Draft guidance on terms and conditions for human and veterinary drugs

This guidance document is being distributed for comment purposes only.

Draft date : 2025-12-12

Health Canada Santé Canada

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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 the regulations and other applicable guidance documents.

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Overview

Purpose

This document provides guidance to manufacturers and Health Canada staff on the use of the terms and conditions (T&Cs) regulatory authority in accordance with Part C, Division 1, section C.01.014.21 of the Food and Drug Regulations (FDR).

Introduction

The Food and Drugs Act (FDA) and its regulations give Health Canada the authority to regulate food, drugs (including natural health products and veterinary health products), medical devices and cosmetics. As a drug regulator, our role is to verify that regulatory requirements for the safety, efficacy and quality of human and veterinary drugs are met through scientific assessments. This includes issuing product and establishment licensing, conducting monitoring and surveillance, and carrying out compliance and enforcement activities.

To be authorized for sale in Canada, drugs for human and veterinary use (excluding natural health products and veterinary health products) must meet certain requirements under the FDR. They must also satisfy all applicable requirements in Part C, Division 1. As well, drugs that meet the definition of a new drug under Part C, Division 8 of the FDR must also satisfy the requirements of Division 8 to be authorized for sale.

When we authorize a drug to be marketed in Canada, we assign a drug identification number (DIN) to the manufacturer, which is printed on the package labels. A DIN indicates that the evaluation of the drug determined that it met the relevant requirements of the FDA and its regulations, and that it has a favourable benefit-risk profile.

Manufacturers of prescription and non-prescription drugs must obtain a DIN before they are marketed in Canada. For new drugs that fall under Division 8 of the FDR, market authorization requires that a notice of compliance (NOC) also be issued.

The DIN assigned to a drug is unique and helps with the post-market activities of products on the market, such as:

- product identification and verification by health care professionals
- recall of products
- inspections
- quality monitoring

For information on DINs, refer to:

- Guidance document: Regulatory requirements for drug identification numbers (DINs)

On December 6, 2013, the Government of Canada introduced the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law). On November 6, 2014, it received Royal Assent.

Vanessa's Law introduced amendments to the FDA that allow implementing a lifecycle approach to regulating drugs and medical devices. These amendments improve our ability to collect post-market safety information and take appropriate action when we identify a serious risk to health. We introduced these amendments to better protect patient health and safety and increase consumer confidence in therapeutic products on the market.

The Vanessa's Law amendments also gave the Governor in Council the authority to make regulations under the FDR and the Medical Devices Regulations (MDR) that support the life-cycle approach to regulating drugs and medical devices.

The rapid pace of innovation in industry can lead to significant uncertainties and risks for therapeutic products. These may not be adequately managed through existing regulatory provisions. For this reason, we amended the FDR to include new authorities that allow T&Cs to be imposed and amended on the DIN of a drug. T&Cs are obligations on the market authorization holder (MAH). These obligations may include conducting activities related to the authorized drug when significant uncertainties about a drug's benefits or risks have been identified or to manage identified or potential risks of a drug.

Scope and application

This draft guidance document applies to drugs regulated under Part C, Division 1 of the FDR that are assigned a DIN and the application of T&Cs. It explains the purpose of T&Cs and the processes that apply for imposing them on a DIN.

For this document, "drug" is for human and veterinary use (excluding biocides, natural health products, veterinary health products and some veterinary biologics) and includes:

- pharmaceuticals
    - prescription
    - non-prescription
- biologics
    - therapeutic products made from living organisms or cells
    - vaccines (for human use which includes prescription and non-prescription)
- radiopharmaceuticals

Policy objectives and statements

For a drug to be considered for market authorization, it must be supported by sufficient information as required by the FDR. Data establishing the safety, efficacy and quality of a drug must demonstrate a favourable benefit-risk profile.

T&Cs are a regulatory authority that can be applied for appropriate oversight of an authorized drug's safety, efficacy and quality throughout its lifecycle. The main objective of imposing T&Cs is to ensure that the drug maintains its favourable benefit-risk profile .

