Health Canada Santé Canada

Guidance document

Post-Notice of Compliance changes: Guidance for safety and efficacy of veterinary drugs

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

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Changements survenus après l'avis de conformité : Lignes directrices sur l'innocuité et l'efficacité des médicaments vétérinaires

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1. Overview

1.1 Objectives

This guidance helps to classify safety and efficacy changes made to new drugs that have received a Notice of Compliance (NOC) pursuant to section C.08.004 of the Food and Drug Regulations (the Regulations).

This guidance shows sponsors how to provide us with data that lets us:

- support a proposed label change
- determine the impact of the change on a new drug's safety, efficacy or effective use

1.2 Scope and application

This guidance document applies to sponsors intending to make changes to new drugs for veterinary use.

Read this guidance document in conjunction with:

- Post-Notice of Compliance changes: Framework document for veterinary drugs
- Post-Notice of Compliance changes: Quality guidance
    - A revised guidance for veterinary drugs is currently under consultation: Post-Notice of Compliance changes: Draft guidance for quality of veterinary drugs

Learn more about:

- General submission requirements, processes and standards

1.3 Background

This guidance applies to drugs for veterinary use only. This guidance document replaces the provisions in the Post-Notice of Compliance changes: Safety and efficacy document (2015).

1.4 Note about guidance documents in general

Guidance documents help industry and health care professionals comply with governing statutes and regulations. They also show Health Canada staff how to fairly, consistently and effectively meet mandates and objectives.

Guidance documents are administrative instruments, **not** legal ones. This means that they allow for flexibility. However, you must support alternate approaches to the principles and practices described in this document with adequate justification for Health Canada to accept them. Discuss your approaches with the relevant program area in advance to make sure you meet all statutory and regulatory requirements.

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

You should read this document along with the relevant sections of the Regulations and other applicable guidance documents

- The other applicable guidance documents are listed above under Scope and Application and Guidance for Industry: Preparation of Veterinary New Drug Submissions

2. Reporting categories

This section of the guidance provides criteria and examples to help you classify a safety or efficacy related change. Examples are **not** exhaustive and are meant to provide guidance on types of acceptable changes.

Contact the Veterinary Drugs Directorate submission office if you have questions or need help.

Email: vdd.skmd.so-dgps.dmv.cp@hc-sc.gc.ca

2.1 Level 1 changes: Supplements

2.1.1 Criteria

Level 1 changes are changes to a new drug that are "significantly different" as it relates to the matters specified in C.08.003 (2) of the Regulations. These are changes to the label of a drug that have the potential to increase the exposure levels of the drug, either by:

- increasing individual exposure **or**
- expanding the exposed population (market)

Label changes that can result in increased exposure levels of the drug include the:

- addition of a:
  - new strength
  - new dosage form
  - new route of administration
  - change in duration of treatment
  - change in recommended dose or dosing range
- deletion or reduction of existing risk management measures
- addition or expansion of a safety claim or efficacy claim, whether explicit or implied

This level also includes changes that don't meet the above criteria, but require the filing of a Level 1 change as per C.08.003 and C.08.005.1 of the Regulations. Examples include:

- Significant changes exclusive to label design elements.

- A submission for the purpose of obtaining a data protection extension.
- The brand name of the new drug has been changed, but the Drug Identification Number (DIN) remains the same.
- An existing indication has been modified or withdrawn in its entirety for risk or harm management, including a reduction in scope.
- An existing route of administration, dosage form and/or strength has been removed following the cancellation of the DIN(s).
- A submission for the purpose of obtaining data protection extension.

Learn more about:

- Data protection extensions

2.1.2 Examples

Examples of Level 1 changes include but are not limited to the following:

2.1.2.1 Changes to label text

Health Canada initiated label changes that may include, but are not limited to:

- the addition of a warning or caution
- the addition of a new contraindication
- a change in an existing contraindication
- tightening of clinical monitoring that requires a change to the labels or sections of the package insert

Changes to existing label text that reference any potential benefits of the drug (implied or explicit), including references to:

- possible claims regarding side effects
- claims regarding the safety profile or efficacy
- sub-populations, such as different age groups (puppies versus dogs) or production types (dairy versus beef cattle)

An existing contraindication, warning or cautionary text anywhere in the package insert that has been:

- deleted in its entirety
- modified to reflect a reduction or diminishment in:
    - risk or harm
    - a risk management measure
    - an existing withdrawal or withholding period

Note: changes from existing contraindications, warnings or cautionary texts may result from a range of supporting data, such as post-marketing data, safety studies and pharmacokinetic data.

