes place when the Bureau of Biologics has completed an evaluation of the manufacturer's production methods and when appropriate sample testing is complete.

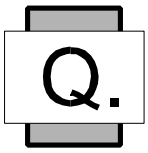
The NOC and a Canadian licence are issued when the Bureau of Biologics is assured through its inspection, evaluation, and testing, that the manufacturer is able to produce a product that is safe and effective for the indicated use.

6

If the preclinical data have been submitted with the IND, can they be cross-referenced with the NDS, or must the data be resubmitted in the NDS?

There is no need to resubmit data; they can be cross-referenced in the submission.

7



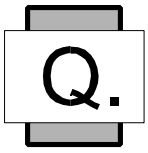
What is the difference between a Product Master File and a Plant Master File?

A Product Master File is filed by a manufacturer. It contains complete information about facilities, processes, and articles used in the manufacture, processing, or packaging of a drug product. For further information consult the Drugs Directorate Guideline entitled *Product Master Files*.

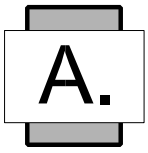
A Plant Master File is filed by a manufacturer or an agent. It describes the manufacturing capability of a fabricator to produce drugs in dosage form.

Plant and Product Master Files can be used, as authorized, in support of many submissions. For further information, consult Appendix B of the Drugs Directorate Guideline entitled *Good Manufacturing Practices*.

8



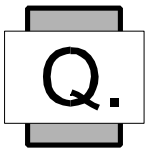
What drugs are considered generic, and are there special requirements for marketing such drugs?



A generic drug is a duplicate of, or similar to, a marketed new drug product.

The term "generic drug" is not expressly defined in the *Food and Drugs Ac*t and Regulations. It is considered to describe drug products that enter the market after an established product and that mimic the drug delivery of an established product. A New Drug Submission (NDS) must be filed for a generic drug when it is considered as a new drug according to the definitions of the *Food and Drug Regulations*. The New Drug Submission for a generic drug must, therefore, address the issues of safety, efficacy, and quality. Where information on the product of another manufacturer is used to substantiate the claims of a generic product, comparative data are required to show that both products are similar and have the same medicinal ingredients.

9



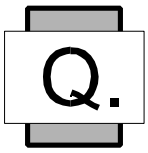
When is a drug new and when does it cease being a "new drug"?

A "new drug" is one that has not been sold in Canada for sufficient time and in sufficient quantity to establish its safety and efficacy in Canada as defined in Division 8 of the *Food and Drug Regulations*.

A drug is not a "new drug" when sufficient data to demonstrate its safety and efficacy have been amassed so that the drug no longer must meet the requirements of Division 8 of the *Food and Drug Regulations*.

Product Monographs

1



What is a Product Monograph?

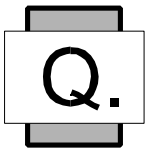
A Product Monograph is a factual, scientific document on a drug product. It is devoid of promotional material and describes the properties, claims, indications, and conditions of use of the drug. A Product Monograph should contain any other information that may be required for optimal, safe, and effective use of the drug.

2

What is an Annotated Product Monograph?

An Annotated Product Monograph is a draft of the text for a Product Monograph included in the New Drug Submission. It is typed, double-spaced, and cross-referenced to the comprehensive summary and sectional reports of the submission, with the page and volume numbers of the referenced data indicated.

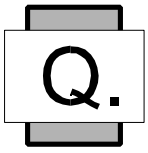
3



When filing an NDS or S/NDS, is a package insert required for each product along with a Product Monograph?

The regulations do not specify that a package insert must be provided for each product. However, if there is insufficient space on the label to fully inform the public or health professionals about a product, the Drugs Directorate may suggest that the manufacturer provide a package insert with the necessary information.

4



Is a deletion of a dosage form from the Product Monograph a Notifiable Change (NC), Additional Data (A/D), or a Supplemental New Drug Submission (S/NDS)?

A deletion of a dosage form from the Product Monograph does not affect the safety and efficacy information in the Product Monograph and is classified as a Notifiable Change.

