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Please note: On June 13, 2015, the *Regulations Amending the Food and Drug Regulations (Labelling, Packaging and Brand Names of Drugs for Human Use)*, commonly known as the Plain Language Labelling amendments, come in to force for **prescription products and products administered or obtained through a health professional for human use**. As a result, the current guidance no longer provides the most up to date information for these products.

For more information on the interpretation of the new amendments as they apply to prescription products and products administered or obtained through a health professional for human use, please consult the following documents:

- *Guidance Document: Questions and Answers on Plain Language Labelling* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/pll_qa_fin_qr_elc-eng.php);
- *Frequently Asked Questions – Guidance document for Industry – Review of Drug Brand Names* (http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2014-review-examen_drug-medicament_names-marques/faq-eng.php)
- *Guidance for Industry – Review of Drug Brand Names* (http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2014-review-examen_drug-medicament_names-marques/index-eng.php)

Canada 



December 20, 2013

NOTICE

Our file number: 13-119235-57

Guidance for Industry- Management of Drug Submissions

On June 19th, 2013, Health Canada published in *Canada Gazette*, Part II amendments to the *Food and Drug Regulations*. The *Regulations Amending Certain Regulations concerning Prescription Drugs* (Repeal of Schedule F to the *Food and Drug Regulations*) provides for the repeal of Schedule F and incorporation by reference of a list of prescription drugs. This regulatory amendment comes into effect on December 19, 2013.

As a result of this amendment, a number of existing Guidance Documents have been identified that make reference to Schedule F and the regulatory process for assigning prescription status. Due to the replacement of Schedule F with the Prescription Drug List and the replacement of a regulatory process with an administrative process, the identified Guidance Documents required updating.

Accordingly, the *Management of Drug Submissions Guidance Document* has been updated. The Document Change Log has been revised to reflect the changes.

Any questions should be directed to:

Submission and Information Policy Division
Therapeutic Products Directorate
Health Canada
Finance Building
101 Tunney's Pasture Driveway
Address Locator 0201A1
Ottawa, Ontario
K1A 0K9

Fax: (613) 941-0825
Email: osip-bppi@hc-sc.gc.ca



GUIDANCE FOR INDUSTRY

Management of Drug Submissions

Published by authority of the
Minister of Health

| | |
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| Date Adopted | 1993/01/18 |
| Revised Date | 2013/12/19 |
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Health Products and Food Branch

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| <p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p> | <p>The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by:</p> <ul style="list-style-type: none"> • Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. <p style="text-align: right;"><i>Health Products and Food Branch</i></p> |
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Également disponible en français sous le titre : Gestion des présentations de drogues

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

| Registre des modifications du document | | | |
|---|---|-----------------|---|
| Version | Guidance for Industry: Management of Drug Submissions | Replaces | Guidance for Industry: Management of Drug Submissions |
| Date | December 19, 2013 | Date | November 30, 2013 |

| Modification | Nature et motif de la modification |
|--|---|
| December 19, 2013 Some revisions throughout the document. | Changes were made to the document to reflect an amendment to the <i>Food and Drug Regulations</i> that replaced Schedule F with the Prescription Drug List. |

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1. PURPOSE

This guidance is intended to provide clarification to sponsors of the way in which the Therapeutic Products Directorate (TPD) and Biologics and Genetic Therapies Directorate (BGTD) manage information and material submitted by sponsors in accordance with the *Food and Drugs Act and Regulations*. The guidance to follow supercedes the policy, **Management of Drug Submissions**, effective May 9, 2001.

The benefits of the Guidance document for the Management of Drug Submissions include:

- Assisting sponsors with acceptable practices, performance targets and access to information related to submissions currently under review; and
- Providing a framework for Health Canada to manage the flow of drug submissions.

2. BACKGROUND

The Guidance for the Management of Drug Submissions (MDSG) is a fluid document that outlines the way in which the Therapeutic Products Directorate (TPD) and Biologics and Genetic Therapies Directorate (BGTD) manage information and material submitted by sponsors in accordance with the *Food and Drugs Act and Regulations*.

Industry representatives and Health Canada employees, including review staff and those responsible for areas of submission management, rely on the MDSG for guidance and operational direction in numerous areas including: the handling of submission information, procedures related to drug review, requests for clarification and performance targets for review.

In order to maintain consistency and enhance transparency, the MDSG is regularly updated to reflect effective changes in policies related to the drug submission and review process. It is anticipated that amendments to the current guidance, as well as the introduction of additional information and clarification, will reduce the number of requests for clarification received by Health Canada staff.

3. SCOPE

This guidance document applies to all drug submission types¹ including:

New Drug Submission (NDS),
Supplement to a New Drug Submission (SNDS),
Supplement to a New Drug Submission - Confirmatory (SNDS-C)
Abbreviated New Drug Submission (ANDS),
Supplement to a Abbreviated New Drug Submission (SANDS),
Notifiable Change (NC),
Clinical Trial Applications (CTA) and Amendments (CTA-A),
Periodic Safety Update Report - Confirmatory (PSUR-C), and
Applications for Drug Identification Number (DINA) ((includes DIN for biological product (DINBs) and DIN for disinfectant product (DINDs))

All submitted information and material will be screened to ensure that it is complete and of suitable quality to be reviewed. The same management principles will be applied consistently to all submission types. Time frames referred to in this guidance are the current Health Canada Target Performance Standards. Submissions shall contain all the information and material required for purposes of Part C of the *Food and Drug Regulations*.

Health Canada has published numerous guidelines and policies to assist sponsors in the preparation and filing of drug submissions. Sponsors of pharmaceutical or biological drug submissions should refer regularly to the Health Canada web site for those guidelines and policies relating to a particular submission type of interest. Note: The web site is subject to continual update and improvement.

Any subsequent solicited or unsolicited information submitted by the sponsor will be screened to ensure that it is complete for the purpose intended.

The following sections specify the way in which information and material submitted to Health Canada will be managed:

1. Filing and Classification of Information and Material
2. Submission Holds

¹ Excludes Blood Establishment Submissions and Applications for Medical Device Licences. For information on the management of these submission types, refer to Health Canada Guidelines: “Management of Blood Establishment Submissions” and “Management of Application for Medical Device Licenses and Investigational Testing Authorization”, respectively.

3. Screening of Information and Material
4. Evaluation of Submissions
5. Refiled Submissions
6. Accessing Submission Information
7. Fees

4. DEFINITIONS

ADMINISTRATIVE SUBMISSION: a submission that does not require scientific review (for example [e.g.] change in manufacturer or product name).

BIOLOGIC(AL) DRUG: A drug listed under Schedule D of the *Food and Drugs Act*.

COMBINATION PRODUCT: Therapeutic product that combines either a drug (biological or pharmaceutical) component and a device component (which by themselves would be classified as a drug or a device), or a biological pharmaceutical combination, such that the distinctive nature of the two components are integrated in a singular product².

DRUG IDENTIFICATION NUMBER (DIN): an eight (8) digit numerical code assigned to each drug product approved under the *Food and Drugs Act and Regulations* (except for Schedule C drugs).

FILING DATE: refers to the final central registry (CR) file date allocated to the submission once it is deemed administratively complete by Health Canada (that is [i.e.] once all elements and forms required for processing are completed and submitted to Health Canada). This date may differ from the date of original filing should the submission be considered administratively incomplete at the time of receipt.

MEDICAL DEVICE: a “device” within the meaning of the *Food and Drugs Act*, but does not include any device intended for use in relation to animals.

PRIORITY REVIEW: A review status granting eligible new drug submissions and supplements to new drug submissions a shortened review target. This status is granted following review and approval of a request submitted by the sponsor of the drug.

² Does not apply to combinations of drugs and medical devices where the two drug components and/or drug and device components can be used separately (that is, products sold together in procedure packages and trays).

5. PROCEDURES

5.1 Pre-submission Meetings and Package Requirements

Sponsors may wish to deliver a brief presentation to the appropriate Directorate within Health Canada³ prior to filing a New Drug Submission (NDS), Supplement to a New Drug Submission (SNDS), Abbreviated New Drug Submission (ANDS), Clinical Trial Application (CTA), combination product classification request or request for Priority Review or NOC/c status.

