# Guidance on post-notice of compliance changes: Framework for biologic and Schedule C drugs for human use

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Health Canada Santé Canada

Canada

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Également disponible en français sous le titre :
Ligne directrice sur les changements survenus après l'avis de conformité : Cadre pour les médicaments biologiques et les médicaments de l'Annexe C destinés à l'usage humain

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# Document change log

| Date | Nature of and reason for change |
|---|---|
| **May 15, 2026** | • Framework document specific to biological and Schedule C drugs<br>• Introduction of Level III immediate notification<br>• Introduction of ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management |

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# Introduction

After a new drug (defined in section C.08.001 of the Food and Drug Regulations) has been granted a notice of compliance (NOC), it's common for sponsors to make changes to the drug. Any change made to a new drug that has received an NOC is called a post-NOC change (C.08.004).

These types of changes are usually made to improve the quality of the drug, the efficiency of the manufacturing process or for marketing considerations. An example of an NOC change would be making changes to a drug's labelling, such as:

- adding new indications
- changing the dosage regime
- limiting the target population
- improving the management of risk for a drug by adding warnings

## Policy objectives

In this guidance document, Health Canada outlines the overarching authorities, reporting categories and drug submission filing information for post-NOC changes for biologic and Schedule C drugs for human use.

You will also find an updated interpretation of section C.08.003 of the regulations. For example, the guidance:

- outlines the criteria used to define what is meant by significantly different as it relates to the matters specified in C.08.003(2)
    - Section C.08.003 states: "Despite 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 under 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."
- gives recommendations on the data required to help us accurately determine the impact of a change on the new drug's safety, efficacy and quality

## Policy statements

Health Canada recognizes that any change to:

- a drug may impact its safety, efficacy and quality
- the information provided with or on the drug (for example, labelling) may impact its safe and effective use

To help us manage risks that may be associated with a change to a new drug, we ask that you report or document any change to a drug that has received an NOC. Documentation should follow these categories:

- Level I – Supplements (major quality changes)
- Level II – Supplements (safety)
- Level II – Notifiable changes (moderate quality changes) (for human biologic and radiopharmaceutical drug quality changes)
- Level III – Notifications (minor quality change)
- Level IV – Changes not reported (quality changes with no impact) based on the criteria and conditions indicated in the companion guidance documents

The implementation date of a quality change is the date the change is recorded in your company's change management system. This is usually when the first batch made after incorporating the change is released for marketing, anywhere in the world.

The implementation date for a labelling (safety) change is the date when the change is made to the label in Canada.

Also note that you should submit data to us to review before you implement a change. This requirement includes affected documents, such as a certified product information document (CPID) or product monograph (PM), that are provided to support any of the following:

- Level I – Supplement
- Level II – Supplement (safety)
- Level II – Notifiable changes
    - Visit the section on associated guidance documents
- authorized as part of a post-approval change management protocol (PACMP)
    - This takes precedence over the general guidance

Data to support a Level III – Immediate notification should be generated as authorized in the PACMP or recommended in the associated companion guidance documents. Supporting data not submitted with the notification should be made available to us within 30 calendar days of the date we request it.

Data to support a Level III – Annual notification change should be made available to us upon request.

Data to support a Level IV – Changes not reported should be managed within the relevant pharmaceutical quality system (PQS). The data should be available for routine inspection of good manufacturing practices (GMP).

## Scope and application

The guidance documents on the framework, safety and efficacy, and quality apply if you intend to make changes to new drugs that have received an NOC (C.08.004 of the regulations). These new drugs include:

- biologics
- Schedule C drugs (radiopharmaceuticals and kits) for human use
    - includes submissions for which an NOC has been recommended but has not been issued (placed on hold)

There isn't guidance specific to quality changes to drugs that were approved through a drug identification application - biologics (DIN-B drugs). In this case, the guidance on quality applies.

As this guidance outlines the overarching authorities, reporting categories and drug submission filing information, we recommend that you refer to other relevant documents. You should also consult the following companion guidance documents on post-notice of compliance (NOC) changes:

- Guidance on post-notice of compliance changes: Overall quality document for biologic and Schedule C drugs for human use
- Guidance on post-notice of compliance changes: Quality for biologics
- Guidance on post-notice of compliance changes: Quality for Schedule C drugs
- Post-notice of compliance (NOC) changes: Safety and efficacy (for pharmaceutical, biologic and radiopharmaceutical drugs for human use only)

For information on general submission requirements and target performance standards, consult:

- Management of drug submissions and applications

When developing a new drug, we ask that you apply the principles outlined in all of these guidance documents to similar quality changes that occur in the development phase. You should also include the recommended supporting data with your:

- new drug submission (NDS)
- extraordinary use new drug submission
- abbreviated new drug submission (ANDS)
- abbreviated extraordinary use new drug submission

## Background

The guidance documents on post-NOC changes supersede the following documents:

- 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)

The "New drug: Sufficient time policy" was developed to fast-track 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 that has been marketed in Canada for at least 7 years. The policy was based on the amount of time a drug has been marketed, but it lacked modern evidence-based risk management principles. We then issued an interim notice to allow for better management of the potential risks that may be associated with a change to a drug regardless of how long it has been on the market.