Reordering text on the label necessary for the safe and effective use of the product, such as:

- moving label information to different panels
- changing the order of information presented on the principal display panel, including:
    - warnings
    - population
    - expression of strength
    - product name (proprietary and non-proprietary)

Examples of other label text changes may also include:

- A response to a Health Canada-issued advisement letter specifically soliciting a labelling only Supplement to an Abbreviated New Drug Submission.
- Changes regarding an adverse event or set of events to reflect an apparent reduction in risk or harm. This includes changes related to non-target species data.
- The existing text of the label or package insert has been deleted, reworded or otherwise modified to diminish a risk or harm management measure. This would include any change in the conditions of use as a result of new pharmacokinetic data related to a special or sub-population or new species.

2.1.2.2 Changes based on new data

These changes can include, but are not limited to, the addition of:

- a new species
- a delivery device
- a new route of administration
- a new dosage form or strength
- a revision to existing text of a current indication that received a NOC and was subsequently withdrawn
- a new indication or reintroduction of an indication that received a NOC and was subsequently withdrawn
- data from an efficacy or safety study in a special population

Other examples of these changes can also include:

- a change in condition of use from prescription to non-prescription status
- a change to the safety and efficacy study information of the package insert which results in a new claim, explicit or implied, such as:
    - listing of additional outcome measures
    - revision to the description of study design that implies a new benefit for a specific sub-population
- a change in the drug's mechanism of action that results in an explicit or implicit claim (as detailed in the clinical pharmacology for veterinary drugs section of the package insert)

2.1.2.3 Changes to label design

Changes to label design can include, but are not limited to:

- adding an innovative label to a package

- changing the size or colour of text or background in connection with:
    - product name (proprietary and non-proprietary)
    - dosage and strength
    - population
    - route of administration
    - warnings
    - storage
- changing the package design, where the package is the immediate container
- changes that will impact readability of key elements of the inner or outer label, such as:
    - reducing overall label size
    - increasing the size of company logo or graphics
    - adding new graphics or symbols other than symbols required by regulations
    - changing locations of graphics (such as adding a symbol related to the type of packaging)

2.1.3 Submission filing

File changes included in this reporting category, along with the recommended supporting data, with Health Canada as a:

- Supplement to New Drug Submission (SNDS) **or**
- Supplement to Abbreviated New Drug Submission (SANDS)

Do **not** implement Level 1 changes until you receive a NOC.

2.2 Level 2 changes: Notifiable changes

2.2.1 Criteria

A Level 2 notifiable change is a change to the label that could improve the management of risks or harms to the population currently indicated for use of the drug, or in any other way exposed to the drug by:

- identifying or characterizing any risk or harms
- identifying subgroups or conditions of use where the benefit or risk profile of the new drug could be less favourable
- adding or strengthening risk management measures, including instructions on dosing or any other conditions of use

2.2.2 Examples

Examples of Level 2 changes include, but are not limited to:

2.2.2.1 Changes to label text

Text additions that strengthen or clarify information anywhere in these labelling sections:

- cautions
- warnings
- adverse events

- contraindications

These additions may include recommended risk or harm management actions such as:

- ensuring awareness of certain risks
- specific monitoring during product use
- required testing prior to initiation of the drug

These additions may also include the identification that a specific sub-population is at greater risk, such as:

- a specific age group
- those with a concomitant condition
- those taking concomitant medicine

These changes can also include:

- changes made to these sections of the package insert:
    - toxicology
    - microbiology
    - pharmacology
- changes related to the overdose section, such as additional overdose signs or treatments
- improving the clarity of the information in the animal owners section of the package insert
- revisions to existing label text to add clarity to the safe use of the drug, but without expanding, explicitly or implied, the claims of the drug
- rewording or altering the package insert, including dosage and administration, with respect to risk or harm management to optimize the safe use of the drug

2.2.2.2 Changes based on new data

Examples of these changes can include, but are not limited to:

- An existing drug interaction has been better characterized.
- Additions or changes to text or data (other than Level 3 changes):
    - for which the sponsor is not seeking a statement that may be interpreted as a new claim
    - that do **not** result in any other changes to the information provided to the veterinarians or animal owner
- A change to the toxicology data, explicitly or implied, stating an increase in risk or harm to the target population.
- A new drug interaction or pharmacokinetic study has been added and does not expand the claim of the drug, explicitly or implied.

2.2.3 Submission filing

File any changes included in this reporting category to Health Canada as a Level 2 notifiable change. Include your recommended supporting data. Sponsors should **not** implement Level 2 changes until issued with a No Objection Letter.

Note: Some changes that meet the Level 2 criteria may require sponsors to file a Level 1 change.

3.3 Level 3 changes: Annual notifications

3.3.1 Criteria

Level 3 or annual notifications are changes to a label that have minimal potential to impact the safety, efficacy or effective use of the drug. Sponsors can implement changes included in this reporting category without Health Canada reviewing the data supporting such a change beforehand.