Note: Please see the Drugs Directorate Guideline entitled *Glossary of Terms* for definitions of these terms.

5

Is a submission certificate required when the Drugs Directorate requests a revised Product Monograph?

A submission certificate certifies that the information included in the sectional reports and comprehensive summaries provided as part of the submission is accurate and complete, and correctly represents and interprets the raw data, A submission certificate is therefore not required with a revised Product Monograph.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

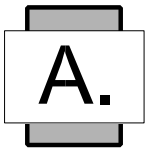
SECTION D

LICENCING

Schedule C and D Drugs

1

What is a product licence?



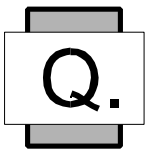
A "licence" or "Canadian licence" is a permit issued by the Drugs Directorate to a manufacturer of a Schedule C or D drug. The licence indicates that the premises in which a drug product is manufactured and the processes and conditions of manufacture are suitable to ensure that the drug is safe.

2

Who requires a product licence?

Any Canadian or foreign manufacturer involved in the manufacture of a drug in Schedule C or D requires a licence. A licence is required not only for the manufacturer of the final dosage form, but also for the manufacturer of any significant intermediate or raw material.

3



How is a licence obtained?

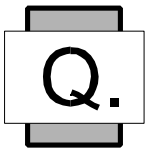
A licence is issued when an applicant supplies the information required under sections C.03.003 or C.04.004 of the *Food and Drug Regulations*, and receives a satisfactory inspection report.

4

At what stage in the development of a Schedule C or D drug is a licence usually applied for?

Manufacturers of Schedule C or D drugs normally apply for a licence when they plan to market their drug and can prove consistency of production methods in the manufacturing process. When a New Drug Submission is filed, an application for a licence is usually made at the same time.

5



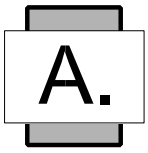
Is a licence required for the sale of a Schedule D drug used solely for clinical investigations?

No. However, prior submissions of samples from material to be used for clinical investigations may be requested. Inspections for new biological manufacturers and for novel drug entities must also be conducted.

Narcotic, Controlled, and Restricted Drugs

1

What is the difference between *narcotic, controlled,* and *restricted* drugs?

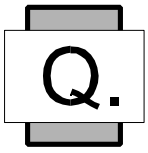


Narcotic drugs are controlled by the *Narcotic Control Act* and *Regulations* and are listed in the Schedule to that Act. Examples of narcotic drugs are cocaine, opium, codeine, morphine, and cannabis (marijuana). Some narcotic drugs have a legitimate medicinal use, such as the relief of pain. However, the ability of such drugs to modify mental activity (psychotropic effects), as well as the addictive properties of such drugs, have led to stringent restrictions on their availability.

Controlled drugs are stimulants (e.g., amphetamines) and sedatives (e.g., barbituric acid, methaqualone), They are listed in Schedule G to the *Food and Drugs Act*.

Restricted drugs (e.g., LSD) have hallucinogenic effects and no recognized medicinal use. They are listed in Schedule H to the *Food and Drugs Act* and are only available to research scientists who are involved in highly specialized research.

2

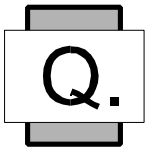


Who requires a licence for narcotic, controlled, and restricted drugs?

A licence is required by those wishing to manufacture, distribute, import, export, or sell a narcotic, controlled, or restricted drug.

A licence for narcotic, controlled, or restricted drugs, is issued by Health and Welfare Canada. Part G of the *Food and Drug Regulations*-Importing and Exporting-pertains to controlled drugs, and Part H pertains to restricted drugs. Narcotic drugs are regulated by the *Narcotic Control Act* and *Regulations*.

3



Is a licence required to manufacture, distribute, import, or export a narcotic, controlled, or restricted drug?

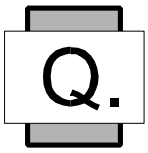
Both international law and Canadian drug legislation require that these activities be licenced. The International Control and Licencing Division (Telephone (613) 954-6766) of the Bureau of Dangerous Drugs can explain licencing requirements and application procedures.