The "Changes to marketed new drug products policy" was developed to provide an interpretation of the requirements of section C.08.003 of the regulations. A tiered structure for changes to marketed drugs was introduced and the number of supplement to a new drug submission (SNDS) filings was decreased to reduce the review workload. We also

grouped the changes into 4 categories (Levels I, II, III and IV) based on the significance of the change and its potential impact on safety and efficacy.

A regulatory proposal to introduce a graduated system of requirements for changes to new drugs marketed in Canada was proposed in *Canada Gazette, Part I*. However, this proposal was later withdrawn. Current thinking at the time was that regulatory information is better conveyed to stakeholders in the form of policies and guidance documents, not embedded in the regulations. Health Canada would also have greater ability to adapt to a rapidly changing international regulatory environment.

Since this "Changes to marketed new drug products policy" was introduced, a number of international developments have taken place. For example, competent regulatory authorities were stressing an integrated approach to the review and inspection process based on scientific risk management principles.

As a result, we developed a "post-NOC changes" series of guidance documents. These documents take into consideration the concepts of risk management and the practices of regulatory agencies, such as those in the United States, European Union and Australia. Examples include the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance:

- "ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management"
- ICH Q12 associated annexes

These documents incorporate a number of concepts, such as:

- established conditions (ECs)
- post-approval change management protocols (PACMPs)
- product life cycle management (PLCM)

The reporting category for safety changes was updated to reflect modern harm management principles for post-NOC changes. These updates were made by the Pharmaceutical Drugs Directorate, Natural and Non-prescription Health Products Directorate, and Biologic and Radiopharmaceutical Drugs Directorate.

Notifiable changes are now Level II - Supplements (safety) (refer to C.08.003(1) of the regulations). Safety changes are considered "significantly different" as they relate to the matters specified in C.08.003(2). Thus, post-NOC safety changes must be submitted as Level II – Supplement (safety) changes for pharmaceutical, biologic and Schedule C drugs.

# Guidance for implementation

## Change classification for categories

This section briefly describes the reporting categories.

Find more information on safety and efficacy criteria or quality-related changes, along with examples, in the section on associated guidance documents. We will notify you at the screening stage if your submission has been incorrectly categorized.

### Level I – Supplements (major quality changes)

Level I - Supplements are changes to an approved drug that are "significantly different" (refer to C.08.003(2) of the regulations). The changes have the potential to impact the safety, efficacy, quality or effective use of the drug.

Any changes included in this reporting category should be filed, along with the recommended supporting data, to us as follows:

- supplement to a new drug submission (SNDS)
- supplement to an extraordinary use new drug submission
- supplement to an abbreviated new drug submission (SANDS) **or**
- supplement to an abbreviated extraordinary use new drug submission

You must not implement the change until we have issued an NOC.

If the same change applies to multiple drugs, you may use the same supporting data package. However, a separate submission is required for each drug.

Cross-referencing a supporting data package is only permitted if the data has been previously approved. It may be appropriate and beneficial to indicate in a "Note to reviewer" that information in the submissions is identical.

## Level II - Supplements (safety)

There are 2 types of Level II – Supplements (safety) in this category:

- risk/harm management changes to a new drug that are "significantly different" (C.08.003(2) of the regulations)
    - defined as any change to the label that has the potential to improve the management of risk/harm to the population currently indicated for use of the drug, or in any other way exposed to the drug
- changes that do not meet the criteria of a Level I - Supplement, Level II - Supplement (safety) that are risk/harm management changes or Level III - Change, but our prior approval is required

## Level II - Notifiable changes (moderate quality changes)

Notifiable changes are those that have a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug, which may relate to the drug's safety or effectiveness. These changes do not require an NOC.

You should file any changes included in this reporting category, along with the recommended supporting data, to us as a notifiable change.

You should not implement the changes until we have issued a "No objection letter" (NOL).

Multiple Level II – Notifiable changes for the same drug may be filed in a single submission provided the changes are related or supported by the same information. If related, you should indicate the association between the proposed changes.