3.3.2 Examples

Examples of Level 3 related changes include but are not limited to:

- Any change in spelling of the text of the label, including correcting spelling errors
- Any change to the layout of the label that does not represent a change to the requirements of:
    - the terms of market authorization
    - Sections C.01.004 and A.01.016 of the Regulations (such as font, contrast, artwork and position)
- The existing text of the labels have been revised to add clarity and maintain consistency with common label phrase standards, such as 'Keep out of reach of children'.

For non-prescription drug products, examples of Level 3 changes include but are not limited to the following non-significant label changes:

- Correcting spelling errors
- Updating contact information such as:
    - website addresses
    - a customer service number

3.3.3 Submission filing

File your notification of a Level 3 label change:

- at the time the change is implemented, **or**
- during the annual drug notification period in accordance with C.01.014.5 of the Regulations

Only submit a copy of revised annotated labels and package inserts when you file the next Level 1 or 2 changes that necessitate a label or quality change as well. Clearly identify the implementation dates for these Level 3 changes.

Do not submit supporting data for Level 3 changes recommended in this guidance document. However, the data should be available to Health Canada within 30 calendar days of a request.

File your changes using the Post-Notice of Compliance changes: Level 3 form.

3. Pre-submission enquiries

Contact Health Canada **before** filing a submission if any of the following conditions apply to the proposed change:

- For Level 1 changes, the data package is comprised solely of publications.
- The clinical study makes use of an end point or statistical method that is new or not validated.
- The clinical study does not reach statistical significance for the primary endpoint or the endpoint used to support the change.
- The clinical study made use of a comparator authorized but not available on the Canadian market.
- For subsequent entry products (generic drugs) where the:
    - Canadian reference product is no longer marketed
    - clinical study or publication makes use of a non-Canadian reference product as a comparator
    - sponsor seeks approval of a strength outside of the Canadian reference product dosing range

Sponsors should also contact us before filing a submission if:

- you wish to discuss product specific data requirements
- the existing guidance or policies are unclear or do not cover specific situations

Depending on the issue or concern, we may arrange a pre-submission meeting to allow for more in-depth discussion.

Learn more about:

- Use of a foreign-sourced reference product as a Canadian reference product

Contact us

Email: vdd.skmd.so-dgps.dmv.cp@hc-sc.gc.ca.

4. Documentation

Health Canada is responsible for:

- assessing drug submissions received for a changes to new drugs
- making decisions based on evidence and context within a specified time frame

This section highlights the range in categories of data and contextual information that may be relevant to the evaluation of a particular submission.

We can optimize our regulatory decision-making if you provide us with contextual information, such as:

- the sponsor's interpretation of the data
- the interpretation by other major international agencies (for example, as per labels approved by that jurisdiction)
- information that no other major agency has rendered an opinion on at the time of the evaluation or if discussions are currently underway
- characterization of the treated population in question
- regional clinical practice standards
- the availability of alternative therapies
- The presence of an information category in these lists does not necessarily mean the data is required. However, when a specific topic is relevant to a submission, the sponsor should acknowledge and address it by providing the information **or** a rationale as to the absence of the information.

This will help to minimize delays that can result when a submission is silent on a relevant topic. Health Canada may accept alternate approaches to the principles and practices described in this document if they're supported by adequate justification.

Include or comment on the recommended data in the submission package for Level 1 and 2 changes, where applicable.

4.1 Filing formats for submission supporting data

Prepare and file the data that supports the changes as prescribed in:

- Guidance for Industry: Preparation of Veterinary New Drug Submissions
- Guidance Document: Preparation of regulatory activities in non-eCTD format

4.2 Supporting data for Level 1 and 2 changes

Provide clinical and/or non-clinical study data relevant to the submission. This may include but is not limited to:

- bioequivalence studies

- risk management plans
- pharmacokinetic studies
- pharmacodynamic studies
- pharmacovigilance plans
- pharmacovigilance studies
- epidemiological data and study results
- Periodic Safety Update Report data
- clinical studies (whether focused on efficacy or safety)
- review reports and analyses of specific safety concerns

Provide other data which may be relevant to the submission. This may include, but is not limited to:

- rationales
- real world information regarding drug use
- publications in peer-reviewed scientific journals
- conference presentations
- drug utilization information
- opinion papers
- declarations and attestations

Where applicable, sponsors should submit a complete set of labelling in both official languages, including:

- inner labels
- outer labels
- package insert
- all sizes of labels

Submit these labels as an annotated electronic copy of the labels in a Microsoft Word document with tracked changes, comparing the previous approved labelling version. This includes tracking in a new version date, which should appear in the footer or header of each page.

If you provide the proposed labelling as a PDF, you must submit an annotated and non-annotated version. In the annotated version:

- highlight additions to the text
- indicate deletions using strikeouts
- make sure there are no comment bubbles

Provide supporting data and explanations for the proposed changes in a separate document within the submission.

