Health Canada Santé Canada

Regulatory cooperation- Canadian guidance on veterinary drug simultaneous reviews with the United States

Canada

Foreword

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance 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 flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They 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 always, 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 that decisions are clearly documented.

This document should be read along with the relevant sections of other applicable guidance documents.

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Overview

Purpose

This Health Canada guidance outlines the Canadian process for simultaneously reviewing veterinary drug submissions by:

- Health Canada's Veterinary Drugs Directorate (VDD) and
- U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM)

The review is conducted under the Regulatory Cooperation Council (RCC) initiative.

The purpose of the simultaneous review process is to create a more favourable environment for manufacturers and animal owners without compromising domestic standards and scientific rigour. The process:

- offers simultaneous access to 2 major markets for veterinary drug manufacturers
- encourages harmonization where possible while respecting independent, sovereign decision-making by the 2 regulators
- provides faster access and more treatment options for Canadian animal owners and food producers
- creates a stronger global review community that allows both regulators to share knowledge and expertise

Note: Unless indicated, “sponsor” means the Canadian manufacturer that has filed a new drug submission or a supplement to a new drug submission. Unless specified, “submission” means the Canadian veterinary new drug submission or a supplement to the new drug submission as submitted to VDD.

For questions about the U.S. process, send an email to AskCVM@fda.hhs.gov.

For information on administrative processes and data requirements for Canadian veterinary drug submissions, please consult:

- Guidance documents on legislation and guidelines for veterinary drugs

Defining a simultaneous review

Simultaneous reviews may occur when manufacturers submit a veterinary drug submission to both regulators at the same time. Typically, simultaneous reviews with CVM are reviewed in a rolling fashion. Subsections C.08.002(8) and (9) and C.08.003(8) and (9) of the *Food and Drug Regulations* (regulations) set out the requirements for a rolling collaborative review with a foreign regulatory authority.

Submissions must also meet all applicable Canadian regulatory requirements. Health Canada conducts our evaluation independently, in parallel with the U.S. evaluation, with the objective of issuing regulatory decisions at the same time.

The simultaneous review process typically follows CVM's phased review process. For this process, a sponsor may file all or part of the data or information needed to address the regulatory requirements of both countries at the most appropriate and productive times in the drug development process. If all the data is filed at the same time, the simultaneous review is not considered a rolling review.

Simultaneous review involves exchanging submission information between the regulators and the sponsors. This exchange between the U.S and Canadian regulators is facilitated by the “Confidentiality Commitment Statements of Legal Authority and Commitments” between our Health Products and Food Branch and the FDA.

Eligible products

When indicating their intent to conduct a review of the submission with a foreign regulatory authority under paragraphs C.08.002(8)(a) or C.08.003(8)(a) of the regulations, the Minister will consider the submission's eligibility for the pathway.

Eligible submissions may be for new veterinary drug products or for new uses of veterinary drug products that already hold marketing authorizations in both countries. In Canada, this includes a new drug submission (NDS) and supplement to a new drug submission (SNDS).

The veterinary drug product submitted for review must:

- not have been subject to relevant or significant safety-related regulatory action in either country
- be identical in formulation and manufacturing in each country, including the source of the medicinal ingredient
    - may be differences in product labels

Submissions for drug products for minor uses/minor species (MUMS) are encouraged. New biologic entities are handled on a case-by-case basis.

The following are **not** eligible for simultaneous review at present:

- veterinary health products as defined in section C.01.001 of the regulations
- products that are seeking to be indexed in the U.S.
- products seeking approval in the U.S. through expanded conditional approval or conditional approval under the U.S. *MUMS Act*

As well, products are not eligible for this process if they cannot be reviewed at the same time, for example, if:

- the sponsor has already filed the submission in Canada and VDD has accepted the submission into review
- 1 or more technical sections have been filed and are already under review in the U.S.

Sponsors interested in filing a submission for a generic drug under the RCC pathway should contact VDD to discuss the drug product's eligibility.

Pre-submission

Expression of interest

Early interactions by industry with the regulators are important for assessing the feasibility and admissibility of a submission. We encourage sponsors to learn about the simultaneous review process and to begin a dialogue with both regulators as soon as possible. This should be at the protocol or investigational/experimental study stage.