T&Cs may be used to manage a drug’s:

- significant uncertainties
- known or anticipated risks

T&Cs are not intended to be used to address deficiencies in a drug submission. They cannot be imposed to gather required information to support a drug submission or application where a manufacturer is seeking authorization to market the drug where the submission does not otherwise meet the requirements for authorization.

Before imposing T&Cs, we will consider if other regulatory mechanisms can address any identified risks or significant uncertainties. We will consider whether the obligations imposed using T&Cs are technically feasible and whether less burdensome means exist to achieve those objectives.

We will impose T&Cs fairly and consistently, and regulated parties will have an opportunity to be heard. T&Cs can be amended at any time during the lifecycle of a drug. MAHs are responsible to fulfill their T&Cs by the date specified in their T&C letter. MAHs that do not comply with their T&Cs may be held criminally liable.

Definitions

Biosimilar drug ("biosimilar"): A biosimilar is a biologic drug that is highly similar to a biologic drug that was already issued market authorization, such that there are no expected clinically meaningful differences in efficacy and safety between the biosimilar and the biologic drug that was already authorized for sale.

Clinical benefit: Outcomes that have positive impact on the course of a disease.

Canadian reference product (CRP): As per section C.08.001.1 of the Food and Drug Regulations, CRP means:

a. a drug in respect of which a notice of compliance is issued pursuant to section C.08.004 and which is marketed in Canada by the innovator of the drug
b. a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued pursuant to section C.08.004 cannot be used for that purpose because it is no longer marketed in Canada **or**
c. a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph (a)

Canadian reference biologic drug (CRBD): A biologic drug previously issued market authorization and used as a comparator to support market authorization of a biosimilar biologic drug ("biosimilar"). There are no expected clinically meaningful differences in efficacy and safety between a biosimilar and the biologic drug that was already authorized for sale.

Market authorization holder (MAH): The market authorization holder (MAH) is also referred to as sponsor or manufacturer. The MAH is the legal entity that holds the NOC and the DIN.

Promising evidence of efficacy: Evidence based on well-designed and well-conducted clinical trials and veterinary studies establishing that the drug product has an effect on an acceptable surrogate or clinical endpoint that is reasonably likely to predict clinical benefit.

SNDS-C: Supplement to a new drug submission (SNDS) - confirmatory is to be filed to provide results from the confirmatory clinical trials and veterinary studies specified in the 'terms and conditions letter'.

Surrogate endpoint: Parameters based on available evidence which predict an effect of a drug on recognized clinical outcomes such as morbidity and mortality. A validated surrogate marker is predictive of the clinical benefit of a drug.

About terms and conditions

Regulatory provision in section C.01.014.21 of the Food and Drug Regulations

We may impose terms and conditions (T&Cs) when necessary to manage risks or address significant uncertainties. We may also impose T&Cs when new or additional information is received that may affect the drug's benefit-risk profile.

As per section C.01.014.21, the provision states:

(1) The Minister may, at any time, impose terms and conditions on a drug identification number assigned for a drug or amend such terms and conditions after considering

a. whether there are significant uncertainties relating to the benefits or risks associated with the drug
b. whether the requirements under the Act are sufficient for the following objectives to be met:
    i. optimizing the benefits and managing the risks associated with the drug
    ii. managing the uncertainties relating to the benefits and risks **and**
    iii. collecting information to enable the continuous assessment of the benefits and risks, the identification of any changes to them and the management of the uncertainties
c. whether the proposed terms and conditions may contribute to those objectives being met
d. whether compliance with the proposed terms and conditions is technically feasible **and**
e. whether there are less burdensome ways for those objectives to be met

(2) The Minister shall notify, in writing, the manufacturer who was issued a document under subsection C.01.014.21(1) that sets out the drug identification number of any terms and conditions imposed on the drug identification number and of any amendment to those terms and conditions.

Why we impose terms and conditions

We will review drug submissions and applications as per existing guidance and policy documents and apply the appropriate requirements of each submission or application type or class.