4

Can a licence be amended to add or delete a drug?

A licence can be amended by forwarding the current licence along with the request to the International Control and Licencing Division of the Bureau of Dangerous Drugs.

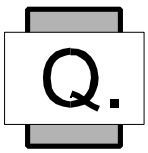
5



Who can order narcotic, controlled, and restricted drugs from a licenced dealer? Can such a licenced dealer honour a request from a university scientist?

Narcotic, controlled, and restricted drugs can be ordered from a licenced dealer by another licenced dealer, a duly registered pharmacist, a practitioner (in medicine, dentistry, or veterinary medicine), or a research scientist with a Ministerial authorization.

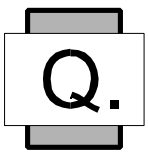
6



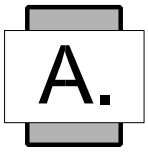
How does a licenced dealer dispose of narcotic, controlled, and restricted drugs that are out of date and have been returned by a pharmacy?

An application to dispose of or destroy such drugs can be made by the licenced dealer to the regional office of the Bureau of Dangerous Drugs. The destruction of such drugs must conform with all applicable environmental laws. Disposal of such drugs should also be witnessed by an inspector during an inspection.

7



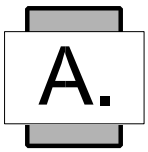
Can a salesperson representing a licenced dealer authorize a pharmacist to return out-of-date narcotic or controlled drugs to the dealer?



A salesperson cannot authorize the return of out-of-date drugs. For reasons of security and drug accountability reasons, only certain people located on the licenced dealer's premises are authorized to requisition drugs for the licenced dealer, including returns.

8

Can licenced dealers transfer to other licenced dealers requisitions for drugs that are in short supply?



No. Licenced dealers can fill only requisitions made out in their names and must maintain such requisitions on their premises for audit purposes.

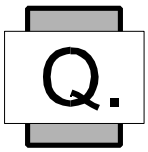
DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

SECTION E

INSPECTIONS

This section contains questions that pertain only to inspections undertaken by the Drugs Directorate staff.

1

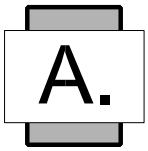


Do the premises of licenced manufacturers (Canadian or foreign) have to be inspected?

Yes, all licenced manufacturers of Schedule D drugs must have their premises inspected before issue of a licence and periodically thereafter. In the case of narcotic, controlled, and restricted drugs, the inspections are carried out by the Bureau of Dangerous Drugs to ensure compliance with Parts G and J of the *Food and Drug Regulations* and the *Narcotic Control Regulations*, to identify and investigate problems of diversion, and to exchange information. The premises of biologics manufacturers and suppliers of raw material are inspected by the Bureau of Biologics.

2

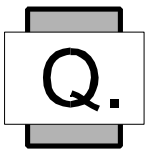
When and how does an inspection take place, and is it before or after the issue of a Notice of Compliance (NOC)?



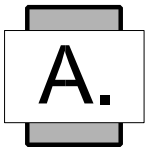
The licence is usually issued at the same time as the NOC. Inspection takes place when the Bureau of Biologics methods evaluation and sample testing is complete.

In the case of narcotic, controlled, and restricted drugs, site visits or inspections are conducted at various times: prior to licencing; when changes in security are being planned or undertaken; following a loss of narcotic, controlled, or restricted drugs; as part of an investigation; on a routine basis; and when circumstances warrant.

3



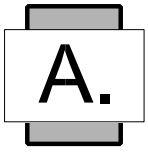
Is there a charge for inspections?



There is no charge for inspections relating to narcotic, controlled, or restricted drugs. However, for biologics inspections that are required by the *Food and Drug Regulations*, the Minister may charge for accommodations and travel expenses. Such charges have not been implemented to date.

4

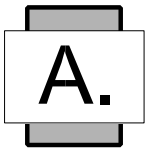
What can cause a re-inspection of a biological drug?