Sponsors should send an expression of interest by emailing the Veterinary Drugs Directorate (VDD) at vdd.international-international.dmv@hc-sc.gc.ca. VDD will work with the sponsor to answer any questions and set up a pre-submission meeting if one has not yet taken place.

Pre-submission discussions

Pre-submission discussions help to inform the Minister's decision on whether to conduct a review of the submission with the U.S. Center for Veterinary Medicine (CVM) under paragraphs C.08.002(8)(a) or C.08.003(8)(a) of the *Food and Drug Regulations* (regulations). This is an exploratory meeting between the sponsor, including its representatives in both countries, and both regulators.

The sponsor introduces their new drug product or new claim to the regulators and discusses whether the product is a good candidate for this process.

Where possible, VDD encourages sponsors to request joint pre-submission discussions. Pre-submission discussions may also be held just with VDD if the sponsor:

- has already held a pre-submission meeting with CVM **or**
- wishes to clarify Canadian requirements

The sponsor should:

- present a plan for submitting missing information intended to satisfy subparagraphs C.08.002(8)(b)(i) or C.08.003(8)(b)(i) of the regulations and
- indicate if the submission is a comparative submission

For more information on pre-submission meetings with VDD, please consult:

- Management of regulatory submissions guidance

Intent to conduct a simultaneous review

Sponsors wishing to pursue a simultaneous review must send a formal letter to VDD outlining their request. An authorization permitting the discussion and exchange of product information between VDD and CVM should accompany the letter.

VDD and CVM will then consult on whether the veterinary drug submission is an appropriate candidate for the Regulatory Cooperation Council (RCC) pathway.

On behalf of the Minister, VDD will issue a formal letter to the sponsor. The letter will indicate our intent to conduct a simultaneous review of the submission with CVM. This formal letter is outlined in paragraphs C.08.002(8)(a) or C.08.003(8)(a) of the regulations.

The letter asks the sponsor to:

- confirm their participation in the simultaneous review process and
- authorize VDD to discuss all information included and related to the submission with CVM

This letter also outlines VDD's expectations for the simultaneous review process.

At this stage, VDD informs CVM about the sponsor's intent to conduct a simultaneous review.

Expectations for sponsors

The technical information about the drug and packages that the sponsor submits to both regulators should be identical in every way (for example, drug formulation, proposed dosage, proposed indication). Both regulators should receive the submissions at relatively the same time.

Sponsors should submit any amendments requested during the review process to both regulators. Please note that VDD and CVM will be invited to participate in or observe all sponsor-regulator meetings or teleconferences related to the review of any technical sections.

The success of a simultaneous review depends on open and constant communication between the regulators and sponsors, and between sponsors and the Canadian and U.S. affiliates. Good communications:

- supports a streamlined and timely review process
- ensures informed decision-making
- contributes to greater harmonization between the regulators

For this reason, VDD asks that sponsors commit to:

- sharing identical information with both regulators at the same time
- establishing strong communication channels with both regulators and drug sponsor counterparts by, for example:
    - submitting all additional information related to the submission to both regulators, such as information submitted in response to:
        - VDD's request for information or
        - CVM's “technical section incomplete” letter or other requests for information (such as through email)
    - inviting both regulators to all sponsor-regulator meetings or teleconferences related to the review of the submission
    - having regular meetings between the Canadian and U.S. sponsors (if different) to coordinate a streamlined filing process

Study protocols and experimental studies

Study protocols and experimental studies are designed and conducted to support a future regulatory submission for market authorization of a drug product.

If a study is conducted in Canada, sponsors may be required to acquire an Experimental Studies Certificate (ESC). For more information on ESC requirements, please consult the ESC application.

If the study does not require an ESC (for example, it takes place outside of Canada), the sponsor may still wish to seek VDD's review of study protocols. We strongly recommend this for:

- pivotal studies that are conducted outside Canada
- new or novel studies that lack established guidelines

If a sponsor does not wish to seek VDD's advice on a study protocol, they should still submit the protocol to VDD when submitting to CVM. This applies to other types of study protocols as well.

Submitting these types of study protocols to VDD gives us a chance to reference the protocols through the simultaneous review process and communicate with CVM about these studies, as needed.

Learn about:

- Fees associated with protocol reviews

Submission filing

Coordinated filing

The sponsor must file data with both the Veterinary Drugs Directorate (VDD) and the U.S. Center for Veterinary Medicine (CVM) at the same time. The sponsor should let VDD know as soon as possible if they foresee any delays in filing. The sponsor will need to obtain agreement to ensure the late filing does not affect the simultaneous review process.