For information on drug submissions and applications, refer to:

- For human drugs: Guidance on management of drug submissions and applications
- For veterinary drugs: Management of regulatory submissions guidance

In order for a drug identification number (DIN) to be assigned to a drug, the information supporting the drug submission or application must demonstrate that:

- the drug has a favourable benefit-risk profile **and**
- the information complies with the Food and Drugs Act (FDA) and the Food and Drug Regulations (FDR)

To be assigned a DIN, manufacturers must submit information to satisfy the requirements of section C.01.014.1 of the FDR. The DIN permits the drug to be marketed in Canada.

T&Cs may be imposed on the DIN of a drug to:

- optimize the benefits and manage any risks or significant uncertainties that could cause harm
- collect information to:
    - continuously assess the benefits and risks
    - identify changes (such as increased frequency of an adverse drug reaction)
    - reduce uncertainties related to the drug's safety, efficacy or quality
- manage significant uncertainties, including for:
    - compliance monitoring and enforcement of pharmacovigilance **or**
    - risk minimization activities, including those in a human drug’s risk management plan (RMP)

For information on risk management plans, refer to:

- Submitting risk management plans guidance document

We may also impose or amend T&Cs if new risks or significant uncertainties are identified about the drug's safety, efficacy or quality. New risks or significant uncertainties could be identified, for example, through:

- post-market safety assessments
- assessments of real-world evidence
- new information from foreign regulators
- review of information submitted for post-authorization changes
- new evidence from studies or reports, including from information filed to fulfill T&Cs

Prior to imposing T&Cs on the DIN, we will consider the factors listed in the proposed section C.01.014.21 of the FDR. That is, we will consider if:

- the proposed T&Cs are technically feasible
- there is a less burdensome way of meeting the objectives of the proposed T&Cs **and**
- another regulatory mechanism could address the issues identified

Significant uncertainties

All drug submissions must have the necessary information to enable the Minister to assess the safety, efficacy and quality of the drug. Data from clinical trials can be limited in providing information about how the drug will perform in the real world once it is on the Canadian market.

Limitations in the methodologies of clinical trials may lead to uncertainties in the benefits and risks of a drug. Therefore, limitations of the information obtained from clinical trials may, for example, include:

- effects of the drug when used with other drugs
- unknown long-term safety and effectiveness of the drug
- inclusion or exclusion criteria that limits the use of the drug in the real world (such as effects of the drug on populations not identified in the trial)

As a result of these limitations, our review of the information in a drug submission may identify significant uncertainties. Examples include uncertainties related to the:

- clinical trial methodology
- risks when the drug is used in real-world conditions

To address these significant uncertainties we may impose T&Cs on the DIN to monitor the safety of the drug and mitigate risks that occur in the real world. T&Cs allow us to verify that a market authorized drug maintains a favourable benefit-risk profile over time.

Promising evidence of efficacy and significant uncertainties

A new drug submission (NDS) or supplement to a new drug submission (SNDS) for human and veterinary drugs, shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug. In accordance with sections C.08.002 and C.08.003 of the FDR, sufficient evidence must be provided to support the safety and effectiveness of the drug for its indicated use and conditions of use.

New drugs under development for serious or severely debilitating conditions may have promising evidence of clinical efficacy, but the available data is limited. We recognize that efficacy data may be limited due to various important considerations such as:

- the availability of only preliminary or interim data on relevant endpoints
- the long duration of time required to collect data on conventional endpoints **or**
- a small number of patients who participated in clinical trials due to limited availability of patients, such as in cases of rare diseases or conditions

While the available data may be limited, it may provide promising evidence that a drug could help reduce or prevent serious signs, symptoms, or adverse clinical outcomes of a disease or condition. This evidence may demonstrate a clinical benefit and that the benefits outweigh the known risks associated with the drug's use.

New drugs supported by promising evidence of clinical efficacy should be made available to individuals with serious or severely debilitating conditions where there is an unmet medical need. If the supporting information shows that the benefits outweigh the known risks and meets the requirements of the FDA and the regulations, a notice of compliance (NOC) may be issued to allow market authorization of the drug.

However, when a drug is supported by promising evidence, significant uncertainties about its effectiveness may remain. In such cases, the available evidence may still meet regulatory requirements if additional confirmatory studies are performed to further verify the new drug's effectiveness. T&Cs can be imposed to support a market authorization by applying section C.08.003.2 of the FDR. This allows us to take into account whether T&Cs could provide more information about any significant uncertainties on a new drug's effectiveness.