A re-inspection may be necessary when an additional product is added to the licence, when a problem arises, when a significant change takes place in the premises or methods of manufacture, or when required to ensure that the problems or concerns identified during the previous inspection have been addressed.

5

Can inspections be carried out without warning?



Inspections may be carried out without prior notification and at any time during normal working hours. However, for Schedule D drugs, inspection is normally most productive when the relevant product is in production and when responsible personnel are present.

6

How and when are the results of an inspection communicated to the company?

At the end of an inspection, the inspector reviews the results with the person in charge. Recommendations and directions for corrective action are discussed at this time. Serious violations and relevant requirements or restrictions are confirmed in writing from the appropriate bureau as soon as possible following the inspection.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

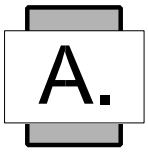
SECTION F

COSMETICS, DISINFECTANTS, AND HOMEOPATHICS

Cosmetics

1

Are cosmetics subject to regulation in Canada?



Cosmetics are regulated under three federal acts and their regulations: the *Food and Drugs Act*, the *Consumer Packaging and Labelling Act*, and the *Broadcasting Act*.

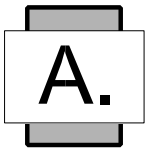
2

What is the distinction between a drug and a cosmetic?

The composition of a product may determine its classification as a drug or cosmetic. A key consideration for the classification of a product is the claim made on the label of a product that indicates its intended use. Cosmetics, which include deodorants and soaps, are intended to cleanse or improve the appearance. Claims that indicate therapeutic or physiological activity are unsuitable for a cosmetic.

3

Must HPB approve the labelling and ingredients of a cosmetic before it is sold in Canada?



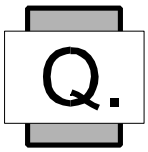
No. Manufacturers are required to notify HPB prior to importing or within ten days of first selling the product. Notification forms are available from the Bureau of Nonprescription Drugs. The manufacturer is responsible under Section 16 of the *Food and Drugs Act* for ensuring that the product is safe when used according to labelled instructions and that the labelling meets the requirements of the *Food and Drugs Act* and the *Consumer Packaging and Labelling Act*.

4

Who must make notification for a cosmetic?

The manufacturer or agent authorized by the manufacturer. The manufacturer's name must appear on the label of the product.

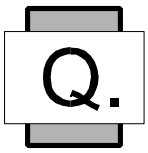
5



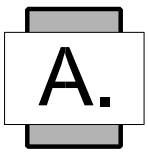
Are certain ingredients prohibited?

Only four ingredients are specifically prohibited in the *Cosmetic Regulations*: chloroform, estrogen/estrogen-containing substances, saccharin and its salts, and mercury and its salts (unless used as a preservative in products to be used in the area of the eye). Section 16 of the *Food and Drugs Act* specifies, however, that it is unlawful to sell a cosmetic that may be unsafe when used according to its labelled directions. Responsibility rests with the manufacturer to ensure that the ingredients used in cosmetic products are safe.

6



How can additional information be obtained?

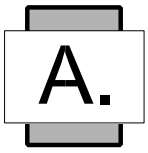


Copies of the *Food and Drugs Ac*t and Regulations, the Cosmetic Regulations, and the Drugs Directorate Guidelines *Labelling of Cosmetics* are available from the Canadian Government Publishing Centre, Ottawa, Canada K1A 0S9 (Telephone (819) 956-4800 / Fax (819)-994-1498), or from an authorized bookstore agent or local bookseller.

Disinfectants

1

Are disinfectants subject to regulation in Canada?



Disinfectants are regulated as drugs under the *Food and Drugs Act* and under the *Pest Control Products Act*. Disinfectants for use on medical devices and on environmental (i.e., inanimate or hard) surfaces in hospitals and premises where food is processed are considered drugs under the *Food and Drugs Act* and require a Drug Identification Number (DIN). For further information, consult the Drugs Directorate Guideline entitled Disinfectants: *Preparation of Application for Drug Identification Number*.