The purpose of pre-submission meetings is to discuss the presentation of data in support of the submission. In addition, such meetings:

- familiarize Health Canada review staff with the forthcoming submission prior to its arrival, and provide a forum to discuss the data in the submission to facilitate its review;
- have the potential to uncover any major unresolved problems or issues and manage disputes early in the submission process;
- identify studies the sponsor is relying on as adequate and well controlled in establishing the effectiveness of the drug (NDS, SNDS, ANDS);
- provide an opportunity for the sponsor to discuss details of the submission with the Regulator and obtain feedback regarding any areas of concern based on current experience and regulatory requirements, as well as the potential eligibility of the submission for Priority Review or NOC/c consideration (NDS, SNDS); and,
- provide Directorates the opportunity to re-align resources, if necessary, to accommodate the arrival of the submission.

Best practices will be followed to ensure meetings are well-organized, efficient, productive, and properly documented.

³ For further information on pre-meetings related to Priority Review requests or requests for advance consideration under the NOC/c policy, refer to Health Canada “Guidance to Industry; Priority Review of Drug Submissions” and “*Guidance to Industry; Notice of Compliance with Conditions*” respectively.

5.1.1 Meeting requests

Meeting requests are to be submitted to the appropriate Regulatory Affairs Division (BGTD) or Regulatory Project Manager (TPD) **in writing or by fax** no less than 1 month prior to the proposed meeting date (see Appendix 1).

Sponsors should address requests to the Bureau/Centre Director and should include the following information:

- the purpose of the meeting
- a brief description of the product to be discussed at the meeting
- three proposed dates for the meeting, including whether an afternoon or morning meeting is being requested.

In order to ensure efficient use of Health Canada resources, requests should include adequate information to determine the utility of the meeting and to identify appropriate staff necessary to discuss proposed issues.

Meeting requests should be sent to the appropriate Directorate below⁴:

| Biologics and Genetic Therapies Directorate | Therapeutic Products Directorate |
|---|--|
| Director, (<i>choose one</i>) | Director, (<i>choose one</i>) |
| * Centre for Biologics Evaluation | * Bureau of Metabolism, Oncology and Reproductive Sciences, |
| * Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics | * Bureau of Gastroenterology, Infection and Viral Diseases, |
| | * Bureau of Cardiology, Allergy and Neurological Sciences, |
| | * Office of Clinical Trials, or |
| | * Bureau of Pharmaceutical Sciences, |
| c/o Regulatory Affairs Division See Appendix 1 for address details | c/o Regulatory Project Manager See Appendix 1 for address details |

The sponsor will be contacted to discuss the content of the pre-submission package (Section 5.1.2), the number of Health Canada staff attending and therefore, the number of copies of the package required, and the number of industry staff attending the meeting.

⁴ For further information, refer to Appendix 1: Review Bureaux/Centre Responsibilities.

5.1.2 Pre-submission Packages

Sponsors will be requested to submit a pre-submission meeting information package at least 2 weeks in advance of the meeting. Packages should be no longer than 1 binder in length and contain the following information:

Pre-NDS/SNDS meetings

- a cover letter
- an agenda for the meeting
- a list of specific issues (grouped by discipline) the sponsor would like to discuss or have addressed
- a brief summary of the drug product for which the meeting is being called
- proposed strengths and dosages
- an overview of the market history of the product including the foreign regulatory status of the drug
- a summary of the development of the product, including any changes in production process, dosage form, testing methods etc. leading up to a description of the manufacturing process for the product to be marketed
- a summary of the clinical development plan for the drug, including identification of clinical trials completed in Canada (if any) and confirmation of which trials are still ongoing (if any)
- identification of the indication(s) for which approval is sought
- brief summaries of the safety and efficacy data relating to the drug (e.g. draft of the product monograph)

Pre-CTA Meetings

Pre-CTA packages should contain the information listed in “*Guidance for Clinical Trial Sponsors - Clinical Trial Applications*”.

5.2 Filing of Information and Material to Health Canada

A control number will be assigned to the original information and material. All information and material received, except CTAs, CTA-As and responses to clarification requests, will be acknowledged by mail by the Submission and Information Policy Division (SIPD). CTAs and CTA-As will be acknowledged by mail by the Regulatory Affairs Division (BGTD) or the Submission Management Unit, Office of Clinical Trials (TPD).

SIPD will target to have all information and material processed and sent to the reviewing Bureau/Centre **within 10 calendar days**.

5.2.1 NDS, SNDS, SNDS-C, PSUR-C, ANDS, SANDS, NC, DINA, and Related Documents:

Sponsors are requested to send their information and material to the Submission and Information Policy Division (SIPD) at the following address:

Submission and Information Policy Division

Therapeutic Products Directorate
Finance Building # 2
Tunney's Pasture, A.L. #0201A1
Ottawa, ON K1A 0K9
Fax: (613) 941-0825

Responses to Notices (including Screening Deficiency Notices, Notices of Non-Compliance, Notices of Deficiency) should also be sent to the above address.

5.2.2 Clinical Trial Applications and Amendments:

Sponsors are requested to send information and material to the appropriate Bureau/Centre:

Biologics and Genetic Therapies Directorate

Director, (*choose one*)

- * Centre for Biologics Evaluation
- * Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics

c/o Regulatory Affairs Division
See Appendix 1 for address details

Therapeutic Products Directorate

Office of Clinical Trials
Holland Cross, Tower B
5th Floor, A.L. 3105A
1600 Scott Street
Ottawa, ON K1A 0K9

For additional information on Clinical Trial Applications and Amendments, sponsors should refer to "*Guidance for Clinical Trial Sponsors - Clinical Trial Applications*".

5.2.3 Combination Submissions

Submissions for combination products, as defined in Section 4.0, will be handled in accordance with the relevant Health Canada Policy, (*e.g.* "*Drug/Medical Device Combination Products*", May 1999 for device-drug combinations) and be subject to either the *Medical Devices Regulations* or the *Food and Drug Regulations* according to the principal mechanism of action by which the claimed effect or purpose is achieved. Both principal and ancillary components must meet acceptable standards of safety, efficacy and quality.

A) Classification of Combination Products

Sponsors are encouraged to deliver a brief presentation to Health Canada for the purposes of classifying products, in particular those incorporating a new active substance or new technology (see Section 5.1).

Sponsors of a submission for a combination product not previously classified may present a written request for a classification decision to the relevant review Directorate in advance of the submission filing. Where possible, a decision will be rendered within 14 calendar days of receiving the request.

Requests for product classifications and/or related pre-submission meetings for drug-device or drug-drug combinations should be sent **in duplicate** by fax or mail to either of the two relevant directorates at the addresses provided below.

Therapeutic Products Directorate

Licensing Services Division
Medical Devices Bureau
Room 1605
Main Statistics Canada Building # 3
Tunney's Pasture, A.L. 0301H1
Ottawa, ON K1A 0L2
Fax: (613) 957-6345

Therapeutic Products Directorate

Director, (*choose one*)

- * Bureau of Metabolism, Oncology and Reproductive Sciences,
- * Bureau of Gastroenterology, Infection and Viral Diseases,
- * Bureau of Cardiology, Allergy and Neurological Sciences,
- * Bureau of Pharmaceutical Sciences,

c/o Regulatory Project Manager
See Appendix 1 for address details

OR

Biologics and Genetic Therapies Directorate

Director, (*choose one*)

- * Centre for Biologics Evaluation
- * Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics

c/o Regulatory Affairs Division
See Appendix 1 for address details

B) Submission Filing

Where there is no question as to the classification of the product, sponsors are to submit to the lead organization duplicate copies of the information to be reviewed. Sponsors are requested to send their information and material (for Biological or Pharmaceutical submissions) to the Submission and Information Policy Division (SIPD) at the following address:

Submission and Information Policy Division

Therapeutic Products Directorate
Finance Building # 2
Tunney's Pasture, A.L. #0201A1
Ottawa, ON K1A 0K9
Fax: (613) 941-0825

For combination products classed as medical devices, information and material should be sent in duplicate to:

Therapeutic Products Directorate

Licensing Services Division
Medical Devices Bureau
Room 1605
Main Statistics Canada Building #3
Tunney's Pasture, A.L. 0301H1
Ottawa, ON K1A 0L2
Fax: (613) 957-6345

For combination products involving Clinical Trial Applications, refer to Section 5.2.2.

For further information on drug-device combination products, including information to be included within the classification request, sponsors should refer to the Health Canada policy on "Drug/Medical Device Combination Products", May 1999.

5.2.4 Requests for Priority Review Status (Biological and Pharmaceutical Products)

Sponsors are requested to send advance requests for Priority Review status, consistent with the format provided in "Guidance for Industry; Priority Review of Drug Submissions" to the appropriate Bureau/Centre, addressed to the Director.