For more information on drug submissions based on promising evidence of efficacy, refer to:

- Draft guidance on human and veterinary drug submissions based on promising evidence and terms and conditions

Examples of why we may impose terms and conditions

We may impose T&Cs to manage risks and uncertainties related to:

- long-term use of a drug
- safety risks in veterinary drugs
- the impact of certain marketed veterinary drugs on food safety
- compliance monitoring and enforcing elements of an RMP for human drugs
- limited safety or efficacy information in a specific population using the drug
- outcomes of studies or pharmacovigilance activities which may impact the benefit-risk profile
- new information from markets outside Canada or from published evidence in scientific journals

Examples of terms and conditions that may be imposed

We may impose T&Cs to:

- conduct additional studies
- verify impurities identified in a drug
- require implementation of an ongoing quality, risk mitigation or monitoring program
- increase the frequency of preparing summary reports and submitting them as stated in the T&C letter (more frequently than annually as required by the FDR)

Drugs authorized by a foreign regulator may already have conditions imposed on them that oblige the MAH to pursue further studies. On a case-by-case basis, we may consider conditions imposed by a foreign regulator when imposing T&Cs on the Canadian DIN.

Subsequent-entry drugs

Subsequent-entry drugs (generic and biosimilar submissions) can use a Canadian reference product (CRP) or Canadian reference biologic drug (CRBD) with T&Cs as a

comparator. In such cases, T&Cs imposed on the DIN of the subsequent-entry drug may be the same or similar to those imposed on the CRP or CRBD as described below.

Sometimes the comparator has a T&C to conduct a confirmatory trial, because the authorization of the CRP or CRBD was based on promising evidence of clinical effectiveness. In this case, the MAH of a subsequent-entry drug will not necessarily have to complete the same study. For human drugs, generic or biosimilar products that compare to a CRP or CRBD that has T&Cs to confirm clinical benefit may need to reflect the promising nature of efficacy in their Product Monograph and include a copy of the Package Insert within the product packaging materials. For specific wording for subsequent entry products, refer to:

- Guidance document - Product monograph

There may be instances, however, where MAHs of subsequent-entry drugs may be required to conduct trials to address significant uncertainties related to the effectiveness of the drug.

An example of this could be when the MAH of a CRP or CRBD cancels their DIN before completing and submitting the confirmatory trials. A T&C may require the MAH of the subsequent-entry drug to provide data verifying the clinical benefit. When we consider imposing a T&C to conduct a trial, we will take into account the feasibility of the trial. This will include such factors as the:

- ethical considerations for requesting a duplicative trial
- status of the original trials imposed upon the CRP or CRBD
- potential to affect subject recruitment in both the original and subsequent trials
- potential competition for the same and possibly limited human, animal and material resources to conduct the trial

Health Canada will determine, on a case-by-case basis, which T&Cs will be imposed on the DIN of a generic or biosimilar drug. Our goal in these considerations is to avoid:

- unnecessary delay of confirmatory trials
- possibly undermining the objective of the use of T&Cs to verify the clinical benefit of a drug

Terms and conditions letters

Anticipatory terms and conditions letter

Health Canada will inform you (the market authorization holder [MAH] or sponsor of the drug submission) of our intent to impose terms and conditions (T&Cs). We will do so by issuing an anticipatory T&Cs letter ("anticipatory letter").

The anticipatory letter will:

- explain any risks and uncertainties that were identified
- outline the reasons for imposing the T&Cs
- describe the expected outcome from the T&Cs imposed
- define timeframes for fulfilling the T&Cs **and**
- provide you with an opportunity to be heard

Timing for issuing an anticipatory terms and conditions letter

T&Cs can be imposed at any time on a DIN assigned to a drug; therefore, there is flexibility on when the anticipatory letter may be issued. If T&Cs are needed because of an issue that arises during pre-market submission review, the timing of the anticipatory letter will depend on the nature of the issue(s) to be addressed and the details of the pre-market submission under review, as applicable.