If the same change applies to multiple drugs, you may use the same supporting data package. However, a separate submission is required for each drug. Cross-referencing a supporting data package is only permitted if the data has been previously approved. It may be appropriate and beneficial to indicate in a "Note to reviewer" that information in the submissions is identical.

## Level III – Notifications (minor quality changes)

### Level III - Immediate notifications (minor quality change)

Level III - Immediate notifications are for changes that have low potential to adversely affect the drug's quality, including its identity, strength, purity or potency.

As these factors may have an impact on the safety or effectiveness of the drug, you should notify us 21 days before to 14 days after the implementation date. Refer to the section on policy statements.

This reporting category includes the majority of major and moderate changes that have been downgraded to minor quality changes as a result of implementing an approved post-approval change management protocol. In all cases, a moderate change can only be classified as an immediate notification when conditions are met and specific supporting information is available to confirm the change is not significant.

You may implement changes included in this reporting category without prior review by us. We will inform you that you should submit a supplement or notifiable change (for biologics and Schedule D drugs only) to obtain authorization for the change if the conditions for the category have not been met. You will not be allowed to release any more batches of the affected product until all appropriate regulatory requirements and expectations have been met. A product recall may be required.

### Level III - Annual notifications (minor quality change)

Level III - Annual notifications are for changes to a new drug that have minimal potential to impact the drug's safety, efficacy, quality or effective use. You may implement the changes included in this reporting category without prior review by us. The implementation date is the date when the product is manufactured using the new equipment or applying new methods.

You should submit the notification within 12 months of implementing the change. Refer to the section on policy statements. Supporting data should not be submitted unless specifically identified in one of the associated guidance documents or as part of a multi-jurisdiction filing. This annual notification is considered by the Minister to fulfil the requirements of the annual drug notification.

Section C.01.014.5 of the 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."

For biologic and Schedule C drugs for human use, we recommend that you file Level III - Safety and efficacy changes when you implement the changes. The implementation date is the date when the change is made to the labels.

### Level IV - Changes not reported (quality changes with no impact)

Level IV changes are not expected to have an adverse effect on the drug's identity, strength, quality, purity or potency. You may implement the changes included in this category without prior review by us. These changes should be managed within the relevant PQS and comply with the GMP requirements set out in of Division 2 of the regulations.

Examples of Level IV changes are provided in the associated guidance documents.

## Drug submission filing information

Refer to the Guidance on management of drug submissions and applications for instructions on submission filing, procedures and review target dates.

For your convenience, we have included some details from this guidance document in the following sections along with information on post-NOC change submissions.

### Pre-submission enquiries

The list of changes outlined in the associated guidance documents are not exhaustive. They do not cover all possible situations. If you're in doubt as to the reporting category or supporting documentation, you are encouraged to contact us, in writing, for clarification. Verbal enquiries should be followed up in writing. We will provide a written response within 15 calendar days of receiving a pre-submission enquiry.

We also encourage you to contact us about the number and proposed filing dates for planned changes to existing drugs,. This will help us plan how best to allocate our review resources. You should contact the appropriate directorate to determine the best method for submitting this information.

## Submission filing for Level I - Supplements, Level II - Supplements (safety) and NCs

### Items to be included in the submission

You should include the following items, where applicable, in the submission package for Level I – Supplements, Level II – Supplements (safety) and Level II – Notifiable changes:

- covering letter that includes:
  - the type of submission (for example, SNDS, SANDS, NC)
  - a brief description of the changes
- general note to reviewer that includes:
  - description of the changes, with a brief rationale
  - other relevant information
  - an indication of the general type of supporting data (for example, 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
- completed version of the appropriate forms and templates:
  - regulatory enrolment process (REP): used for applications for pharmaceutical, biologic and radiopharmaceutical drugs for human and veterinary use as well as disinfectants
- submission certification signed and dated
- patent information in accordance with the Patented Medicines (Notice of Compliance) Regulations
- GMP and drug establishment licensing (DEL) information
- letters of access for any supporting master files
- annotated (identifying any changes since the time of the last filing) and non-annotated electronic copy of the:
  - relevant CPID-B or CPID-R
  - PM
- Level I – Supplement label changes and Level II - Supplements (safety) label changes that require bilingual mock-up labels, along with either the:
  - Labels and Packages Certification Form for Prescription Products or
  - Labels and Packages Certification Form for Non-Prescription Drugs

Depending on the submission type, sponsors should provide any data required to support the changes in electronic format. Additional information is available in the following guidance documents:

- Preparation of regulatory activities in the eCTD format (available upon request)
- Regulatory enrolment process (REP): Drugs for human/veterinary use and disinfectants
- Preparation of regulatory activities in the non-eCTD format (available upon request)

Sponsors should also provide a quality overall summary (QOS-B) or quality information summary (QIS-R), where applicable.

