



GUIDANCE DOCUMENT

Post-Notice of Compliance (NOC) Changes: Framework Document

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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 to health 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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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

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 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.

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1. INTRODUCTION

After a new drug as defined in section C.08.001 of the *Food and Drug Regulations* has been granted a Notice of Compliance (NOC), it is not uncommon for sponsors to make changes to the drug. A post-NOC change is any change that is made to a new drug that has received a NOC pursuant to section C.08.004 of the *Food and Drug Regulations*. Many of these changes may be made to improve the quality of the drug product or the efficiency of the manufacturing process, or they could be made for marketing considerations. Changes to the labelling of a drug product could include adding new indications, improving the management of risk for a product by adding warnings, limiting the target population or changing the dosage regime etc..

1.1 Policy Objectives

This guidance document together with the associated documents (refer to Section 2.3) provides an updated interpretation of section C.08.003 of the *Food and Drug Regulations* by:

- (i) providing criteria to define what is meant by *significantly different*¹ as it relates to the matters specified in C.08.003 (2) and ;
- (ii) providing sponsors with recommendations on the data required to enable Health Canada to make an accurate determination of the impact of a change on the safety, efficacy and quality of the new drug.

1.2 Policy Statements

Health Canada recognizes that:

- (i) any change to a drug may impact the safety, efficacy and quality of that drug and;
- (ii) any change to the information associated with the drug (for example [e.g.], labelling) may impact the safe and effective use of that drug.

1 Section C.08.003(1) of the *Food and Drug Regulations* states in part:
“Notwithstanding section C.08.002, no person shall sell a new drug in respect of which a notice of compliance has been issued to the manufacturer of that new drug and has not been suspended pursuant to section C.08.006, if any of the matters specified in subsection (2) are *significantly different* from the information or material contained in the new drug submission or abbreviated new drug submission....”

To enable Health Canada to manage risks that may be associated with a change to a new drug:

- (i) any change to a drug that has received a NOC should be reported according to one of the four following categories: Level I (Supplements), Level II (Notifiable Changes), Level III (Annual Notifications) and Level IV (Record of Changes) Changes based on the criteria and conditions indicated in the associated guidances and;
- (ii) data to support a Level I or Level II change, as recommended in the associated guidances, should be submitted to Health Canada for review prior to implementing the change. Data to support a Level III change should not be submitted, but should be available to Health Canada upon request. Data to support a Level IV change should be retained by the sponsor or manufacturer.

1.3 Scope and Application

These guidance documents (that is [i.e.] Framework, Safety and Efficacy and Quality) apply to sponsors intending to make changes to new drugs that have received a NOC pursuant to section C.08.004 of the *Food and Drug Regulations*. These drugs may include pharmaceuticals, biologics, and radiopharmaceuticals for human use and pharmaceutical, radiopharmaceutical and certain biotechnological products for veterinary use². In the absence of a guidance specific to Quality changes to drugs which were approved through a Drug Identification Application - Biologics (DIN-B drugs), the Quality guidance document applies to those products. This guidance document also applies to those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold.

This guidance document should be read in conjunction with the associated Health Canada guidance documents entitled *Post-Notice of Compliance (NOC) Changes: Quality* and *Post-Notice of Compliance (NOC) Changes: Safety and Efficacy* as well as other related Health Canada guidance documents. Information regarding general submission requirements and target performance standards may be found in the Health Canada guidance documents: *Guidance for Industry: Management of Drug Submissions* for drugs intended for human use and *Guidance for Industry: Management of Regulatory Submissions* for drugs intended for use in animals.

² The Veterinary Drugs Directorate (VDD) should be consulted to determine if the submission constitutes a veterinary biotechnological drug under the *Food and Drugs Act*.

It is recommended that the principles established in these guidance documents be applied to similar Quality changes that occur during the development of the drug and the recommended supporting data be included with the initial New Drug Submission (NDS) or Abbreviated New Drug Submission (ANDS).

As of the effective date, the Post-NOC Changes guidance documents will supersede the following guidances and policies:

New Drug: Sufficient Time policy (1991)
Extension of Expiration Dates (1991)
Changes to Marketed New Drug Products policy (1994)
Stability Requirements for Changes to Marketed New Drugs (1994)
Changes in Product-Specific Facility Information (revised in 2004)
New Drug: Sufficient Time notice (2005)
Draft Guidance for Industry: Changes in Product Colours or Markings (2005)

1.4 Background

The *New Drug: Sufficient Time* policy released in 1991, was developed to "expedite the review process and reduce the backlog of New Drug Submissions". This was accomplished by eliminating the requirement for sponsors to file specified changes made to a drug, provided that the drug had been marketed for a minimum of seven years in Canada. The policy was based on the amount of time a drug has been marketed and has since been recognized as not encompassing modern evidence-based risk management principles. Therefore, in January 2005, the *Notice: New Drug - Sufficient Time* was issued as an interim measure to allow for better management of the potential risks that may be associated with a change to a drug regardless of the time it has been on the market.

