PROGRAMME DES PRODUITS THÉRAPEUTIQUES
THERAPEUTIC PRODUCTS PROGRAMME

Regulatory Guidance
How to Market a Biological (Schedule D) Drug

General Overview

This fact sheet provides general information about the approval and sale of Biological (Schedule D) drugs in Canada as well as the Canadian regulatory requirements for Investigational New Drug Submissions (INDSs) and New Drug Submissions (NDSs) as they relate to these drugs. Attachment 1 is a reference list of some of the relevant guidance documents, policies, and forms.

Most of the documents may be found on the Therapeutic Products Programme (TPP) website. However, there are some documents which are only available by placing an order with the Canadian Government Publishing Centre (formerly Canada Communication Group - Publishing).

All drugs that marketed in Canada are subject to the **Food and Drugs Act** and **Regulations**. You may purchase a copy from the Supply and Services Canada Publishing Centre, either directly by telephone at (819) 956-4800, or by completing the order form found on the TPP website and faxing it to (819) 994-1498.

For the regulatory requirements specific to **Biological** (Schedule D to the **Regulations**) or **Radiopharmaceutical** (Schedule C to the **Regulations**) drug products, you are referred to Divisions 3, 4 and 8 of Part C of the **Regulations**. The Bureau of Biologics and Radiopharmaceuticals is responsible for the review and approval of all drug submissions for Biological (Schedule D) and Radiopharmaceutical (Schedule C) drug products, including but not limited to NDSs and INDSs.

Management and Performance Standards

The **Management of Drug Submissions** policy outlines the way the TPP manages information and material submitted by sponsors in accordance with the **Food and Drugs Act** and **Regulations**. This policy applies to all submission types including NDSs and INDSs. Sponsors are encouraged to peruse this document as it is key to the management of drug submissions submitted to the Programme.

Clinical Trials

Health Canada's authority to regulate clinical trials stems from the **Food and Drugs Act** and **Regulations**, Section C.08.005. Sponsors are directed to the **Clinical Trial Review and Approval** policy found on the TPP website. The aim of this policy is to define the information required by the TPP from sponsors, as well as the evaluation process for the conduct of clinical trials in Canada. In practice, sponsors may be manufacturers, practitioners or research institutions.

Currently, the guideline **Good Clinical Practice: Consolidated Guideline** supersedes existing guidelines **Preparation of Investigational New Drug Submissions (1991)** and **Conduct of Clinical Investigations (1989)**. However, Section 4.1, Subsection 1.8 of **Preparation of Investigational New Drug Submissions** is used as a guidance document for the labelling requirements for drugs used in conjunction with a proposed clinical trial. You must follow additional guidelines regarding the nature of clinical studies. These guidelines include, but are not limited to the following.

- **Toxicological Evaluation (revised with ICH inserts)**
- **Clinical Safety Data Management: Definitions and Standards for Expedited Reporting**
- **Structure and Content of Clinical Study Reports**

We emphasize that the INDS process and reporting criteria are the same for pharmaceutical, biological and radiopharmaceutical drugs.

For Schedule C (Radiopharmaceuticals) and Schedule D (Biologicals) drugs, the sponsor must file complete quality (chemistry and manufacturing) information. The TPP has introduced updated electronic quality (chemistry and manufacturing) templates for biological (Schedule D) products: the draft **Quality Information Summary - Biologicals** (QIS-B).

Sponsors obtain an electronic copy of the blank templates (available in an IBM-compatible, WP 6.1 format only) through the TPP internet site. Also posted to the same internet site, under "qisbhelp.zip", is an accompanying document which was developed to assist sponsors in the completion of the QIS-B template. Sponsors are encouraged to read this document before completing the templates.

The entire QIS-B template consists of four parts.

- Part 1: G. General Information
- Part 2: S. Drug Substance
- Part 3: P. Drug Product
- Part 4: O. Other Information

The QIS-B has a specifically designed module (Part 2 only) available for submissions for the following biological product types.

- recombinant DNA products and monoclonal antibodies [QIS-B-rDNA/MAbs]
- blood products [QIS-B-BLD]
- general biological product lines [QIS-B-GEN]
- vaccines [QIS-B-VAC]

Upon initial filing of an INDS, a sponsor is required to complete **only** those subsections or parts of a table which are identified with a check mark (i.e., ✓) to the left of the heading under Parts 1-4 of the QIS-B template. It should not be used in lieu of a table of contents and ***full*** chemistry and manufacturing information is still required.