Biologics and Genetic Therapies Directorate

Director, (*choose one*)

- * Centre for Biologics Evaluation
- * Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics

c/o Regulatory Affairs Division
See Appendix 1 for address details

Therapeutic Products Directorate

Director, (*choose one*)

- * Bureau of Metabolism, Oncology and Reproductive Sciences,
- * Bureau of Gastroenterology, Infection and Viral Diseases,
- * Bureau of Cardiology, Allergy and Neurological Sciences,
- * Bureau of Pharmaceutical Sciences,

c/o Regulatory Project Manager
See Appendix 1 for address details

For further information on Priority Review requests, refer to the “*Guidance for Industry; Priority Review of Drug Submissions*” , available on the Health Canada web site.

For information on Medical Device Licence Management process and the Medical Devices Priority Review policy, refer to the following policies on the Health Canada web site:

- *Priority Review of Medical Device Licence Applications Policy*, and
- *Management of Application for Medical Device Licences and Investigational Testing Authorizations*.

5.2.5 Requests for Advance Consideration under the Notice of Compliance with Conditions (NOC/c) policy

Sponsors seeking advance consideration of a submission under the NOC/c policy must request a pre-submission meeting with Health Canada review staff (Section 5.1) and receive prior approval, consistent with procedures outlined in the NOC/c policy. In addition, the submission covering letter must clearly indicate the sponsor’s wishes for advance consideration under the NOC/c policy. For further information on eligibility and procedural requirements related to the NOC/c policy, refer to “*Guidance for Industry; Notice of Compliance with Conditions*”.

5.2.6 Responses to Clarification Requests

Sponsors are requested to send their responses to clarification requests directly to the person who requested the information. Responses should be received within 15 calendar days of the original request. Responses to clarifaxes for CTAs and CTA-As should be received within 2 calendar days of the request.

5.2.7 Requests for Reconsideration

Following the issuance of one of the following final decisions, sponsors may file a Request for Reconsideration:

- Rejection of Priority Review Request under the “*Guidance for Industry; Priority Review of Drug Submissions*” ;
- Rejection of Request for Advance Consideration under the *Notice of Compliance with Conditions Policy*;
- Screening Rejection Letter (SRL) (including New Drug Letter);
- Notice of Deficiency - Withdrawal Letter (NOD/W);
- Notice of Non-compliance - Withdrawal Letter (NON/W); or
- Not Satisfactory Notice (NSN).

Sponsors are requested to send the Letter of Intent (two copies) and the formal Request for Reconsideration⁵ (two copies) to the Submission and Information Policy Division (SIPD) at the following address:

Submission and Information Policy Division

Therapeutic Products Directorate
Finance Building #2
Tunney's Pasture, A.L. #0201A1
Ottawa, ON K1A 0K9
Fax: (613) 941-0825

For further information, refer to the *Guidance: Reconsideration of Final Decisions Issued for Human Drug Submissions*.

5.3 Submission Holds

At various stages of the Therapeutic Evaluation Process (includes processing and screening) of original information and material submitted to Health Canada, it may be necessary to place administrative holds on a submission. Examples of such holds include SIPD/CR holds, patent holds, cost-recovery holds, switch holds and regulatory holds.

5.3.1 SIPD/CR Holds

Health Canada defines a CR date as the date when a submission is considered administratively complete (Section 4), such that the Submission and Information Policy Division (SIPD) or relevant Submissions Management Unit (e.g. in the case of CTAs), can process the submission. In the event that additional information is requested (e.g. forms), the CR date will be the date the requested information is received by Health Canada and the submission is considered administratively complete. While awaiting the additional information from sponsors, the submission may be placed on "SIPD" or "CR Hold".

5.3.2 Patent Hold

For submissions subject to the provisions of the *Patented Medicines (Notice of Compliance) Regulations*, Health Canada will ensure that all relevant patents have been satisfactorily addressed through the filing of a Form V - Declaration Re: Patent List. Such submissions will not be transmitted to the relevant review Bureau/Centre until such time as all the required Form V documentation has been provided. A CR date will only be assigned when all Form V requirements are met.

⁵ For further information on Requests for Reconsideration refer to the *Health Canada Guidance: Reconsideration of Final Decisions Issued for Human Drug Submissions*

When, upon completion of the review of a submission, a NOC would be issuable but for the provisions of the *Patented Medicines (Notice of Compliance) Regulations*, the sponsor will be so notified. The sponsor will also be notified of the date that the submission would have been eligible to receive a NOC but for the provisions of the *Patented Medicines (Notice of Compliance) Regulations*. In these circumstances, a NOC will not be issued until all matters under the *Patented Medicines (Notice of Compliance) Regulations* have been resolved; until this time, the submission will be placed on “Patent Hold”.

5.3.3 Switch Hold

Upon approval of an application related to a switch in status from prescription to non-prescription, the submission is placed on “switch hold” pending the removal of the medicinal ingredient from the Prescription Drug List.

5.3.4 Cost-recovery Hold

In accordance with the “Guidance Document: Fees for the Review of Drug Submissions and Applications”, submission fees less than \$10,000 are payable when the submission is filed. In the event that fees are not provided with the submission, SIPD will request them of the sponsor. Pending receipt of the fee, the submission may be placed on “Cost-recovery hold”. If fees are not received in a timely manner, the submission will be returned at the expense of the sponsor.

5.3.5 Regulatory Hold

A Regulatory hold arises in a situation where the review of the submission is complete however delays arise as a result of pending related regulatory amendments or satisfaction of regulatory requirements (e.g. in completing the On-Site Evaluation (OSE) related to the review of a biologic). In such an instance, the administrative review clock is stopped and the submission is placed on “Regulatory hold” until such time as the regulatory requirements are satisfied.

5.4 Screening of Information and Material

Original information and material, and solicited and unsolicited information and material, will be screened by Health Canada for acceptability (with the exception of PSUR-Cs).

Health Canada expects original information and material to contain the requisite information for the type of submission and to be submitted in an acceptable format as outlined in the applicable guideline(s). The relevant drug submission screening form(s) is to be completed by the sponsor where applicable.

All subsequent solicited and unsolicited information will also be screened to ensure that it is complete for the purpose intended. Sponsors should clearly identify in a covering letter the

control number of the relevant submission, the purpose of the correspondence and whether the information and material is solicited or unsolicited. All solicited information should be submitted in a question and answer format which is cross-referenced to replacement volumes where appropriate.

Health Canada will target to have original, solicited and unsolicited information and material screened as follows:

- Information related to NDSs, SNDSs, SNDS-Cs, ANDSs, SANDSs, and DINAs within 45 calendar days from receipt in the responsible review Bureau/Centre.
- Priority Review submissions and submissions accepted for advance consideration under the NOC/c policy within 25 calendar days from receipt in the responsible review Bureau/Centre, and
- Information and material related to NCs within 7 calendar days from receipt in the responsible review Bureau/Centre.

5.4.1 Acceptable Original Information and Material

If **original** information and material is found to be acceptable on screening, it will be accepted for review and considered to be a submission. All submission types will be considered workload from the date of acceptance.

For NDSs, SNDSs, SNDS-Cs, ANDSs, SANDSs and those DINAs with a submission fee greater than \$10,000, the sponsor will be notified of the acceptability by mail.

The date of acceptance for CTAs and CTA-As will be considered the date of receipt in the appropriate review Directorate, provided the information and material is accepted on screening. The days allocated to the screening of CTAs and CTA-As are considered part of the days allocated for the submission review.

5.4.2 Unacceptable Original Information and Material

If deficiencies are identified during screening of **original** information and material⁶ relating to an NDS, SNDS, ANDS, SANDS, SNDS-C, DINA or NC, the sponsor will be issued a Screening Deficiency Notice identifying the deficiencies. The sponsor will be required to submit all of the requested information and material identified in the Screening Deficiency Notice, within 45 calendar days from the date of request. As a

⁶ For information on deficiencies identified in CTAs and CTA-As, refer to “*Guidance for Clinical Trial Sponsors - Clinical Trial Applications*”.

general rule⁷, submissions containing interim analyses of pivotal trial data or safety studies will be considered deficient on screening.

If the sponsor fails to provide all requested information within 45 calendar days, or the submitted information is incomplete, deficient or contains unsolicited information, the original information and material will be rejected and returned to the sponsor at the sponsor's expense. A Rejection Letter will be issued by Health Canada. If the sponsor wishes to resubmit the information and material at a future time, it will be processed as new information and material, and will be assigned a new control number.

After receipt of the information requested in the Screening Deficiency Notice, a new screening period commences (with a new performance target), and the requested material and information will be screened for completeness. The original information and material will be considered a submission when all requested information is found to be acceptable. The sponsor will be notified of the acceptability as delineated in 5.4.1.