T&Cs may also be imposed on a DIN(s) of a drug that has already been authorised for a long period of time. The anticipatory letter may be issued either:

- during the pre-market review period (Figure 1)
- at the time of authorization (Figure 2)
- shortly after authorization (Figure 3) **or**
- at any time post-authorization (Figure 4)

If T&Cs are needed because of an issue identified during review, an anticipatory letter may be issued at different times depending on the progress of review and the issues to be addressed. For example, in cases where the activities under the T&Cs must be implemented immediately upon marketing the product, an anticipatory letter may be issued during the review period (Figure 1). It could also happen if certain elements of the T&Cs are to be included in product labels, such as the product monograph (Figure 1).

For drug submissions based on promising evidence of efficacy where the Minister may consider T&Cs as part of the review as per section C.08.003.2 of the FDR, the anticipatory letter will be issued during the review. For more information on drug submissions based on promising evidence of efficacy, including timing of the anticipatory letter, refer to:

- Draft guidance on human and veterinary drug submissions based on promising evidence and terms and conditions

Figure 1: Anticipatory letter issued during review of a pre-market submission

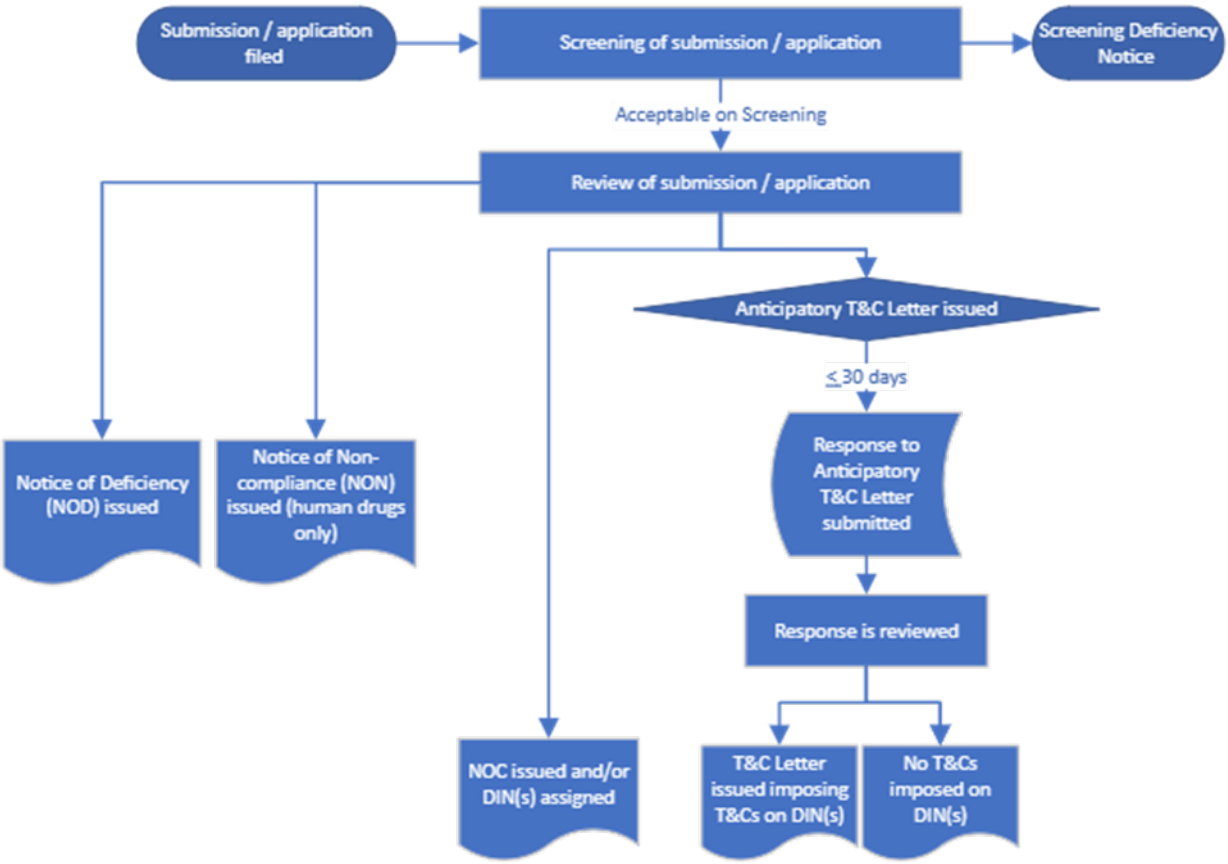


Figure 2: Anticipatory letter issued at the time of authorization, upon issuance of a NOC and DIN assignment