In April 1994, Health Canada released the policy entitled *Changes to Marketed New Drug Products*. The purpose of this policy was to provide an interpretation of the requirements of section C.08.003 of the *Food and Drug Regulations*, to introduce a tiered structure for changes to marketed drugs and to reduce the review workload by decreasing the number of Supplemental New Drug Submission (SNDS) filings. The changes were grouped into four categories (Level 1, 2, 3 and 4) based on the significance of the change and therefore the potential impact on safety and efficacy.

As a follow-up to this, in March 1997, *Schedule 733 - Changes to Marketed New Drugs* was proposed in *Canada Gazette Part I*. The intent of this regulatory proposal was to introduce into the *Food and Drug Regulations* a graduated system of regulatory requirements for changes to new drugs marketed in Canada. However, this proposal to amend the *Regulations* was withdrawn in October 1998. It was believed at the time that this type of guidance would better be conveyed to stakeholders in the form of policies and

guidance documents, rather than embedded in the *Regulations*, in order to allow Health Canada a greater ability to adapt to a rapidly changing international regulatory environment.

A number of international developments have occurred since the *Changes to Marketed New Drug Products* policy was first introduced in 1994. This includes the trend amongst competent regulatory authorities to emphasize an integrated approach to review and inspection based on scientific risk management principles.

As such, the Post-NOC Changes series of guidance documents have been written taking into consideration the concepts of risk management, the practices of other Regulatory Agencies (specifically those of the United States, the European Union and Australia) as well as guidances produced by the *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* or the *International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)* and adopted by Health Canada.

As the Branch is undertaking efforts to modernize the *Food and Drugs Act* and the frameworks for the regulation of therapeutic products, a decision was made that until this modernization is completed, it would be most efficient to keep the existing terminology and process structure for the four Levels (i.e. Supplement, Notifiable Change, Annual Notification and Record of Change), but with substitution of the new criteria. Thus these levels, although redefined to reflect modern risk-management principles, will retain their current status with respect to the existing *Regulations*.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Reporting Categories

A brief description of the reporting categories is provided below. More details regarding criteria specific to safety and efficacy and quality-related changes, along with examples are provided in the associated guidance documents listed in section 2.3 below. If the submission has been inappropriately classified, the sponsor will be notified at the screening stage.

2.1.1 Level I - Supplements

Level I or Supplemental changes are those changes to a new drug that are “significantly different” as it relates to the matters specified in C.08.003 (2) of the *Food and Drug Regulations* and have the potential to impact the safety, efficacy,

quality and/or effective use of the drug.³ The changes included in this reporting category shall be filed, along with the recommended supporting data, to Health Canada as a Supplemental New Drug Submission (SNDS) or Supplemental Abbreviated New Drug Submission (SANDS). The change may not be implemented by the sponsor until a NOC has been issued.

2.1.2 Level II - Notifiable Changes

Level II or Notifiable Changes (NC) are changes to a new drug that have the potential to impact the safety, efficacy, quality and/or effective use of the drug but do not require the issuance of a NOC. The changes included in this reporting category should be filed, along with the recommended supporting data, to Health Canada as a Notifiable Change. All Level II changes should not be implemented by the sponsor until a No Objection Letter (NOL) has been issued.

Multiple Level II (Quality) changes for the same drug product may be filed in a single submission provided those changes are related and/or supported by the same information. If the changes are related, the sponsor should indicate the association between the proposed changes.

Multiple Level II (Safety and Efficacy) changes for the same drug product may be filed in a single submission provided those changes are within the same reporting category (i.e. multiple 90 day NCs in one submission or multiple 120 day NCs in one submission).

If there are too many changes filed within the same submission or major issues are identified with a change which would require extensive time to review, Health Canada may divide the changes into separate submissions.

For submissions that include multiple changes, the sponsor should clearly specify which supporting data supports which change.

If the same change is applicable to multiple drugs, a separate submission is required for each drug product but the data may be cross-referenced.

2.1.3 Level III - Annual Notifications

Level III or Annual Notifications are changes to a new drug that have minimal potential to impact the safety, efficacy, quality and/or effective use of the drug.

³ There are some changes in the Safety and Efficacy guidance that do not meet the criteria of a Level I change but are included in this section because they require the issuance of a new NOC.