The sponsor must send in a submission plan when they file their submission. The sponsor should also send in an updated submission plan when they file subsequent data packages.

Electronic filing and submission format

Use electronic tools, such as the Regulatory Enrolment Process (REP), to send in submissions to VDD.

Submissions should be in electronic-only format. For reference, please refer to the following guidance document:

- Preparation of drug regulatory activities in the non-eCTD electronic-only format

VDD will place the submission on process hold if:

- the submission does not follow this format
- the file path name is too long or
- the forms are missing or not signed

We recommend that sponsors use 1 of the following 2 format options for the RCC pathway:

1. organize all data according to the folder structure within the Canadian drug registration framework
    - please consult the following:
        - folder structure for veterinary drugs' zip file (refer to the Non-eCTD format only section of Filing submissions electronically webpage)
        - Preparation of drug regulatory activities in the non-eCTD electronic-only format
2. submit the files using the U.S. file submission structure as follows:
    - submit a crosswalk to the Canadian table of contents that clearly indicates the location of the information and highlights country-specific deviations
    - name the main folder with the dossier ID number
    - name the subfolder using the CVM submission identifier, which includes the 8-character INAD number before the P/G/H-submission number
    - make sure the folder and file names are meaningful

Option 2 is preferred as it opens up discussions between regulators and reduces the chance of missing documents.

Sponsors should discuss how they will file their submission at the pre-submission meeting.

Filing date and administrative completeness

The Canadian official filing date is when a submission is deemed administratively complete. This is when all elements and forms required for processing are completed and have been submitted to Health Canada. This date may differ from the date of original receipt should the submission or application be considered administratively incomplete at that time.

If the information received in a submission does not meet all applicable administrative requirements, the submission will be placed on process hold. Examples of not meeting the requirements include:

- non-eCTD electronic-only format was not followed
- file path name is too long
- forms are missing or incomplete

The sponsor is not required to submit all sections in order for the submission to be considered administratively complete if the requirements of C.08.002(8) or C.08.003(8) have been met. For a submission to be considered administratively complete, it must contain at least the following elements:

- submission certificate and
- a major data package

When submitted within the REP, you must use the following file:

- REP regulatory transaction (RT) file and REP product information (PI) file

To meet the requirements of C.08.002(8) or C.08.003(8):

- the Minister must have indicated an intent to conduct a review of the submission with the CVM
- there is a submission plan
- some or all of the information required under any of the paragraphs C.08.002(2)(d) to (h), (m) and (n) (a major data package) is included
- there must be a drug identification number for the drug that is being referenced as a direct or indirect comparison (if applicable)

A major data package means a technical section that contains 1 of the following:

- a description of the plant and equipment to be used in manufacturing, preparing and packaging the new drug (C.08.002(2)(d))
- details of the method of manufacture and the controls to be used in manufacturing, preparing and packaging the new drug (C.08.002(2)(e))
- details of the tests to be applied to control the potency, purity, stability and safety of the new drug (C.08.002(2)(f))
- detailed reports of the tests made to establish the human or animal safety of the new drug for the purpose and under the conditions of use recommended (C.08.002(2)(g))
- substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended (C.08.002(2)(h))
- evidence that all test batches of the new drug used in any studies conducted in connection with the submission were manufactured and controlled in a manner that is representative of market production (C.08.002(2)(m)) **or**
- the withdrawal period of the new drug (C.08.002(2)(n)) administered to food-producing animals

For details on specific document requirements for each major data package, consult:

- Guidance for industry preparation of veterinary new drug submissions

The contents of a major data package are similar to the contents of a CVM P submission.

Fees

The sponsor should not include payment when they file a technical section. We will verify and adjust the fee, and issue an invoice if applicable.

When we invoice depends on the nature and timing of receipt of the technical sections. Invoicing typically occurs in stages after the last technical section of the clinical, quality or human safety sections are accepted for review.

For more information on the fee process, consult the following guidance document:

- Fees for the review of veterinary drug submissions and applications

VDD encourages sponsors to confirm applicable Canadian fees before they submit. For updated fee amounts, refer to:

- Veterinary drug submission application and fee form

Data requirements

The content in the submission sent to VDD should be the same as the content in the U.S. submission. Any documents required by CVM, including administrative documents, must also be submitted to us.