DINAs may be rejected during screening, without the issuance of a Screening Deficiency Notice, for several reasons, e.g., if the drug is considered a new drug and an NDS is required, if a proposed ingredient is a prohibited substance, or if a monograph attestation is found not to reflect the submission content.

NCs may be also be rejected for several reasons during screening, without the issuance of a Screening Deficiency Notice, e.g. if the change is such that it necessitates the filing of an SNDS.

In either case, should the sponsor wish to resubmit the information at a future time, it will be processed as new information and material and will be assigned a new control number.

For clarification of any points of the SDN or Screening Rejection Letter, or the rationale for its issuance, the sponsor should contact the Regulatory Project Manager for the review division (TPD), or the Regulatory Project Officer for the submission (BGTD).

A sponsor may file a Request for Reconsideration of a Screening Rejection Letter (see Section 5.6 for further information).

⁷ In exceptional circumstances (that is, for products qualifying for advance consideration under the NOC/c policy), allowances may be granted.

5.5 Evaluation of Submissions

5.5.1 Solicited Information

A) Update Notices

If it becomes evident that the review of the submission will not commence⁸ prior to the Health Canada performance target date, an Update Notice will be issued by the Director of the reviewing Bureau/Centre.

There are no restrictions on the information that may be added to or removed from the original NDS, SNDS, ANDS, or SANDS in the updated submission. New dosage forms, new routes of administration, new strengths and new indications may be submitted. It is the responsibility of the sponsor to integrate the updated information into the original submission and to submit a revised comprehensive summary, if applicable. Note that the addition of any of this information to a DINA would require a separate submission.

If the sponsor intends to update the submission the sponsor must inform the Bureau/Centre Director within 30 calendar days from the date of the Update Notice of this intention. The sponsor will be given 60 calendar days, from Health Canada's receipt of their response to the Update Notice, to submit the updated submission. The scheduling of the review will be finalized once the response to the Update Notice is screened and accepted for review.

If the sponsor does not respond to the Update Notice, Health Canada will assume that the submission will not be updated and the submission will be scheduled for review. If the sponsor responds within the 30 day period that the submission will not be updated, the submission will be scheduled for review.

A submission update will not be accepted, and will be returned to the sponsor, if the intent to update letter or the updated submission is received late with respect to either the 30 day or the subsequent 60 day time frame.

⁸ That is, if none of the review divisions have commenced the review (clinical, chemistry and manufacturing)

B) Requests for Clarification During Screening or Review of the Submission - all submission types

The purpose of a Clarification Request, or Clarifax, is to expand on, add precision to or re-analyse existing information or data in the submission. **Clarifaxes do not contain requests for new data, such as, new Clinical and/or Pre-Clinical information, including bioavailability data not previously submitted.** Health Canada uses this mechanism of addressing elements requiring clarification in high quality submissions as frequently as possible.

During the screening or review of the submission, including the label review, a Bureau/Centre may seek clarification of specific information in the submission. Requests will be solicited by facsimile and must be responded to in writing, directly to the requester. Responses up to 15 pages that do not contain data in tabular format should be faxed directly to the requester with no hard copy. If the response exceeds 15 pages or includes data in tabular format, hard copy only should be sent by courier directly to the requester.

The sponsor will be advised that the solicited information must be submitted within 15 calendar days (2 calendar days for CTAs, CTA-As, and Priority Review requests) from the date of the request. The review of the submission will not be interrupted if a complete response is submitted within the given time frame. A response is considered complete if all clarifications or questions identified in the clarifax are addressed. Should a sponsor feel that it is not necessary to develop or file requested information, a sound scientific rationale for this position must be presented in order for the response to be considered complete.

For clarification of any points of the clarifax, or the rationale for its issuance, the sponsor should contact the Regulatory Project Manager for the review division (TPD), or the Regulatory Project Officer for the submission (BGTD).

There is no limitation on the number of clarifaxes that may be issued for one submission. However, no particular issue will be addressed more than once in a Clarification Request. If a request for clarification is identified in a clarifax and the response is not satisfactory, a Screening Deficiency Notice, NOD, NSN or NON will be issued.

C) *Notices of Deficiency (NOD) - NDSs, SNDSs, ANDSs, SANDSs, DINAs*

If deficiencies and/or significant omissions that preclude continuing the review are identified during the review of a submission, a NOD⁹ will be issued. For submissions under the jurisdiction of TPD, the NOD will be issued by the unit manager in the appropriate review Bureau for DINAs and by the Director General for all other submission types. For BGTD submissions, the NOD will be issued by the Director General for all submission types. The difference between a NON and NOD is that the review of the submission is not complete when a NOD is issued.

A NOD will be issued if, during the review of a DINA, the product is identified as a New Drug. If the product has been identified as a New Drug, the submission should be refiled as an NDS, or ANDS.

Health Canada aims not to issue many NODs but rather to rely on the use of clarifaxes and NONs to address clarifications and deficiencies respectively in high quality submissions. Emphasis will continue to be placed on improved screening of submissions in the Directorate and the production of guidelines for the preparation of submissions.

All deficiencies identified in those parts of the submission that have been reviewed to date will be specified. Only one NOD per submission will be issued. Review of the submission will stop on the date of the NOD. The review of the submission in the other review streams may or may not be complete at the time of the issuance of a NOD.

For clarification of any points of the NOD, or the rationale for its issuance, the sponsor should contact the Regulatory Project Manager for the review division (TPD), or the Regulatory Project Officer for the submission (BGTD).

- For NDSs, SNDSs, SNDS-Cs, ANDSs and SANDSs the sponsor will be given 90 calendar days, or such time as the Bureau/Centre Director and sponsor may agree upon, to submit all of the solicited information.
- For DINAs, the sponsor will be given 45 calendar days, or such time as the Bureau/Centre Director and sponsor may agree upon, to submit all the solicited information.

⁹

Pursuant to Division 1 and Division 8 of the *Food and Drug Regulations*.

The solicited information is to include a copy of the NOD and is to be submitted in a question and answer format which is cross-referenced to replacement volumes where appropriate. When the response to a NOD is received, a new Screening 1 period (with an associated performance target) begins. If during the screening process, the response to a NOD is found to contain unsolicited information, is incomplete or deficient, the response to the NOD will be rejected and the submission will be considered withdrawn without prejudice to a refiling. A NOD-Withdrawal Letter will be issued by Health Canada.

If the response to a NOD for an NDS, SNDS, ANDS, SANDS, or DINA is found acceptable for review, the sponsor will be notified by mail. All submissions will be considered workload from the date of acceptance, and a new Review 1 period (with an associated performance target) will begin. A submission having received a NOD during an earlier review may ultimately be issued an NOD-W, NON or NOC by Health Canada, as an outcome of the review.

A Bureau/Centre may seek clarification of specific information in the NOD as defined in Section 5.5.1 (B).

If, following the acceptance and review of the information and material submitted in response to a NOD, it is determined that the submission remains deficient, a NOD-Withdrawal Letter may be issued. Such a decision to withdraw is without prejudice to refiling the submission.

Health Canada will consider a sponsor's failure to submit the solicited information within the assigned time frame as a request to withdraw the submission and a NOD-Withdrawal Letter will be issued. Such a decision to withdraw is without prejudice to refiling the submission.

Refer to Section 5.7 of this guidance for information related to refiling submissions.

A sponsor may file a Request for Reconsideration following the issuance of a NOD-Withdrawal Letter (see Section 5.6 for further information), including a withdrawal of a submission as a result of the sponsor's failure to submit the requested information in the designated time frame, a withdrawal as a result of the rejection of the response to a NOD, or a withdrawal during the review of the response to a NOD.

D) *Notices of Noncompliance (NON) - NDSs, SNDSs, SNDS-C, ANDSs, SANDSs, DINAs*

After the comprehensive review of a submission is complete, a NON¹⁰ will be issued if the submission is deficient or incomplete in complying with the requirements outlined in the *Food and Drugs Act and Regulations*. For submissions under the jurisdiction of TPD, the NON will be issued by the unit manager in the appropriate review Bureau for DINAs and by the Director General for all other submission types. For BGTD submissions, the NON will be issued by the Director General for all submission types.

The deficiencies identified in all parts of the review will be specified. Only one NON per submission will be issued. Review of the submission will stop on the date of the NON.

For clarification of any points of the NON, or the rationale for its issuance, the sponsor should contact the Regulatory Project Manager for the review division (TPD), or the Regulatory Project Officer for the submission (BGTD).