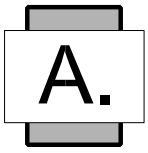
Disinfectants for use on environmental surfaces in all other situations (e.g., schools, restaurants, hotels, swimming pools) are regulated under the *Pest Control Products Act* and require a Pest Control Products Number. These products are regulated by the Pesticide Directorate, Agriculture Canada, Ottawa, Ontario K1A 0C5 (Telephone (613) 993-4544).

A disinfectant that is a sanitation product, for use solely in premises where food is processed, is not considered to be a drug, and an application for a DIN is not required. However, the manufacturer should contact the Bureau of Chemical Safety, Food Directorate (Telephone (613) 957-1827) for information on the acceptability of products of this type.

Specific questions concerning disinfectants as drugs should be addressed to the Pharmaceutical Assessment and Cosmetics Division of the Bureau of Nonprescription Drugs (Telephone (613) 954-1254).

2

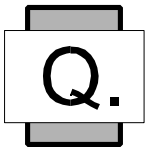
Must efficacy data be submitted with a DIN application for a disinfectant?



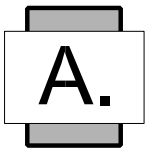
It is expected that a manufacturer will have data to support the safety and efficacy of the disinfectant. The manufacturer is not normally required to submit data at the time the application for a DIN is submitted, but may be asked to provide data if questions concerning the product arise during the evaluation process.

Homeopathics

1

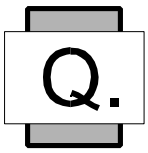


Are homeopathic preparations subject to regulation in Canada?

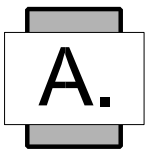


Because homeopathic preparations are used in the treatment of disease, they are classified as drugs by the *Food and Drugs Act and Regulations*. They must therefore have a DIN on the label prior to sale.

2



Are homeopathic preparations subject to the same evaluation process as other drugs?



No, the evaluation process reflects the unique nature of these preparations.

DINs are issued for homeopathic preparations that are considered to be non-toxic; however, there is no assessment of the efficacy of these products.

A homeopathic preparation may contain only an ingredient or combination of ingredients for which a monograph as a homeopathic medicinal ingredient is defined in the current editions of the *Homeopathic Pharmacopeia of the United States (HPUS)* or the *Pharmacopée Française (PhF)* and which is offered for sale in a dosage form defined by, and prepared in accordance with, the procedures prescribed by these compendia. Ingredients that are otherwise prohibited from drugs may not be present in homeopathics.

The labelling of the product must identify it as a homeopathic preparation. It must also indicate that the product is to be used only on the advice of a physician or homeopathic practitioner. No therapeutic claims, explicit or implied, may be made for the product. Labelling is not subject to pre-market review by HPB. Responsibility for conforming to labelling guidelines as outlined in the Drugs Directorate Guidelines entitled *Homeopathic Preparations: Application for Drug Identification Numbers* rests with the manufacturer. However, a homeopathic preparation must comply with Good Manufacturing Practices (Division 2 of the *Food and Drug Regulations*).

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

SECTION G

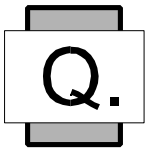
LABELLING AND ADVERTISING

1

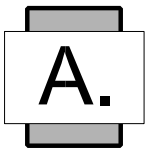
What information is required on a drug label?

All drugs must be labelled in compliance with the *Food and Drugs Act and Regulations*. In general, these requirements can be found in Section C.01 .004 of the Regulations. Product-specific labelling requirements or restrictions can be found in the appropriate section, for example, Part C, Division 4 respecting drugs of biological origin, Part D, Division 4 respecting vitamins, and Part D, Division 5 respecting minerals.

2

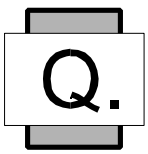


Must drug labelling be bilingual?