## Level III – Immediate and annual notifications (minor quality changes)

All Level III - Notifications should be submitted using the Post-Notice of Compliance Changes: Notices of Change (Level III) Form. The data to be generated in support of the change are described in the associated guidance documents.

We may periodically audit Level III changes by reviewing the supporting data. We may ask you to file a Level I - Supplement or an NC (for biologic and Schedule C drug quality changes) if you have categorized the change incorrectly or the data to support the change is not acceptable. If we consider that the change has impacted the drug's safety, efficacy, quality or effective use and may be harmful to human health, we will apply section C.01.013 of the regulations.

You should only submit a copy of the revised annotated labels, PM/package insert, CPID or other data for a notification:

- when identified as necessary in the associated guidance documents **or**
- with the filing of the next Level I – Supplement, Level II – Supplement (safety) or Level II – Notifiable change (quality) that requires a label or quality change

You should clearly identify the dates of implementation for these Level III changes.

Many quality changes may affect a drug's labelling. Where the PM should be updated to support a change, it may be necessary to submit the labelling changes as a supplement even when the quality change is classified as a notification.

Level III label changes do not require that you submit mock-ups (as set out in the plain language labelling requirements).

## Level III - Immediate notifications

The supporting data to be generated with Level III – Immediate notifications are described in the section on associated guidance documents or as authorized as part of a PACMP. Supporting data not submitted with the notification should be available to us within 30 calendar days if requested at any time.

## Level III – Annual notifications

Annual notifications should include all Level III changes implemented for each drug that has received an NOC and that have occurred in the preceding 12 months. Refer to the Notice - Post-Notice of Compliance (NOC) Changes: Notices of Change (Level III) Form.

You should generate the supporting data for Level III – Annual notification changes recommended in the associated guidance documents before you make the change. Unless specifically identified, you do not need to submit this data. We may request the data at any time, in which case you will need to submit the information within 30 calendar days.

## Level IV - Changes not reported (quality changes with no impact)

The quality changes included in this category should be managed within the relevant PQS and comply with the GMP requirements set out in Division 2 of the regulations. You should annotate these changes in the affected documents (for example, CPID) and then include them when you file the next Level I or Level II quality submission.

## Associated guidance documents

Consult the appropriate guidance document:

- Post-notice of compliance (NOC) changes: Safety and efficacy
    - instructions on the categorization of a change
    - recommended supporting data for changes to safety and efficacy information (including labelling documentation) associated with the new drug
    - specific examples of changes
- Post-notice of compliance changes: Overall quality document for biologic and Schedule C drugs for human use
    - information common to biologic and Schedule C drugs related to changes to quality information (including labelling documentation) associated with the new drug
- Post-notice of compliance changes: Quality for biologics
    - instructions on the categorization of a change
    - recommended supporting data for any changes to quality information (including labelling documentation) associated with the new biologic drug
    - specific examples of changes
- Post-notice of compliance changes: Quality for Schedule C drugs
    - instructions on the categorization of a change
    - recommended supporting data for any changes to quality information (including labelling documentation) associated with the new Schedule C drug
    - specific examples of changes

# Acronyms

**ANDS**
abbreviated new drug submission

**CTD**
common technical document

**DIN**
drug identification number

**eCTD**
electronic common technical document

**DEL**
drug establishment licence

**EU-SNDS**

extraordinary use supplement to a new drug submission

**EU-SANDS**
extraordinary use supplement to an abbreviated new drug submission

**GMP**
good manufacturing practices

**ICH**
International Council for Harmonisation

**IVIVC**
in vivo/in vitro correlation

**NC**
notifiable change

**NDS**
new drug submission

**NOC**
notice of compliance

**NOL**
no objection letter

**PACMP**
post-approval change management protocol

**PQS**
pharmaceutical quality system

**QOS**
quality overall summary

**SANDS**
supplement to an abbreviated new drug submission

**SNDS**
supplement to a new drug submission

**YBPR**
yearly biologic product report

## Note about guidance documents in general

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide assistance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that Health Canada may consider alternative approaches to meeting the regulatory requirements that stakeholders may propose. However, to be acceptable, alternative approaches to the principles and practices described in this document must be supported by adequate justification. Stakeholders should discuss their proposals with the relevant program area in advance so that Health Canada can determine whether the applicable statutory or regulatory requirements can be been met.

Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and decisions are clearly documented.