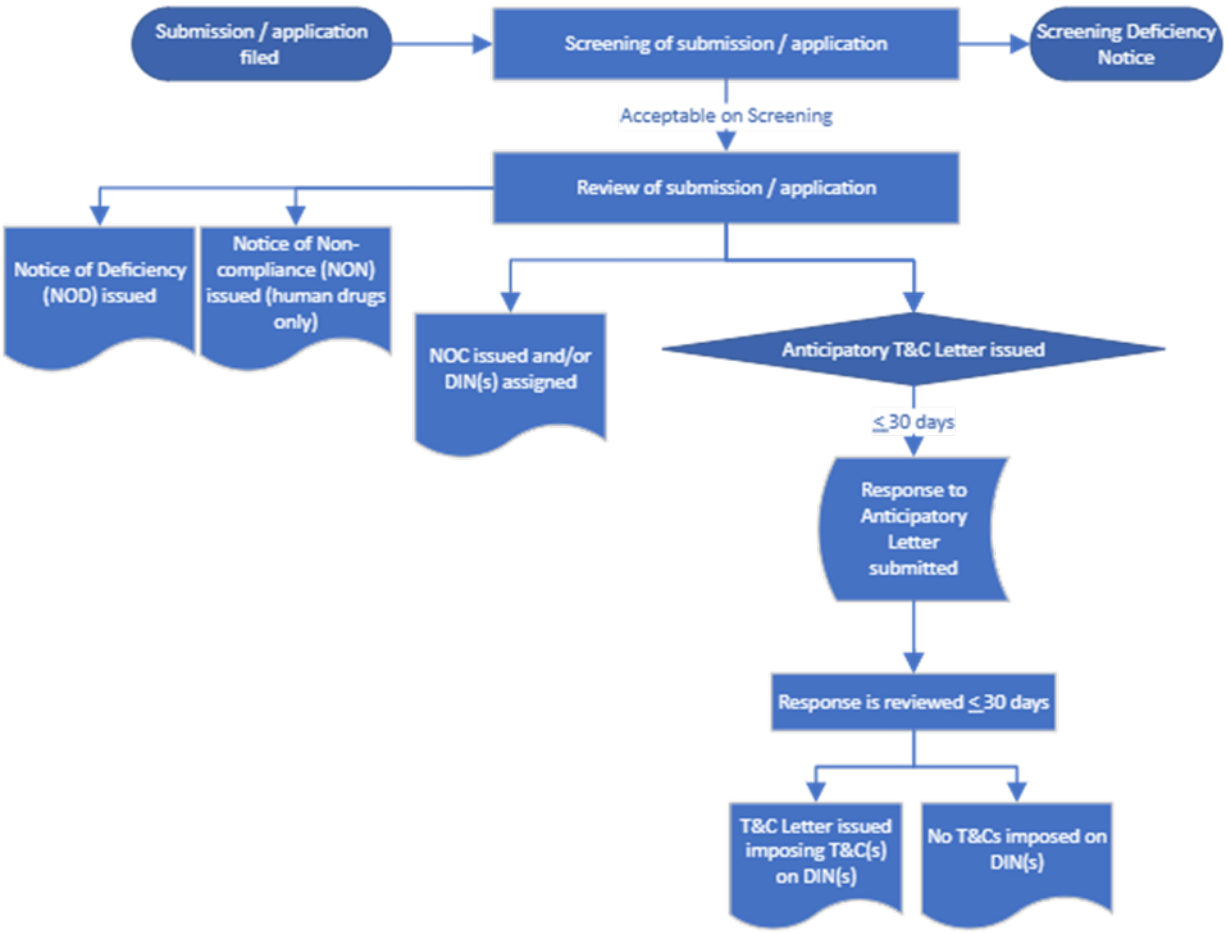


Figure 3: Anticipatory letter issued shortly after issuance of a NOC and assignment of a DIN