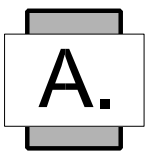


All labels must be in either French or English in addition to any other language. If the drug is available for sale without a prescription in an open self-selection area, adequate directions for use (general indications, dosage directions, and warnings or cautions) must be displayed in both French and English on the outer and inner labels of the drug. Provincial requirements for drug labelling may vary and should be considered in addition to the federal requirements.

3



Must all drug products be sold in a security package?



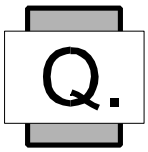
According to Section A.01.065 of the *Food and Drug Regulations*, a drug that is a mouthwash, is to be inhaled, ingested, or inserted into the body, or is for ophthalmic use must be sold in a security package if it is available to the general public in an open self-selection area.

4

Must non-medicinal ingredients be declared on drug product labels?

No. An exception is the preservatives in injectable preparations, which must be declared quantitatively on the label. Manufacturers are encouraged, however. to include this information on their labelling.

5



Is drug advertising reviewed on a regular basis?

All drug commercials intended for radio or television broadcast must be reviewed by HPB and comply with the *Food and Drugs Act and Regulations*.
HPB issues a continuity clearance number to each drug commercial it approves. Newspaper and magazine advertisements and direct mail advertisements are not subject to clearance requirements but must be in compliance with the Act and Regulations. Drug advertising directed to health professionals is reviewed and pre-cleared by the Pharmaceutical Advertising Advisory Board (PAAB), which consults with the Drugs Directorate.

6

Can prescription drugs be advertised to the general public?

Yes, with the exception of narcotic or controlled drugs. However, no representation other than the name, price, and quantity of such a drug can be made.

This does not apply to drugs in Part II of Schedule F to the *Food and Drug Regulations* (drugs sold without prescription for animal use).

7

Can drugs be distributed as samples to the general public?

The distribution of any drug to the public as a sample is prohibited by Section 14 of the *Food and Drugs Act*. Samples of drugs other than narcotic, controlled, or restricted drugs may be distributed to physicians, veterinary surgeons, dentists, and pharmacists under the conditions described in Section C.01.048 of the *Food and Drug Regulations*.

A sample of a drug, except a narcotic or controlled drug, may be included in the packaging of another drug, provided that the package is purchased and that the labelling of the package clearly indicates to the consumer the entire contents of the package.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

SECTION H

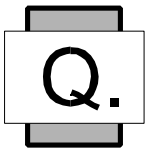
LOT RELEASE OF BIOLOGICAL DRUGS

1

What is a lot?

A lot is a quantity of any drug in bulk or final dosage form that is homogeneous within specified limits and that is identified by a distinctive lot number.

2



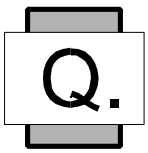
What products are on lot release and for how long?

Upon written request from the Director of the Bureau of Biologics, a manufacturer must submit protocols of tests together with samples of any lot a drug prior to its being sold.

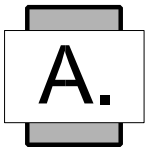
All biological drugs, with the exception of traditional allergenic extracts, are released on a lot-by-lot basis. This approval procedure includes the review of production protocols submitted by the manufacturer for each lot, plus selective confirmatory testing by the Bureau of Biologics on submitted samples.

The lot release procedure continues indefinitely. However, after the testing performance of each product is assessed for several years, routine testing may be replaced by random testing.

3



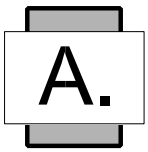
What size should samples be and should they be selected from bulk or final containers?



The samples should be in an amount that is sufficient to determine whether the drug or raw material complies with specifications for that drug or raw material. The specifications also determine from which containers the sample selection is to be made.

4

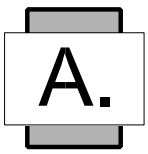
What tests are performed on lot releases by the Bureau of Biologics?



The Bureau of Biologics has a policy of selective testing. For some products, all criteria tests are performed. The choice depends on the consistency of past results, as well as any specific concerns.

5

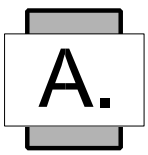
Should company protocol and test results be submitted with samples?