- For NDSs, SNDSs, SNDS-C, ANDSs and SANDSs the sponsor will be given 90 calendar days, or such time as the Bureau/Centre Director and sponsor may agree upon, to submit all of the solicited information.
- For DINAs, the sponsor will be given 45 calendar days, or such time as the Bureau/Centre Director and sponsor may agree upon, to submit all the solicited information.

The solicited information is to include a copy of the NON and is to be submitted in a question and answer format which is cross-referenced to replacement volumes where appropriate. Should a sponsor feel that it is not necessary to develop or file requested information, a sound scientific rationale for this position must be presented in order for the response to be considered complete.

When the response to a NON is received, a Screening 2 period begins (with an associated performance target). If during the screening process, the response to a NON is found to contain unsolicited information, is incomplete or deficient, the response to the NON will be rejected and the submission will be considered withdrawn without prejudice to a refiling. A NON-Withdrawal Letter will be issued by the responsible Health Canada Directorate.

¹⁰

Pursuant to Division 1 and Division 8 of the *Food and Drug Regulations*.

If the response to a NON for a submission is found to be acceptable for review, the sponsor will be notified by mail. The submission will be considered workload from the date of acceptance, and a Review 2 period will begin (with an associated performance target).

A Bureau/Centre may seek clarification of specific information in the response to a NON as defined in Section 5.5.1 (B).

If, following the acceptance and review of the information and material submitted in response to a NON, it is determined that the submission remains deficient, a NON-Withdrawal Letter may be issued by the Director General of the responsible Health Canada Directorate. Such a decision to withdraw is without prejudice to refileing the submission.

Health Canada will consider a sponsor's failure to submit the solicited information within the assigned time frame, as a request to withdraw the submission. A Withdrawal Letter will be issued by Health Canada. Such a decision to withdraw is without prejudice to refileing the submissions.

Refer to Section 5.7 of this guidance for information related to refileing submissions.

A sponsor may file a Request for Reconsideration following the issuance of a NON-Withdrawal Letter (see Section 5.6 for further information), including a withdrawal of a submission as a result of the sponsor's failure to submit the requested information in the designated time frame, a withdrawal as a result of the rejection of the response to a NON, or the withdrawal of the submission following the review of the response to the NON.

E) Not Satisfactory Notice (NSN) - CTAs, CTA-As, NCs

A Not Satisfactory Notice (NSN) will be issued¹¹ by the Director of the responsible reviewing Bureau/Centre if deficiencies are identified during the review of a CTA, CTA-A or NC. The deficiencies will be specified and review of the submission will stop on the date of the Not Satisfactory Notice.

For clarification of any points of the NSN, or the rationale for its issuance, the sponsor should contact the Regulatory Project Manager for the review division (TPD), or the Regulatory Project Officer for the submission (BGTD).

¹¹ Pursuant to Sections C.05.006(1)(b) and C.05.008(1)(b) of the *Food and Drug Regulations*.

If the sponsor wishes to submit the appropriate information and material it will be considered a new CTA, CTA-A or NC, and will be assigned a new control number. A default review time of 30 calendar days will commence from the time of receipt of the submission (CTA, CTA-A).

A sponsor may file a Request for Reconsideration following the issuance of a Not Satisfactory Notice (see Section 5.6 for further information).

F) Notice of Compliance with Conditions Qualifying Notice - NOC/c-QN

A NOC/c-QN will be issued by the Director of the responsible reviewing Bureau/Centre upon completion of a review¹², should a submission be determined to qualify for further consideration under the NOC/c policy. The NOC/c - QN will indicate that the submission qualifies for a NOC, under the NOC/c policy, as well as outline the additional clinical evidence to be provided in confirmatory studies, post-market surveillance responsibilities and any requirements related to advertising, labeling, or distribution. Submission review will cease upon issuance of the Qualifying Notice.

The sponsor should submit the appropriate information and material within 30 days of receipt of the NOC/c-QN. Responses to a NOC/c-QN should reference the submission control number and be sent to:

Submission and Information Policy Division

Therapeutic Products Directorate
Finance Building #3
Tunney's Pasture, A.L. 0201A1
Ottawa, ON K1A 0K9
Fax: (613) 941-0825

5.5.2 Unsolicited Information

A) Final Data

Where a published Canadian Guideline specifies that interim data are permissible on filing, final data presentation and analysis will be accepted if filed within 180 days of receipt of the original submission filing.

¹² Subsequent to discussions with the sponsor.

B) *Safety Information*

- *Information to be submitted at any time*

Sponsors are encouraged to submit, at any time, negative safety findings or risk information gleaned from animal studies or clinical experiences that would enhance the safe use of the product resulting in amendments to the wordings in the Contraindications, Warnings, Precautions, and Adverse Reaction sections of the Product Monograph.

- *Information which must be submitted within 180 days of the original submission*

Unsolicited final reports of ongoing safety studies (e.g. renal toxicity, teratogenicity studies) may be submitted within 180 days of receipt of the original submission provided that the existence of these ongoing studies have been clearly identified in the original submission, and that a rationale demonstrating how these studies are expected to modify the wording of the above stated sections of the Product Monograph, has been provided at the time of filing of the original submission.

A revised and appropriately cross-referenced Product Monograph (PM) with the proposed changes must accompany any submission of unsolicited data. Such information will not prejudice the review schedule of the submission.

Sponsors should also clearly identify in a covering letter the control number of the relevant submission, the purpose of the correspondence, and that the information and material is unsolicited.

- *Information not accepted for review*

Unsolicited final reports of safety studies that are:

- not identified at the time of filing;
- not submitted within 180 days of receipt of the original submission, or
- do not enhance the safe use of the product resulting in an amendment to those sections of the Product Monograph, identified above,

will not be accepted for review and will be returned to the sponsor.

Sponsors should file such information in response to a NON, or as an SNDS or NC according to Section 5.2 in accordance with the “*Guidance for Industry - Post-Notice of Compliance (NOC) Changes*”, where applicable.

C) Foreign Regulatory Information

Health Canada will accept as unsolicited information:

Assessment Reports:

- assessment reports prepared by other regulatory authorities, submitted within 120 days of receipt of the original submission filing; submission of these reports outside this time frame or filing of summaries will not be accepted.

Correspondence:

- copies of the actual correspondence between the sponsor and other regulatory authorities may be submitted at any time; summaries of this information will not be accepted. Supporting data or appendices should not be submitted but should be available if requested in a clarifax. Note that new data, such as, new clinical and/or pre-clinical information, including new bioavailability data not previously submitted, will not be requested in a clarifax.

D) Use of Expert Advisory Committees/ Expert Opinions

Expert reports prepared for or by the sponsor will be accepted only:

- at the time that the original submission is filed, or
- following issuance of a NON by Health Canada.

E) Changes in the Name of Sponsor or Product During Review

If, during the review of a CTA, NDS, ANDS, or DINA, a sponsor's name is changed or the sponsor wishes to change a product name, the information may be submitted. The sponsor is required to submit a letter stating the nature of the

change and the name review¹³ to the Submission and Information Policy Division. If the submission or product is being transferred from one sponsor to another, a letter of authorization from the originating sponsor should be provided.

For information regarding changing the name of the manufacturer/sponsor and/or product following the issuance of a DIN and/or NOC, please refer to the Health Canada policy on “*Changes in Manufacturer’s Name and/or Product Name*”.

F) Other Information

If the sponsor submits unsolicited information other than information as in 5.5.2 A), B), C), D) or E) above, the received information will be returned at the expense of the sponsor. If the sponsor wishes to resubmit the information at a future time, the information and material will be processed as a new submission and assigned a new control number.

G) Safety Information and Other Information

If the sponsor submits other information in addition to the information as described in 5.5.2 B), C), D) and E), all received information will be considered unsolicited information as in 5.5.2 B) above, and will be returned to the sponsor. It will be the sponsor's responsibility to separate the safety data, as described in 5.2.2 B), from the other information and return it to the Directorate.

5.6 Dispute Resolution

In accordance with the HPFB Guiding Principles on Dispute Resolution¹⁴, TPD and BGTD will make every effort to identify, manage, and resolve disputes at the level at which they take place. Dispute prevention and early resolution will primarily take place through improved communication among Directorate staff, and between the Directorates and submission sponsors. Appendix 2 outlines specific activities underway within the Directorates that are intended to improve the early identification and resolution of disputes within the drug submission process, without compromising the safety, efficacy, or quality of regulated products.

¹³ Refer to the *Guidance for Industry; Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names* (available on the Health Canada website) for more details.

¹⁴ Available on the Health Canada website.