The changes included in this reporting category may be implemented by the sponsor without the prior review by Health Canada of the data supporting such a change. These changes should be annotated in the affected documents when filing the next submission to Health Canada to indicate those Level III changes that have been implemented. The recommended supporting data should *not* be submitted but should be available to Health Canada within thirty (30) calendar days if requested at any time. Notification of Level III changes shall be included with the Annual Notification as required by section C.01.014.5 of the *Food and Drug Regulations*⁴.

Health Canada may periodically audit Level III changes by requesting and reviewing the supporting data from the sponsor as deemed appropriate. If the classification of the change or the data to support the change is not considered to be acceptable, the sponsor may be requested to file a Level I or Level II submission. In cases where the change has already been implemented, the sponsor may continue to sell the drug until such time as any issues are resolved. If Health Canada considers that the changed drug product has impacted the safety, efficacy, quality and/or effective use of the drug which may be harmful to the Canadian public, section C.01.013 of the *Food and Drug Regulations* will be applied.

2.1.4 Level IV - Record of Changes

Level IV or Record of Changes (Quality only) are changes to a new drug that are not Level I, Level II or Level III and are not expected to impact the safety, efficacy, quality and/or effective use of the drug. The changes included in this reporting category may be implemented by the sponsor without prior review by Health Canada. The changes should be retained as part of the drug product's record by either the sponsor or the manufacturer and comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the *Food and Drug Regulations*.

2.2 Drug Submission Filing Information

2.2.1 Related Guidances for Drug Submission Filings

The following Health Canada guidance documents provide instruction regarding submission filing, procedures and review target dates and should be consulted by the sponsor when preparing a drug submission. For the convenience of the reader,

⁴ Section C.01.014.5 of the *Food and Drug Regulations* states:
“Every manufacturer of a drug shall, annually before the first day of October and in a form authorized by the Director, furnish the Director with a notification signed by the manufacturer or by a person authorized to sign on his behalf, confirming that all the information previously supplied by the manufacturer with respect to that drug is correct”.

some of the detail included in these guidances has been included in the following sections along with additional detail regarding post-NOC change submissions and Annual Notifications. These guidances are available on the Health Canada Web site.

Drugs for Human Use:

Guidance For Industry: Management of Drug Submissions

Drugs for Veterinary Use:

Guidance For Industry: Management of Regulatory Submissions

2.2.2 Pre-Submission Enquiries

The listings of changes in these guidance documents are not considered to be exhaustive such as to cover all possible situations. When in doubt as to the classification or supporting documentation, sponsors are encouraged to contact Health Canada in writing for clarification. Verbal enquiries should be followed-up in writing by the sponsor. Health Canada will provide a written response within fifteen (15) calendar days of a pre-submission enquiry.

To aid in planning the allocation of review resources, sponsors are encouraged to contact Health Canada regarding the number and proposed filing dates for planned changes to existing drugs. Sponsors should contact the appropriate directorate to determine the best method for submitting this information.

Refer to the Health Canada documents, *Guidance For Industry: Management of Drug Submissions* (drugs for human use) or the *Guidance For Industry: Management of Regulatory Submissions* (drugs for veterinary use) for contact information.

2.2.3 Submission Filing - Level I and Level II Changes

2.2.3.1 Drugs for Human Use

Refer to the *Guidance For Industry: Management of Drug Submissions* for details of where to send submissions for pharmaceuticals, biologics, and radiopharmaceuticals.

2.2.3.2 Drugs for Veterinary Use

Refer to the *Guidance For Industry: Management of Regulatory Submissions* for details of where to send submissions for pharmaceutical, radiopharmaceutical and certain biotechnological products⁵.

2.2.3.3 Items to be Included in the Submission

The following items should be included, where applicable, in the submission package for all Level I and Level II post-NOC change submissions:

- (a) A covering letter that includes:
 - (i) the type of submission (i.e. SNDS, SANDS or NC);
 - (ii) a narrative of the change(s) and a brief rationale for the change(s);
 - (iii) any other information relevant to the submission;
 - (iv) an indication of the general type of supporting data (e.g., results of clinical, bioequivalence, toxicological or other *in vivo* studies including any *in vivo/in vitro* correlation studies [IVIVC]), supporting Quality [chemistry and manufacturing] data and the major Common Technical Document (CTD) sections included in the submission;
 - (v) for submissions filed in the electronic Common Technical Document (eCTD) format, include a description of the electronic submission including type and number of electronic media, approximate size of the submission, a statement that the submission is virus free with a description of the software used to check the files for viruses, and the regulatory and eCTD points of contact for the submission;

- (b) The completed documents:
 - (i) Drug Submission Application Form (Health Canada 3011) signed and dated;
 - (ii) Drug Submission Fee Application Form;
 - (iii) Submission Certification Form - signed and dated;
 - (iv) Letter of Attestation for submissions filed in electronic Common Technical Document (eCTD) format - signed and dated;

⁵ The Veterinary Drugs Directorate (VDD) should be consulted to determine if the submission constitutes a veterinary biotechnological drug under the *Food and Drugs Act*.