Submissions to VDD must meet all applicable Canadian regulatory and administrative requirements. For more information on the specific administrative requirements for veterinary drug submissions, consult:

- Guidance for industry preparation of veterinary new drug submissions, Part I: Requirements for master volume

There may be additional or different data requirements that are specific to Canada only.

Note that all Canada-specific data requirements for new drug submissions (NDS) and supplements still apply to drug submissions under the Regulatory Cooperation Council (RCC) pathway. Examples of data requirements include the certified product information document (CPID) and quality overall summary (QOS).

For more information, refer to the relevant guidance documents:

- Guidance documents – Legislation and guidelines – Veterinary drugs

Technical sections

Sponsors should submit technical sections to VDD with the related “acknowledgement of receipt” from CVM.

Unsolicited information

Information that is not required by VDD can be submitted as part of the drug submission but must be labelled “unsolicited information” and accompanied by a summary description. While VDD may look at any provided unsolicited information, we do not review the information for its compliance with the regulations.

Examples of unsolicited information include a memorandum of conference, a technical section complete letter and a technical section incomplete letter.

Environmental data

Submissions that include environmental data help us assess the potential risk to the environment and human health from environmental exposure to substances in veterinary drugs under the *Canadian Environmental Protection Act, 1999* (CEPA).

For more information and guidance on environmental data and requirements under CEPA, email the Environmental Assessment Unit at eau-uee@hc-sc.gc.ca.

Environmental data that is not specifically solicited by VDD may be submitted as “unsolicited information”, along with a brief description of the information.

Submission plan

A sponsor should submit a submission plan with the request to participate in the RCC pathway. The plan should specify when the sponsor intends to provide the missing information and consider a scenario where the sponsor cancels the submission.

Sponsors must submit an up-to-date submission plan at the time of initial filing.

Review process

Submission completeness check (screening)

Health Canada's Veterinary Drugs Directorate (VDD) first looks at the drug submission to ensure it is in an acceptable format and contains sufficient information to enable a proper review.

If there are questions about the content of the submission during this initial screening process, VDD sends a communication to the sponsor, with a copy to the U.S. Center for Veterinary Medicine (CVM). The sponsor should copy CVM on its responses to VDD. VDD should also be copied on any responses to CVM.

Sponsors must ensure that at the end of the screening process, submissions to VDD and to CVM are identical and that no data is missing.

At the end of the screening process, VDD sends a letter to the sponsor indicating that the submission has been accepted for review.

Clarification requests

Once a submission is in review, VDD will discuss the submission, including any questions for the sponsor, with CVM. These discussions continue throughout the submission process. Any questions about the submission are sent to sponsors in the form of a clarification request or a notice of deficiency. This is outlined in the following guidance:

- Veterinary drugs - Management of regulatory submissions

Sponsors are given a certain amount of time in which to submit their responses. Extension requests are considered alongside CVM response timelines.

Sponsors are expected to share their responses to VDD's questions with CVM, and vice versa.

Information reviewed letters

Technical sections of a submission that go through the Regulatory Cooperation Council (RCC) pathway are reviewed on a rolling basis. When applicable, VDD will send an “information reviewed letter” to the sponsor when we have reviewed a technical section and there are no further comments at that time. This letter does not include a decision on the compliance of a technical section.

Meeting requests

Sponsors who wish to meet with VDD at any point during the submission review process must also inform and invite CVM to participate. VDD must also be invited to any discussions with CVM.

Sovereign decision

VDD makes its own sovereign decision in accordance with relevant Canadian legislation.

VDD will undertake the necessary Canadian administrative and legal steps relating to the issuance of a market authorization or negative decision. As much as possible, we will synchronize the timing of communications related to the issuance of decisions with CVM.

Once a product has received market authorization in Canada, the sponsor is responsible for meeting applicable Canadian post-market regulatory requirements. VDD will continue to collaborate and exchange information with CVM to support post-market monitoring, risk assessment and risk management activities, as appropriate.

If there is a negative decision by 1 or both regulators, the sponsor is encouraged to discuss options on how to address deficiencies with VDD, based on the Canadian framework.

VDD will consider opportunities to harmonize maximum residue limits and product labelling when appropriate.

Timelines for review

VDD aims to issue decisions made throughout the RCC process at roughly the same time as CVM. Sponsors should confirm timelines with both regulators before filing a submission.