Yes, the protocol (or certificate of analysis) must be submitted. However, in some circumstances, testing by the Bureau of Biologics and by the company can proceed concurrently, provided that the company results are submitted when testing is complete.

6

Can a company have a product removed from lot release?



No, not unless the drug is removed from Schedule D.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

SECTION I

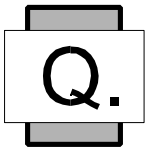
IMPORTING/EXPORTING AND DISTRIBUTING

1

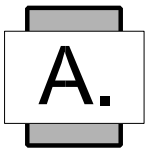
Can drugs without a valid DIN be imported?

A drug that would violate the *Food and Drugs Act* or the *Narcotic Control Act* or their *Regulations* cannot be imported into Canada for sale by any person. A new drug requires a Notice of Compliance, and an old drug must be labelled with the appropriate DIN. Canada Customs will permit importation of a limited quantity of drugs other than narcotic, controlled, or restricted drugs for personal use. Specific provisions are made for drugs subject to Investigational New Drugs and Emergency Drug Release.

2

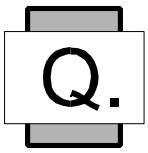


What documentation from the manufacturer does Canada Customs require for importation of Investigational New Drugs (INDs) that do not contain a narcotic, controlled, or restricted drug?

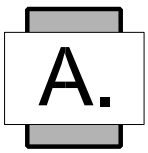


Canada Customs requires a copy of the letter of acknowledgement for receipt of the IND by Drugs Directorate. This letter is to be provided by the manufacturer.

3



Do drug import/export regulations apply to narcotic, controlled, and restricted drugs?



In the case of narcotic drugs, the *Narcotic Control Regulations* apply. Part G of the *Food and Drug Regulations* pertains to controlled drugs, while Part J regulates restricted drugs.

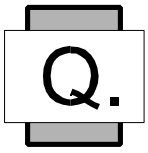
Only licenced dealers may import or export these drugs and only after a permit has been issued.

4

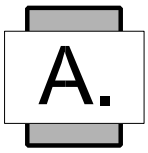
How is an import/export permit obtained for narcotic, controlled, and restricted drugs, and what is its validity period?

Import/export application forms may be obtained from the International Control and Licencing Division of the Bureau of Dangerous Drugs. The permit is valid for a period of three months and two weeks or until December 31st of the year issued, whichever comes first. The Minister may revoke or suspend a permit if the company to which it was issued has violated or failed to comply with any of the terms or conditions of the *Food and Drugs Act and Regulations* and *Narcotic Control Act and Regulations*.

5



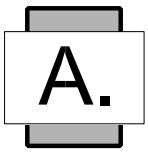
What restrictions apply to a foreign supplier?



Under the Good Manufacturing Practices (GMP) regulations, any person who imports a drug in dosage form for sale must have satisfactory evidence on the premises as to the foreign manufacturer's GMP compliance. This information is monitored during drug plant inspections and should be submitted to HPB on request. For a new drug, the New Drug Submission (NDS) must include evidence (usually in the form of a Plant Master File) of the foreign manufacturer's capability to produce the dosage form in compliance with the GMP regulations.

6

Does a prescription drug marketed in another country automatically become a drug requiring prescription status in Canada?

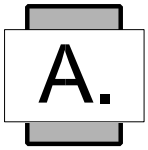


A drug does not automatically become a prescription drug in Canada because of its status elsewhere. When a submission is reviewed, the Drugs Directorate uses established criteria and other evidence supplied by the manufacturer to determine whether the drug requires prescription status. These drugs require additional control because professionals need direction and supervision in their use and because they

have potential for abuse. Prescription drugs are categorized according to the extent of control necessary for their safe use. Prescription drugs are those listed in Schedule F to the *Food and Drug Regulations* and include Folic Acid, Vitamins A, D and K at specified levels, controlled drugs, and narcotic drugs.

7

What are the regulatory requirements for importers regarding storage and shipping for narcotic, controlled, and restricted drugs?