The QIS-B template should also be used to summarize the quality information for premarket submissions.

Clinical Trial Reform

Health Canada is **proposing** amendments to the **Food and Drug Regulations**, concerning the regulation of clinical trials in Canada. The most current documentation available on the TPP website respecting proposed changes to Canada's **Food and Drug Regulations** as they pertain to clinical trials may be found under "What's New", "Regulations and Schedule Amendments: Gazette Part I" (Schedule 1024: Clinical Trials).

Premarket Submissions

A drug product may be considered a **new drug** when it bears a drug claim for a single ingredient or combination of ingredients **presented to the Canadian market for the first time**. A Notice of Compliance (NOC) in accordance with Division 8, Part C of the **Food and Drug Regulations** must also be issued for a new drug prior to sale.

Sponsors are to use the guidance document **Preparation of a Human New Drug Submission**, found on the TPP website, for the preparation of an NDS for presentation to the TPP. This guideline is not intended to be exhaustive or inflexible but will help to ensure that the content of the NDS is factual, relevant, and complete, and that the manner of presentation is uniform and logical. The presentation of information in this manner facilitates effective and speedy review.

Briefly, the requirements for an NDS include, but are not limited to, data to support the safety, efficacy and quality of the proposed new drug.

Facility Information
For Biologics and Radiopharmaceuticals, product-specific facility information is required and is submitted within Part II (Chemistry & Manufacturing) of an NDS. In this regard, you are referred to the guidance document **Product Specific Facility Information** which is available on the TPP website.

Product Labelling

In Canada, the labelling of drugs intended for human use is regulated under the **Food and Drugs Act** and **Regulations**. General labelling requirements are outlined in Section C.01.004 of the **Regulations**. The labelling requirements specific to Schedule C and Schedule D drugs are outlined in Division 3 and 4, respectively, of Part C of the **Regulations**.

Further, the TPP guideline **Product Monographs** should be consulted for the preparation of a Product Monograph.

Good Manufacturing Practices (GMP)

All drugs that are marketed in Canada are subject to Canadian "Good Manufacturing Practices" as outlined in Division 2 of Part C of the **Food and Drug Regulations**. The TPP guideline **Good Manufacturing Practices** explains the principles and practices that are accepted by the TPP.

Establishment Licensing

As of January 1, 1998, an establishment licence is required for all Canadian establishments which handle dosage forms for all drug types, whether pharmaceutical, biological or radiopharmaceutical, and in the case of Schedule C (radiopharmaceutical) and D (biological) drugs, bulk process intermediates intended for use in the fabrication of final dosage forms.

Division 1A of the **Food and Drugs Regulations** provides the regulatory framework which supports establishment licensing.

The TPP **Guidance Document on Establishment Licences and Establishment Licensing Fees** is located on the website under the heading "cost recovery".

Imported Products

For a drug which is imported, it is mandatory that an agent possessing an Establishment Licence, who is responsible for the sale of the drug in Canada, be located **in** Canada. The name of the agent who imports the drug and the address of their principal place of business in Canada must appear on the inner and outer labels of the drug as indicated in C.01.004.1(2) of the **Food and Drug Regulations**. Further, for products of foreign origin, the focus of the Canadian GMP compliance will be on the Canadian importer.

Cost Recovery

Sponsors are required to pay fees for the following activities/services provided by Health Canada in relation to the regulation of drug products.

- drug submission evaluation
- drug master file registration
- the right or privilege to market a drug in Canada (annual Drug Identification Number [DIN] notification)
- establishment licensing
- issuance of export certificates

The **Guidance Document on Cost Recovery Submission Evaluation Fees**, available on the TPP website, identifies the fees payable for the evaluation of various components of different types of drug submissions.

Lot Release

Please note that the Bureau of Biologics and Radiopharmaceuticals has a lot release program in place which applies to biological drugs only. In this regard, you are referred to the guidance document **Evaluation Groups and Lot Testing Requirements** and the draft policy **Review/Testing/Approval of Biological Drug Lots**, both of which are available on the TPP website.