4.3 Contextual information

Contextual information may include copies of the most recent labels authorized in other major regulatory jurisdictions. These jurisdictions must be within the International Council for Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), including:

- NZ Ministry for Primary Industries
- UK Veterinary Medicines Directorate
- European Union European Medicines Agency
- Australian Pesticides Veterinary Medicines Authority
- US Food and Drug Administration Center for Veterinary Medicine

Contextual information may also include:

- relevant correspondence or communications from other major VICH regulatory jurisdictions **or**
- a statement confirming that such communications have not been required by any authorities

For subsequent entry products (generic drugs), include the revision date of the package insert of the Canadian reference product used in preparation of the generic sponsor's package insert.

4.4 Additional contextual information: Level 1 changes

Include the current submission status with other major VICH regulatory jurisdictions. For example, at the time of submitting the proposed change to Health Canada, specify if the changes are:

- rejected
- approved
- not submitted
- currently under review

If other major VICH regulatory jurisdictions have finished their review, include a:

- summary of any significant issues raised and how they were addressed and resolved, **or**
- statement confirming that there were no significant issues identified by those authorities

Where available, include copies of any foreign review reports, correspondence or communications (including questions and answers) which may be relevant to the submission.

If other major VICH regulatory jurisdictions have not completed their review, include a summary of any significant issues being raised.

4.5 Additional contextual information: Level 2 notifiable changes

Additional contextual information can include:

- wording of any related instructions or communications to veterinarians that may have been or is currently required in other major VICH regulatory jurisdictions **or**
- a statement confirming that authorities do not require such instructions or communications

Include the most recent electronic or hard copy of the Periodic Safety Update Reports. Health Canada can cross-reference them against previous versions, if relevant.

4.6 Supporting data for Level 3 changes

Do not submit any data that supports a Level 3 change with your notification. However, make sure it is available to Health Canada within 30 calendar days of a request.

5. Glossary

Adverse drug reaction

As defined in the Food and Drug Regulations means a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function.

Adverse event

Any untoward medical occurrence in animals and/or humans involved in administering a veterinary drug to an animal and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (such as an abnormal laboratory finding), or disease temporally associated with the use of a drug product, whether or not considered related to the drug product.

Claim

A word, sentence, picture, symbol, graph or paragraph on product labels, package inserts or advertisements where the representation for sale is capable of being understood as:

- the capacity of producing a desired result or effect in terms of efficacy
- being safe or comparatively safer from undergoing or causing undue hurt, injury or loss as safety claims

Therefore, a claim may include any representation or statement that would communicate a "positive" interpretation of the drug product rather than a potential risk or harm.

Claims can be considered as explicit or implied by using the following:

i. Choice of language:

- Explicit is when the representation for sale is fully revealed or expressed without vagueness or ambiguity leaving no question as to meaning or intent.
- Implied is when the representation for sale is capable of being misunderstood or misinterpreted so as to imply or suggest something in addition to what is explicit.

ii. Placement within the package insert:
- There are 2 sections of the package insert intended for explicit claims: Indications and Target animal efficacy section.
- The remaining sections of the package insert are not expected to include claims, and if present, would typically be considered as implied.

Conditions of use

Any language used in the labels or package insert that provides instructions or recommendations (explicit or implied) to the prescriber or animal owner regarding the use of the product.

Innovative label

Examples of innovative labels include peel-back, fold-out etc. They must comply with applicable regulation and guidance documents.

Label

Label includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package. Examples include the package insert, and inner and outer labels. (Food and Drugs Act)

Mock-up

A full colour, actual size copy of the labels and a colour representation of the packages intended to be used for the sale of the drug, including all:

- text
- fonts
- colours
- proposed graphics
- presentation and design elements

Mock-ups include a place holder for expiry date, drug identification number (DIN), and lot number.

New drug

As per section C.08.001 (for the purposes of the Act and Division 8 of the Food and Drug Regulations), new drug means a drug, other than a veterinary health product:

A. that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug

B. that is a combination or two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug
C. with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug

Package

Package includes anything in which any food, drug, cosmetic or device is wholly or partly contained, placed or packed. (Food and Drugs Act).

Package insert

The factual, scientific document for a veterinary drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug.

Pharmacovigilance studies

Studies involving the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

Withdrawal period

The length of time between the last administration of a drug to an animal and the time when tissues or products collected from the treated animal for consumption as food contain a level of residue of the drug that would not likely cause injury to human health. (Section C.01.001 (1) of the Food and Drug Regulations).

Withholding time

Refers to the length of time, specified in 12-hour milking intervals, up to maximum of 8 intervals (96 hours) that must elapse after treating a lactating animal with a veterinary drug before milk can be collected for human consumption.