If mechanisms for early dispute resolution fail, sponsors may file a formal Request for Reconsideration of a final decision in accordance with the *Guidance: Reconsideration of Final Decisions Issued for Human Drug Submissions*.

5.7 Refiled Submissions

A refiled submission is a submission that a sponsor files following the cancellation of a submission by a sponsor or subsequent to the issuance of a Withdrawal Letter by the Therapeutic Products Directorate and Biologics and Genetic Therapies Directorate.

As outlined in Section 5.5.1(C) and 5.5.1 (D), a Withdrawal Letter may be issued if a response to a NOD or NON is not received in the designated time frame or not received at all, the response to the NOD or NON is found to contain unsolicited information, is incomplete or deficient upon screening, or if the submission is found to remain deficient following the acceptance and review of the information submitted in response to a NOD or NON.

In all cases, a refiled submission is considered to be a new submission and will be assigned a new control number and managed in accordance with “*Guidance for Industry: Management of Drug Submissions*”. A refiled submission is subject to any new Health Canada policies, procedures or guidelines that may be in effect at the time of refiling (including those related to submission evaluation fees) and sponsors are required to update their submissions accordingly. The applicable performance targets and fees for the submission type and submission class apply.

5.7.1 Refiling within 5 years following the issuance of a letter of withdrawal related to a NON

The sponsor should resubmit the information and material pertaining to all of the deficiencies identified in the NON or related Withdrawal Letter.

For all refilings, sponsors will be requested to provide a summary of the differences between the original and refiled submissions addressing the rationale for a revisit by Health Canada evaluators. References should be made to the previous control number of the original submission.

Sponsors must certify that the information and material previously submitted remains unchanged.

Information which would be classified as Level 2 or Level 3 according to the “*Guidance for Industry - Post-Notice of Compliance (NOC) Changes*”, must also be included with the refiled submission and incorporated into the appropriate section(s) of the submission. The sponsor should provide a summary of the Level 2 and/or Level 3 changes which have been added, cross-referenced to supporting data in the submission.

In order to increase the efficiency of the review process, sponsors must clearly identify both the new and the original information that is being resubmitted. Appropriate cross-referencing to the original submission where applicable should be included.

A complete and adequately cross-referenced Comprehensive Summary will be required for refiled submissions as applicable.

5.7.2 Refiling after 5 years following the issuance of a letter of withdrawal related to a NON

The sponsor is required to resubmit all information and material for the submission. Cross-referencing is not acceptable in lieu of resubmitting the information. In order to increase the efficiency of the review process, information and material which was previously submitted in the original submission and remains unchanged should be clearly identified and certified as such by the sponsor.

5.7.3 Refiling submissions withdrawn related to a NOD

The sponsor is required to resubmit all information and material for the submission. Cross-referencing is not acceptable in lieu of resubmitting the information.

5.7.4 Refiling following a cancellation by the sponsor during the review of the response to a NON (that is, during Review 2)

The sponsor need only respond to the NON comments when refiled. The sponsor does not need to resubmit all information and material for the submission. However, if a submission is refiled following a cancellation by the sponsor at any other point in the review process, the sponsor is required to resubmit all information and material for the submission. Cross-referencing is not acceptable in lieu of resubmitting the information.

6. ACCESSING SUBMISSION INFORMATION

6.1 Reviewer Reports

Sponsors will receive reviewer reports from Health Canada within seven calendar days following the issuance of a NOD, a NOD/W¹⁵, a NON, or a NON/W for all submissions except DINAs. Sponsors may request reports following receipt of a NOL, NOC, or NSN. For DINAs, sponsors may request reports following receipt of a NOD, NON, NOD/W, or NON/W. Such requests

¹⁵ Sponsors should note, evaluation of the submission may not be complete at the time of NOD or NOD/W issuance.

must be made in writing to the Director of the reviewing Bureau/Centre (refer to Section 5.1.1 for contact details). Health Canada will target to provide requested review reports to the sponsor within 30 calendar days from receipt of the request.

As per the combination policy *Drug/Medical Device Combination Products, May 1999*, combination products that are deemed to be "medical devices", are subject to the device regulatory framework. There are inherent differences in the regulatory frameworks for these types of therapeutic products which do not permit the identical processes and procedures. Review reports for combination products deemed to be devices, will be provided to manufacturers, upon request, following the completion of the review. For more information on the device licencing process refer to "*Management of Application for Medical Device Licenses and Investigational Testing Authorizations*", available on the Health Canada web site.

6.2 Drug Submission Tracking System - Industry Access

Sponsors are able to access information about their own submissions via the Drug Submission Tracking System - Industry Access (DSTS-IA). The application is web-based, with 128-bit encryption, support for SSLv3 and cookie controls. Access is granted via user names and passwords. Information available via the DSTS-IA includes:

- tombstone submission information, i.e. control number, submission type, subtype, class, subclass, CR file number, reviewing Bureau/Centre, CR date;
- submission status (includes status and dates);
- drug product information (includes brand name, manufacturer, active ingredient, strength, route and form);
- documents issued and received, including dates, and
- review streams including stream, division, status of the review (i.e. pending, active, completed) and dates.

For information on obtaining accounts, sponsors may contact the Submission and Information Policy Division at **SIPD-ClientInformation@hc-sc.gc.ca**.

6.3 Status Requests

In an effort to streamline administrative processes and expedite drug submission review, Regulatory Project Managers (RPMs) have been assigned to each review bureau in TPD, and Regulatory Project Officers (RPOs) to each submission in BGTD. The RPMs/RPOs will serve as the primary points of contact between the review bureau and the submission sponsor. Consistent with TPD and BGTD's Guidances for Industry, "*Drug Submission Status Requests*", dated 2005/01/31 and <to be published> respectively, the above is intended to prevent reviewer's time from being eroded by repeated calls from sponsors.

Information will be provided to sponsors in keeping with the confidentiality of the process and without pre-empting the final decision of the Department on the disposition of the submission.

Sponsors with questions about the status or progress of their BGTD submission are requested to contact the relevant Regulatory Affairs Division. Sponsors with questions about the status or progress of their TPD submission are requested to contact the Regulatory Project Manager servicing the relevant review division, or the Senior Regulatory Project Manager servicing the relevant review bureau.

| Biologics and Genetic Therapies Directorate | Therapeutic Products Directorate |
|---|---|
| Director, (<i>choose one</i>) | Director, (<i>choose one</i>) |
| * Centre for Biologics Evaluation | * Bureau of Metabolism, Oncology and Reproductive Sciences, |
| * Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics | * Bureau of Gastroenterology, Infection and Viral Diseases, |
| | * Bureau of Cardiology, Allergy and Neurological Sciences, |
| c/o Regulatory Affairs Division | * Office of Clinical Trials, or |
| See Appendix 1 for address details | * Bureau of Pharmaceutical Sciences, |
| | c/o Regulatory Project Manager |
| | See Appendix 1 for address details |

6.4 Advance Notice Letters

In the instance of a backlog situation involving the review of either Clinical or Chemistry and Manufacturing information, Health Canada may provide advance notice of comments arising from the review of submissions filed. This advance notice will pertain only to situations where the Clinical or Chemistry and Manufacturing review component will not be completed prior to the performance target and where the remaining review component has been finalized culminating in a recommendation for the issuance of a Notice of Non-Compliance (NON). When both streams of the comprehensive review are complete, a NON will be issued identifying all deficiencies.

This advance notice is for information purposes only and is not intended to solicit any inquiry or response at this time. Any response to the comments in the advance notice will be interpreted as unsolicited information in accordance with Section 5.4.2 of this guidance and will be returned at the expense of the submission sponsor. The comments provided in the advance notice may change following the comprehensive review.

The decision to provide advance notice of comments does not represent a change in the existing policies and practices relating to the management of drug submissions, but is based on the unique nature of an existing backlog situation.

7. FEES

For information on issues related to fees for the review of drug submissions and applications, refer to the "Guidance Document Fees for the Review of Drug Submissions and Applications" effective April 2011. This is a guidance for the implementation of the *Fees in Respect of Drugs and Medical Devices Regulations* and replaces the "Guidance document on Cost Recovery - Submission Evaluation Fees" revised May 1998.

Health Canada Policy Issues are reviewed regularly. All comments or concerns regarding this guidance should be directed to:

Submission and Information Policy Division

Therapeutic Products Directorate
Finance Building #2
Tunney's Pasture, A.L. 0201A1
Ottawa, ON K1A 0K9

for review and consideration.