Location of Documents

The TPP of Health Canada maintains a **website** where guidelines, policies, regulations, order forms, publications, templates, et cetera may be found and downloaded. These documents are created using WordPerfect. The website can be accessed through the INTERNET at the following address.

http://www.hc-sc.gc.ca/hpb-dgps/therapeut

In addition, on-line searches may be performed to locate previously authorised and currently marketed drug products in our Drug Product Database (DPD) at the following address.

http://www.hc-sc.gc.ca/hpb/drugs-dpd

Finally, the attached list of reference documents should not be considered comprehensive in nature. In addition, the list includes a few guidelines and publications which are not posted to the TPP website but may be ordered from the Canadian Government Publishing Centre. Please note that these documents are subject to a fee. For example, the TPP guidance document, **Preparation of Investigational New Drug Submissions**, is not available on the TPP website but may be purchased for $8.95 (in Canadian funds) from the Canadian Government Publishing Centre (Catalogue No. H42-2-37-1990).

Further Information/Assistance

For additional information with respect to the preparation of a drug submission the following may be contacted.

For information regarding Biological and Radiopharmaceutical drugs

Therapeutic Products Programme
Bureau of Biologics and Radiopharmacuticals
Submission Management Division
1st Floor LCDC Building # 6, Address Locator 0601E3
Ottawa, Ontario
K1A 1B6
Tel.: (613) 957-1722

For information regarding Establishment Licensing

Therapeutic Products Programme
Bureau of Compliance and Enforcement
Tower A, 2nd Floor, Holland Cross, Address Locator 3102A2
11 Holland Avenue
Ottawa, Ontario
K1A 0L2
Tel.: (613) 952-3828

For information regarding Cost Recovery

Therapeutic Products Programme
Bureau of Policy and Coordination
Submission and Information Policy Division
1st Floor Finance Building #2, Address Locator 0201A1
Tunney's Pasture
Ottawa, Ontario
K1A 0L2
Tel.: (613) 941-7282

Attachment 1

Reference List

TPP website address: http://www.hc-sc.gc.ca/hpb-dgps/therapeut

Order Forms
Food & Drug Act and Regulations Order Form
*(forms~fdaorder_e)

Therapeutic Products Programme Publications and Guidelines (available through the Canadian Government Publishing Centre) - Order Form
*(forms~guidelin_e)

Management and Performance Standards
Drug Submissions, Management of
*(policies~issued external policy statements~mangdrug_e)

Forms Used in Conjunction with Submissions
Submission Fee Application Form
*(forms~feeform_e)

Drug Submission Application Form for: Human, Veterinary & Disinfectant Drugs - HPB/DGPS 3011
*(forms~submissn_e)

Submission Certification: NDS, SNDS, NC
*(forms~cetnds_e)

Establishment Licence Application: Form and Instructions
*(forms~el-drugs_appl_e)

BBR Requirements Product Samples and Protocols for Clinical Trials "Fax-Back"
*(forms~bbrctfax_e)

Clinical Trial Investigator & Site Certification
*(forms~ctisite_e)

ADR Expedited Reporting Summary for ADRs Occurring During Clinical Trials
*(forms~ct_adr_e)

Fees: Drug Master File Application
*(forms~feedmf_e)

Clinical Trials: Investigational New Drug Submissions

Clinical Trial Review and Approval
*(policies~issued external policy statements~ctrevapp_e)

E6: Good Clinical Practice: Consolidated Guideline
*(guidelines~ich~goodclin_e) or ICH website at: www.pharmweb.net/pwmirror/pw9/ifpma/ich1.html

Preparation of Investigational New Drug Submissions
**(forms~guidelin_e), Catalogue No. H42-2-37-1990

Toxicological Evaluation (revised with ICH inserts)
**(forms~guidelin_e), Catalogue No. H42-2/15-1990E

ICH - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
**(forms~guidelin_e), Catalogue No. H42-2/67-8-1995E or ICH website at: www.pharmweb.net/pwmirror/pw9/ifpma/ich1.html

E3: Structure and Content of Clinical Study Reports
*(guidelines~ich~efficacy~structur_e) or ICH website at: www.pharmweb.net/pwmirror/pw9/ifpma/ich1.html

E8: General Considerations for Clinical Trials
*(guidelines~ich~efficacy~gclintr_e) or ICH website at: www.pharmweb.net/pwmirror/pw9/ifpma/ich1.html