- (c) Patent information pursuant to the *Patented Medicines (Notice of Compliance) Regulations*;
- (d) Good Manufacturing Practices (GMP) and Establishment Licensing (EL) Information;
- (e) Letters of Access for any supporting Drug Master Files and Site Reference Files;
- (f) An annotated and non-annotated electronic and an annotated hard copy of:
 - (i) the Certified Product Information Document (CPID); and,
 - (ii) the Product Monograph or Package Insert (for Veterinary drugs);
- (g) A sample of the inner and outer labels.

Where applicable, the submission data should be provided in the format defined by the *International Conference on Harmonization (ICH) Common Technical Document (CTD)* with the applicable sections completed. A Quality Overall Summary (QOS-CE or QOS-B) and a *Comprehensive Summary: Bioequivalence (CS:BE)* should also be completed and provided where applicable. For Veterinary Drug Submissions, data should be provided in the format of the *Guidance for Industry: Preparation of Veterinary New Drug Submissions*. For drug submissions filed in the electronic Common Technical Document (eCTD) format, data and filing requirements should be provided as defined in the *Guidance for Industry: Preparation of Drug Submissions in the eCTD Format*.

2.2.4 Level III - Annual Notifications

The following items should be included, where applicable, with the sponsor's Annual Drug Notification:

- (a) A listing of all Level III changes for each new drug that has received a NOC and that have occurred in the preceding twelve (12) months compiled using the Level III form or format;
- (b) a copy of the most recent revised label(s) (inner and outer) if a Level III label change has been made;

Supporting data for the Level III changes recommended in the associated guidance documents should *not* be submitted with the Annual Drug Notification; however,

the data should be available to Health Canada within thirty (30) calendar days if requested at any time. Sponsors may refer to Health Canada's *Annual Drug Notification Guidance* for further information regarding the process. Any Level III changes that have been implemented should be annotated in the affected documents (e.g., Product Monograph/Package Insert or CPID) with the filing of the next submission to Health Canada.

2.2.5 Level IV- Record of Changes

The Quality changes included in this category should be retained as part of the product's record by either the sponsor or the manufacturer and comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the *Food and Drug Regulations*. These changes should be annotated in the affected documents with the filing of the next submission to Health Canada.

2.3 Associated Guidance Documents

2.3.1 Post-Notice of Compliance (NOC) Changes: Safety and Efficacy

This guidance document contains detailed instructions with respect to the categorization of a change, specific change examples and the recommended supporting data for any changes to the Safety and Efficacy information including any labelling documentation, associated with the new drug.

2.3.2 Post-Notice of Compliance (NOC) Changes: Quality

This guidance document contains detailed instructions with respect to the categorization of a change and the recommended supporting data for any changes to the Quality information associated with the new drug including any labelling documentation affected by the change. Specific change examples are included in the appendices to this guidance.

3. EFFECTIVE DATE

This Framework document and the associated Post-NOC Changes guidances came into effect on 2009-09-30. Health Canada recognizes that changes allowed under the *New Drug: Sufficient Time policy (1991)* were not required to be reported. Sponsors are reminded that changes previously implemented under the *New Drug: Sufficient Time* policy need not be reported at this time. All changes from the effective date of the Post-NOC Changes guidances are expected to be reported as per the procedures detailed within.

APPENDICES

Appendix A: Acronyms

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| ANDS | Abbreviated New Drug Submission |
| BPS | Bureau of Pharmaceutical Sciences |
| BCANS | Bureau of Cardiology, Allergy and Neurological Sciences |
| BGIVD | Bureau of Gastroenterology, Infection and Viral Diseases |
| BMORS | Bureau of Metabolism, Oncology and Reproductive Sciences |
| CS:BE | Comprehensive Summary: Bioequivalence |
| CPID | Certified Product Information Document |
| CTD | Common Technical Document |
| DIN | Drug Identification Number |
| eCTD | electronic Common Technical Document |
| EL | Establishment Licence |
| GMP | Good Manufacturing Practices |
| ICH | <i>International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</i> |
| IVIVC | <i>In vivo/in vitro</i> correlation |
| NC | Notifiable Change |
| NDS | New Drug Submission |
| NOC | Notice of Compliance |
| NOL | No Objection Letter |
| QOS | Quality Overall Summary |
| SANDS | Supplement to an Abbreviated New Drug Submission |
| SNDS | Supplement to a New Drug Submission |
| SIPD | Submission and Information Policy Division |
| VDD | Veterinary Drugs Directorate |
| VICH | <i>International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products</i> |
| YBPR | Yearly Biologic Product Report |