Cancellation process, contact us

Cancelling

Sponsors who wish to continue to seek marketing authorization in Canada but not continue with the simultaneous review process must file a new drug submission (NDS) or supplement to a new drug submission (SNDS) to Health Canada's Veterinary Drug Directorate (VDD).

For more information, please consult the following guidance:

- Veterinary drugs - Management of regulatory submissions

The standard VDD review process and targets will apply to the newly submitted submission.

Contact us

For questions on the Canadian RCC regulatory process, contact:

Veterinary Drugs Directorate
Health Products and Food Branch
Health Canada

To express interest in the Regulatory Cooperation Council (RCC) pathway before filing a submission, email:

- vdd.international-international.dmv@hc-sc.gc.ca.

For questions on the Experimental Study Certificate, protocol review, pre-submission meeting and general submission-related inquiries, email:

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

Crosswalk example

This is a fictitious example of a Canadian table of contents that is cross-walked to the U.S. dossier for a submission undergoing simultaneous reviews with the U.S. Center for Veterinary Medicine (CVM). The example focuses on “Part IV: Requirements for efficacy” of the technical section.

Sponsors must provide a complete table of contents, fill out the relevant sections and ensure each submitted technical section is complete. Contact VDD for the complete crosswalk template and requirements for completion.

The crosswalk to the table of contents is similar to Appendix V, “Master Index” of the Guidance for industry preparation of veterinary new drug submissions. However, the crosswalk to the table of contents includes subsections that apply to submissions undergoing simultaneous reviews only, for example:

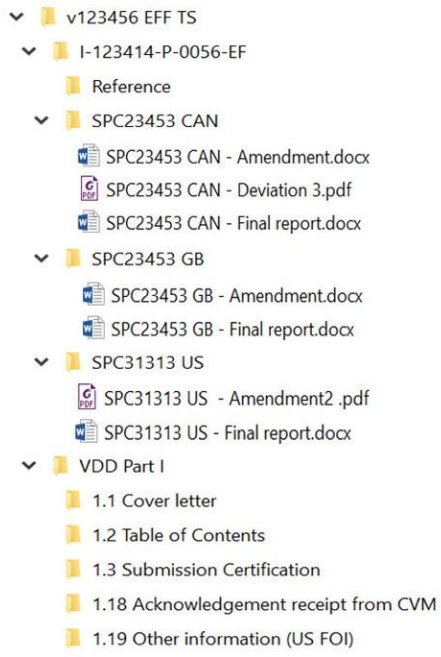
- “Acknowledgement receipt from other regulatory jurisdictions” for Part I, “Master Volume”
- “Protocol concurrence letters” for some technical sections

In the following example, the date of submission refers to the date on which the sponsor submits the information to Health Canada's Veterinary Drugs Directorate (VDD).

Note the following:

- date of submission should be identical to the date of the cover letter submitted to VDD in the data package
- last column, location of information, should include the folder name, file name and location in submission
    - if not applicable, provide a justification such as “not applicable”, “to be provided in the future” or “see previously approved submission”

Sponsor's folder structure



398 Table of content based on the folder structure

Table of content			
Information		**Date of submission to VDD (Month DD, YYYY)**	**Location of information (Folder level 1 / Folder level 2 / Folder level 3), file names or other justification**
Part IV: Requirements for efficacy (Please include the provided study numbers and titles under each subsection.)			
4.2	Sectional reports		
4.2.1	Microbiology studies		
4.2.2	Laboratory studies		
	SPC12345-PK: Pharmacokinetics in rats following oral administration	April 1, 2022	v123456 HFS TS / I-123414-P-0052-HFS / SPC12345-PK
	SPC23453 GB: Non-pivotal laboratory efficacy study in dogs for 5 days	September 1, 2022	v123456 EFF TS / I-123414-P-0056-EF / SPC23453 GB • SPC23453 GB - Amendment.docx • SPC23453 GB - Final report.docx
4.2.3	Animal model efficacy studies		
	SPC23453 CAN: Pharmacokinetics in dogs after topical administration	September 1, 2022	v123456 EFF TS / I-123414-P-0056-EF / SPC23453 CAN • SPC23453 CAN - Amendment.docx • SPC23453 CAN - Deviation 3.pdf • SPC23453 CAN - Final report.docx

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