The regulations require licenced dealers to provide protection against loss or theft of any narcotic, controlled, or restricted drug in their possession. The Minister may require an inspection of the premises used to store narcotic, controlled, or restricted drugs. Licenced dealers may import into or export out of Canada only those narcotic, controlled, or restricted drugs specified in their permit. Licenced dealers must also package such drugs for export in such a manner that the package cannot be opened without breaking the seal, and must ensure its safekeeping during transit. Storage must be on licenced premises with security conforming to the Minister's guidelines.

8

What conditions pertain to emergency drug release as opposed to special import?

In the case of an emergency drug release, the Director may authorize the sale of a quantity of a new drug for human or veterinary use to a practitioner named in the letter of authorization for the emergency treatment of a patient under the care of that practitioner.

A special import procedure applies only to products that are not new drugs, new drugs with a Notice of Compliance that are not available in Canada, or out-of-stock drugs imported in limited quantity to serve valid medical needs. If a similar or identical drug from another company is available in Canada, a special import permit is not normally given. Following a request from a physician or pharmacy for a special import, Drugs Directorate sends a letter to the manufacturer (with copies to the physician or pharmacy), giving permission to import the drug. The amount and potency of the drug are included in the letter. Special imports are exempted from labelling, testing, conditions of manufacture, and drug notification.

9

What is Canada's involvement with the World Health Organization (WHO) Certification Scheme?

This scheme is an administrative instrument through which each participating member state undertakes, upon application by a manufacturer, to attest to the competent authority of another participating member state on whether:

(a) a specific product is authorized for sale or distribution within the exporting member state; and

(b) the plant in which it is produced is subject to inspections at suitable intervals, to establish that the manufacturer conforms to WHO recommendations for Good Manufacturing Practices (GMP).

WHO certification is not provided when the company fails to meet Canadian standards or when the inspection report is more than 18 months old. Normally, drugs for export from Canada are also sold in Canada. When this is not the case, the certificate is modified to identify such limitations.

In those instances in which the export market does not require a certificate pursuant to the WHO Certification Scheme, the manufacturer may elect to obtain an export certificate from the closest regional office of HPB's Field Operations Directorate.

DRUGS DIRECTORATE
QUESTIONS AND ANSWERS

FOR MORE INFORMATION

For further details about the information contained in this guide, contact

Drug Regulatory Affairs Division
Drugs Directorate
Room 139
HPB Bldg, Tunney's Pasture
Ottawa, Ontario K1A 0L2
(613) 957-0372

or one of the following bureaus:

Bureau of Biologics
Drugs Directorate
Virus Bldg, Tunney's Pasture
Ottawa, Ontario K1A 0L2
(613) 957-8065

Bureau of Dangerous Drugs
Drugs Directorate
3rd Floor
Jackson Bldg, 122 Bank Street
Ottawa, Ontario K1A 1B9
(613) 954-6522

Bureau of Pharmaceutical Surveillance
Drugs Directorate
2nd Floor
HPB Bldg, Tunney's Pasture
Ottawa, Ontario K1A 0L2
(613) 957-1831

Bureau of Drug Research
Drugs Directorate
3rd Floor Centre
Frederick G. Banting Bldg,
Tunney's Pasture
Ottawa, Ontario K1A 0L2
(613) 957-1058

Bureau of Human Prescription Drugs
Drugs Directorate
Place Vanier, Tower B
Vanier, Ontario K1A 1B8
(613) 991-0107

Bureau of Nonprescription Drugs
Drugs Directorate
2nd Floor
Place Vanier, Tower A
Vanier, Ontario K1A 1B8
(613) 954-6493

Bureau of Veterinary Drugs
Drugs Directorate
3rd Floor
Brooke Claxton Bldg, Tunney's Pasture
Ottawa, Ontario K1A 1B7
(613) 957-3824

Bureau of Chemical Safety
Food Directorate
3rd Floor Centre
Room 309B
Frederick G. Banting Bldg, Tunney's Pasture
Ottawa, Ontario K1A 0L2
(613) 957-0973