APPENDIX 1: REVIEW BUREAUX/CENTRE RESPONSIBILITIES**Biologics and Genetic Therapies Directorate (BGTD)**

Centre for Blood/Tissues/Organs Evaluation (CBTE): CBTE is responsible for the regulation of biologics, including but not limited to blood and blood products, cells, tissues, organs and xenografts. Key functions include the evaluation of submissions provided in support of product quality, safety, and effectiveness, development of laboratory standards and methods, pre-approval on-site evaluations in support of submission review and managing the lot-release program for biologics.

Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB): CERB is responsible for the regulation of biologics and radiopharmaceuticals, including but not limited to, gene therapies and somatic cell therapies, hormones, monoclonal antibodies, enzymes, allergenic extracts, the clinical review of vaccine products and cytokine products. Key functions include the evaluation of submissions provided in support of product quality, safety, and effectiveness, development of laboratory standards and methods, pre-approval on-site evaluations in support of submission review and managing the lot-release program for biologics.

Centre for Vaccine Evaluation (CVE): CVE is responsible for the regulation of biologics, specifically the chemistry and manufacturing evaluation in support of product quality of vaccine products as well as the lot-release program for vaccines products.

The Office of Regulatory Affairs (ORA) provides screening, regulatory and project management support for all biologic and radiopharmaceutical submissions in BGTD. Additional functions include the regulatory review of product labelling for biologics and radiopharmaceuticals.

Contact Information:

Office of Regulatory Affairs
Health Canada
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Therapeutic Products Directorate

The Therapeutic Products Directorate (TPD) is responsible for the regulation of prescription and non-prescription pharmaceutical (i.e. chemically synthesized) products and medical devices.

Depending upon therapeutic class, prescription/non-prescription status, and the types of studies filed in support of a pharmaceutical submission, the safety and efficacy (clinical and pre-clinical) component may be reviewed by one or more of the five review Bureaux in the TPD, whose functions are described below. The quality (chemistry and manufacturing) component of all pharmaceutical submissions is reviewed by the Bureau of Pharmaceutical Sciences.

The Regulatory Project Management Division, Office of Business Transformation, will serve as the key regulatory contact for submissions, and is responsible for communicating progress internally and externally. The Division is responsible for creating review plans for each submission and monitoring the adherence to review targets through its life cycle. Regulatory Project Managers ensure consistent application of policies, guidelines, processes and practices within and between bureaux, and ensure consistent application by sponsors of minimum requirements during submission screening.

The following is a brief overview of the five pharmaceutical review Bureaux in the TPD.

The Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS) is comprised of the Reproduction and Urology Division, Division of Anti-Neoplastic Drugs, and Metabolic and Musculoskeletal Drugs Division. Responsibilities include, but are not limited to, the clinical, pre-clinical and labelling review of drug submissions indicated for use in/as: hormone replacement, contraceptives, menopause, erectile dysfunction, oncology (includes hormone based therapies), diabetes, obesity, osteoporosis and musculoskeletal anti-inflammatories.

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The Bureau of Gastroenterology, Infection and Viral Diseases (BGIVD) is comprised of the Division of Anti-Infective Drugs, Disinfectants Unit, Gastroenterology Division, AIDS and Viral Diseases Division, and the Non-Prescription Drug Evaluation Division. Responsibilities include, but are not limited to, the clinical, pre-clinical and labelling review of drug submissions indicated for use in/as: anthelmintics, anti-fungals, antibacterials, antibiotics, sterile diluents, antiherpetics, AIDS, influenza, cytomegalovirus, hepatitis B&C, antidiarrheals, antispasmodics, antiulcers, colitis therapy, digestive aids, ophthalmics for macular degeneration and glaucoma, contrast agents and antidotes/poison treatments. The Bureau's responsibilities include the

evaluation of pre-market applications and the management of all issues related to nonprescription drugs, including DIN applications for products subject to Category IV Monographs and to Labelling Standards.

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The Bureau of Cardiology, Allergy and Neurological Sciences (BCANS) contains the Cardio-Renal Division, Allergy and Respiratory Drugs Division, and Central Nervous System Division. Responsibilities include, but are not limited to, the clinical, pre-clinical, and labelling review of drug submissions indicated for use in/as: neurology, anaesthesiology, pain management, psychiatry, obesity, substance related disorders, hypertension, vasodilators, myocardial ischemia, stroke, diuretics, antithrombotics, anticoagulants, antiplatelets, plasma expanders, dialysis, immunosuppressants, allergy, asthma and cough and cold.

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The Bureau of Pharmaceutical Sciences (BPS) is responsible for the chemistry and manufacturing review as well as the evaluation of clinical comparative bioavailability data, including but not limited to bioequivalence studies for all submission types of all therapeutic classes of pharmaceutical products. Responsibilities also include the assessment of pharmaceutical product information and labelling of generic product submissions, and DIN applications for prescription drug products. The Bureau also performs highly specialized research activities in the area of analytical testing and dissolution.

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The Office of Clinical Trials is responsible for managing and evaluating information related to clinical trial applications for drug products used in Phase I, II, or III clinical trials. This includes but is not limited to receiving and reviewing Clinical Trial Applications, serious unexpected adverse drug reactions, and providing guidance to all relevant stakeholders.

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The Office of Risk Management has a diverse range of responsibilities which include; providing scientific and medical advice on cross-cutting medical issues related to pharmaceuticals and administering the Special Access Programme for pharmaceuticals, biologics and radiopharmaceuticals. The Office also provides coordination on drug safety issues for TPD.

APPENDIX 2: DISPUTE PREVENTION AND EARLY RESOLUTION

Dispute prevention and early resolution are key to minimizing the impacts of disputes both internally and externally, and to improving relations between Directorates and their stakeholders. In accordance with the HPFB Guiding Principles on Dispute Resolution (available on the Health Canada web site), TPD and BGTD will make every effort to identify, manage, and resolve disputes at the level at which they take place.

Dispute prevention and early resolution will primarily take place through improved communication among Directorate staff, and between the Directorates and submission sponsors. Mechanisms to improve communication will include the following:

- Improved communication throughout the submission process via the Regulatory Project Managers (RPMs, TPD) and Regulatory Project Officers (RPOs, BGTD), so that the sponsor and the Directorate are fully aware of issues and ongoing activities related to the drug and/or the submission.
- More frequent and effective use of pre-submission meetings; best practices will be followed to ensure meetings are well-organized, efficient, productive, and properly documented. This will allow for greater clarity and discussion of issues earlier in the drug submission process, therefore preventing disputes from arising at later stages.
- More frequent use of post-Notice meetings and teleconferences to provide clarification on the decision and discuss how the sponsor can best respond. These will help to prevent disputes from arising, and allow for informed discussion of those that cannot be prevented.

Disputes that arise within the drug submission process will be initiated at the level at which they take place, and will be addressed as they occur. The RPMs in TPD and the RPOs in BGTD will serve as the primary points of contact between the review bureaux/centres and the submission sponsor, and will be responsible for managing disputes that arise within the submission process. Sponsors who disagree with the way in which their submission is being processed should contact the RPM or RPO assigned to their submission to discuss the issue under dispute. The RPM or RPO will then raise the issue with the review bureau/centre, and will make every attempt to resolve the dispute in a timely manner.

The RPM or RPO is also responsible for ensuring that the dispute and its resolution are appropriately communicated to the review team and to the sponsor. Details of the dispute and its resolution will be documented and filed, including who was involved in the review of the dispute, discussions that took place, decisions that were made, and associated dates. All correspondence will be placed on the file, as will the record of decisions from any meetings or discussions that take place either within the Directorate or with the sponsor (including telephone conversations).

APPENDIX 3: TARGET PERFORMANCE STANDARDS FOR DRUG SUBMISSION REVIEW ¹⁶

TARGET = 90% of the submissions in a category to be processed within the time shown.