Premarket Submissions

General

Preparation of Human New Drug Submissions - Supplement Attached - 1991
*(guidelines~drugs currently regulated as new drugs~prephumn.zip)

Safety & Efficacy Screening Guide for Pivotal Clinical Trials - May 7, 1997
*(guidelines~drugs currently regulated as new drugs~scrgdpvt.zip)

Modified FDA Format Drug Submissions for Products for Human Use
*(policies~draft external policies out for consultation~fdafmt_e)

New Drug List
*(guidelines~drugs currently regulated as new drugs~newdrugs_e)

Templates

(i) Drug Safety & Efficacy InformationTemplates

Preclinical and Clinical Evaluation Report Templates (PCERT)

*(drug submission templates~drug safety & efficacy information templates~pcert~pcerltr.zip)

(ii) Drug Quality (Chemistry & Manufacturing) Templates

Draft Quality Information Summary - Biologicals (QIS-B) - May 18, 1998

*(drug submission templates~drug quality (chemistry & manufacturing) templates~biological (schedule D) products~blnkqisb.zip)

Draft Certified Product Information Document - Biologicals (CPID-B) - May 18, 1998

*(drug submission templates~drug quality (chemistry & manufacturing) templates~biological (schedule D) products~blnkcpidb.zip)

Draft Quality Information Summary - Radiopharmaceuticals (QIS-R)

NOTE: This document is **not** available through the TPP website but will be made available to sponsors upon a request made to the Bureau of Biologics and Radiopharmaceuticals.

Facility Guidance Document

Bureau of Biologics and Radiopharmaceuticals, Guidance to Industry Product-Specific Facility Information

*(guidelines~biologics~biofacil_e)

Bureau of Biologics and Radiopharmaceuticals, Guidance to Industry Changes in Product-Specific Facility Information

*(guidelines~biologics~facilchg_e)

Product Labelling

Product Monograph Guideline

*(guidelines~drugs currently regulated as new drugs~prodmono_e)

Labelling of Special Containers

*(policies~issued external policy statements~lblspcon_e)

Good Manufacturing Practices (GMP)

GMP Guidelines 1998 Edition

*(guidelines~good manufacturing practices~gmpguide98_e)

Good Manufacturing Guidelines for Schedule C Drugs

*(guidelines~good manufacturing practices~schecdrugs_e)

Good Manufacturing Guidelines (GMP) for Schedule D Drugs - Part 1
*(guidelines~good manufacturing practices~schedpart1_e)

Establishment Licensing
Guidance Document on Establishment Licensing & Establishment Licensing Fees - rev. January 1, 1998
*(cost recovery~el-guide.zip)

Cost Recovery
Submission Evaluation Fees Guide
*(cost recovery~drugs~feeguide_e)

Schedule No. 947: Cost Recovery - Right to Market Drugs
*(cost recovery~drugs~sch-0947_e)

Guidance Document on Establishment Licensing & Establishment Licensing Fees - rev. January 1, 1998
*(cost recovery~drugs~el-guide.zip)

Drug Master File Fees
*(cost recovery~drugs~dmfcost.zip)

Export Certification for Drug Products - March 20, 1996
*(cost recovery~drugs~exptcgl.zip)

Lot Release (applies to Schedule D drugs only)
Evaluation Groups and Lot Testing Requirements
*(guidelines~biologics~lotrel_e)

Review/Testing/Approval of Biological Drug Lots
*(policies~draft external policies out for consultation~lotrel_e)

Key:

* DOCUMENTS FOUND WITHIN THE ENGLISH and/or FRENCH SECTION OF THERAPEUTIC PRODUCTS PROGRAMME WEBSITE

** DOCUMENTS WHICH ARE ONLY AVAILABLE THROUGH THE CANADIAN GOVERNMENT PUBLISHING CENTRE: SEE THE THERAPEUTIC PRODUCTS PROGRAMME GUIDELINES AND PUBLICATIONS ORDER FORM
*(forms/guidelin_e)

There is also useful information on the International Conference on Harmonization (ICH) Website which is located at the following internet address.

http://www.pharmweb.net/pwmirror/pw9/ifpma/ich1.html

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The Therapeutic Products Programme is the national authority that evaluates and monitors the safety, effectiveness, and quality of drugs, medical devices and other therapeutic products available to Canadians.