For User Fee -Cost Recovery (UF) purposes the target = average number of days as shown for review 1 iteration 1 only*

| SUBMISSION | | PERFORMANCE STANDARDS (in calendar days) | | | | | |
|--|--|--|------------------------|---------------------------|-----------------------------|--------------------------|--------------------------------|
| TYPE | CLASS | SCREENING 1 | REVIEW 1 ¹⁷ | UF Review 1 (iteration 1) | SCREENING 2 Response to NON | REVIEW 2 Response to NON | REVIEW of Response to NOC/c-QN |
| CTA CTA-A | 1. Phase I - bioequivalence, Phase I - healthy human 2. All other Phase I, Phase II, Phase III | 7 (target) 30 (default) | | | | | |
| NDS ¹⁷ or RESPONSE TO NOD | 1. Priority - NAS, Clin or Non Clin /C&M, Clin or Non Clin Only | 25 | 180 | 300 | 25 | 90 | 30 |
| | 2. NOC/c - NAS, Clin or Non Clin /C&M, Clin or Non Clin Only | 25 | 200 | 300 | 25 | 90 | 30 |
| | 3. NAS | 45 | 300 | 300 | 45 | 150 | 30 |
| | 4. Clin or Non Clin Data/C&M | 45 | 300 | 300 | 45 | 150 | 30 |
| | 5. Clin or Non Clin Only | 45 | 300 | 300 | 45 | 150 | 30 |
| | 6. Comp/C&M | 45 | 180 | 180 | 45 | 150 | 0 |
| | 7. C&M/Labelling | 45 | 180 | 180 | 45 | 150 | 0 |
| | 8. Published Data | 45 | 300 | 300 | 45 | 150 | 0 |
| | 9. Labelling Only | 7 | 60 | 60 | 0 | 0 | 0 |
| | 10. Administrative (X-ref., product or manufacturer name changes) | 45 | 0 | 45 | 0 | 0 | 0 |
| | 11. Disinfectants (submitted as 4-10 class-type, see relevant performance standards above) | | | | | | |
| ANDS or RESPONSE TO NOD | 1. Comp/C&M | 45 | 180 | 180 | 45 | 150 | 0 |
| | 2. C&M/Labelling | 45 | 180 | 180 | 45 | 150 | 0 |
| | 3. Published Data | 45 | 300 | 300 | 45 | 150 | 0 |
| | 4. Labelling Only | 7 | 60 | 60 | 0 | 0 | 0 |
| | 5. Administrative (X-ref., product or manufacturer name changes) | 45 | 0 | 45 | 0 | 0 | 0 |
| SNDS or RESPONSE TO NOD | 1. Priority - Clin or Non Clin/C&M, Clin or Non Clin Only | 25 | 180 | 300 | 25 | 90 | 30 |
| | 2. NOC/c - Clin or Non Clin/C&M, Clin or Non Clin Only | 25 | 200 | 300 | 25 | 90 | 30 |
| | 3. Clin or Non Clin/C&M | 45 | 300 | 300 | 45 | 150 | 30 |
| | 4. Comp/C&M | 45 | 180 | 180 | 45 | 150 | 0 |
| | 5. Clin or Non Clin Only | 45 | 300 | 300 | 45 | 150 | 30 |
| | 6. C&M/Labelling | 45 | 180 | 180 | 45 | 150 | 0 |
| | 7. Published Data | 45 | 300 | 300 | 45 | 150 | 0 |
| | 8. Rx to OTC - No New Indication | 45 | 180 | 180 | 45 | 150 | 0 |
| | 9. Labelling only | 7 | 60 | 60 | 0 | 0 | 0 |
| | 10. Administrative (X-ref., product or manufacturer name changes) | 45 | 0 | 45 | 0 | 0 | 0 |
| | 11. Disinfectants (submitted as 3, 4, 5, 6, 7, 9, 10 class-type, see relevant performance standards above) | | | | | | |

| | | | | | | | |
|--------------------------------|---|----|-----|-----|----|-----|---|
| SANDS or RESPONSE TO NOD | 1. Clin or Non Clin/C&M | 45 | 300 | 300 | 45 | 150 | 0 |
| | 2. Clin or Non Clin Only | 45 | 300 | 300 | 45 | 150 | 0 |
| | 3. Comp/ C&M | 45 | 180 | 180 | 45 | 150 | 0 |
| | 4. C&M/ Labelling | 45 | 180 | 180 | 45 | 150 | 0 |
| | 5. Published Data | 45 | 300 | 300 | 45 | 150 | 0 |
| | 6. Rx to OTC - No New Indication | 45 | 180 | 180 | 45 | 150 | 0 |
| | 7. Labelling Only | 7 | 60 | 60 | 0 | 0 | 0 |
| | 8. Administrative (X-ref., product or manufacturer name changes) | 45 | 0 | 45 | 0 | 0 | 0 |
| DINA, DINB, DIND | 1. Labelling Standard | 45 | 0 | 45 | 0 | 0 | 0 |
| | 2. Clin or Non Clin/C&M | 45 | 210 | 210 | 45 | 150 | 0 |
| | 3. Clin or Non Clin Only | 45 | 210 | 210 | 45 | 150 | 0 |
| | 4. Comp/C&M | 45 | 210 | 210 | 45 | 150 | 0 |
| | 5. C&M/ Labelling | 45 | 210 | 210 | 45 | 150 | 0 |
| | 6. Published Data | 45 | 210 | 210 | 45 | 150 | 0 |
| | 7. Labelling only | 45 | 180 | 180 | 45 | 120 | 0 |
| | 8. Administrative (X-ref., product or manufacturer name changes) | 45 | 0 | 45 | 0 | 0 | 0 |
| | 9. Disinfectants (submitted as 1-8 class-type, see relevant performance standards above) | | | | | | |
| DINF | 1. Category IV Monograph | 45 | 0 | 45 | 0 | 0 | 0 |
| NC | 1. NC (90 day) Safety, NC (90 day) Safety and Quality, NC (90 day) Quality | 7 | 90 | | | | |
| | 2. NC Safety (120 day) | 7 | 120 | | | | |
| | 3. Administrative | 45 | 0 | | | | |
| PDC | 1. Post-authorization Division 1 change | 30 | 0 | | | | |

¹⁶ Add 10 calendar days for processing by the Submission and Information Policy Division for all submissions except CTAs and CTA-As (Section 5.2).

¹⁷ from date of acceptance of submission **OR** "Updated" submission.

* iteration 1 = time from assigned to Review 1 to first decision (e.g. NOL, NOD, NON, NOC) For Administrative, Labelling Standard and DIN F it applies to the Screening 1 performance standard to first decision (e.g. Screening Deficiency Notice, Rejection Letter - Screening, Notification Form, No Objection Letter, Cancellation Letter, etc.) Please also refer to the Guidance Document: Fees for the Review of Drug Submissions and Applications.

APPENDIX 4: NOTES FOR ATTACHED CHART

1. GLOSSARY OF ABBREVIATIONS:

| | | | |
|--------|--|-----------|--|
| CTA: | Clinical Trial Application | NAS: | New Active Substance |
| CTA-A: | Clinical Trial Application - Amendment | OTC: | Over The Counter |
| NDS: | New Drug Submission | Rx: | Prescription |
| SNDS: | Supplement to a New Drug Submission | Clin: | Clinical |
| ANDS: | Abbreviated New Drug Submission | Comp: | Comparative Bio., Clinical, or Pharmacodynamic |
| SANDS: | Supplement to an Abbreviated New Drug Submission | C&M: | Chemistry and Manufacturing/Quality |
| DIN: | Drug Identification Number | BIO: | Bioavailability Study |
| NC: | Notifiable Change | | |
| PDC: | Post-authorization Division 1 Change (PDC) | | |
| DINA: | Application for a Drug Identification Number | NOC: | Notice Compliance |
| DINB: | Application for a DIN - Biological product | NON: | Notice of Non-Compliance |
| | | NOD: | Notice of Deficiency |
| DINF: | Application for a DIN - Category IV product | NOL: | No Objection Letter |
| DIND: | Application for a DIN - Disinfectant product | NSN: | Not Satisfactory Notice |
| | | NOC/c-QN: | Notice of Compliance with Conditions - Qualifying Notice |

2. NOTES ON DEFINITIONS:

| | |
|--------------|--|
| CLASS: | Submission class based on information included in submission. |
| NOC/c: | Submissions which have been accepted for advance consideration under the “ <i>Notice of Compliance with Conditions</i> ” Policy. |
| PRIORITY: | Submissions which have been accepted for priority status according to the “Priority Review of Drug Submissions” policy. |
| SCREENING 1: | Period from date of receipt to date of acceptance, rejection, Screening Deficiency Notice or Withdrawal Unacceptable Response to NOD Screening. |
| REVIEW 1: | Period from date of acceptance to: a) for CTAs, CTA-As & NCs - No Objection Letter or Not Satisfactory Notice b) for all submissions - NOD, NOD-Withdrawal, NON, NOC/c-QN or NOC |
| SCREENING 2: | Period from date of receipt of response to NON to date of acceptance or Withdrawal Unacceptable Response to NON Screening. |
| REVIEW 2: | Period from date of acceptance of response to NON to NOC or NON-Withdrawal letter. |

REVIEW of Response to NOC/c-QN: Period from date of acceptance of response to NOC/c-QN issued under the “*Notice of Compliance with Conditions*” Policy.