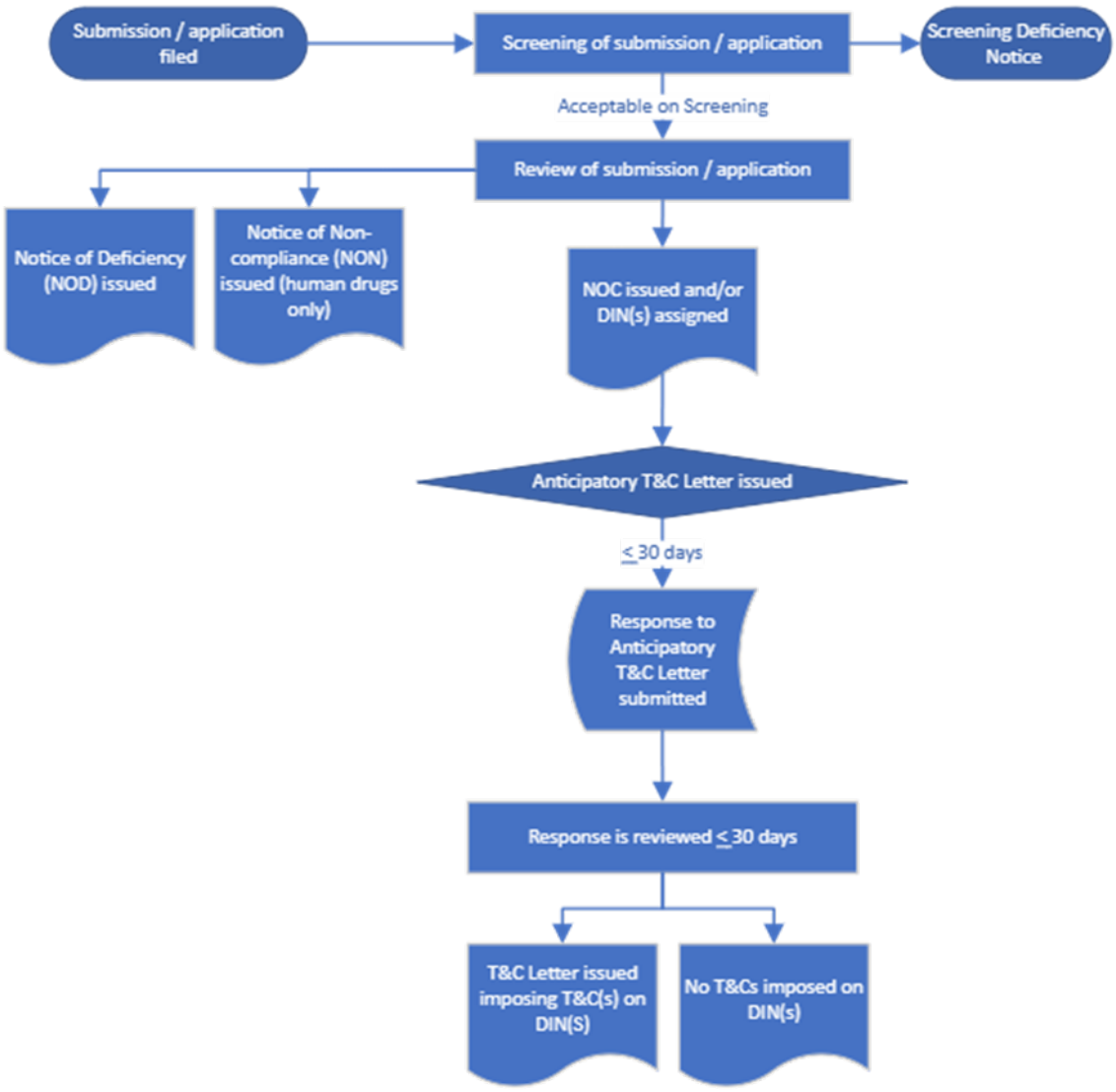
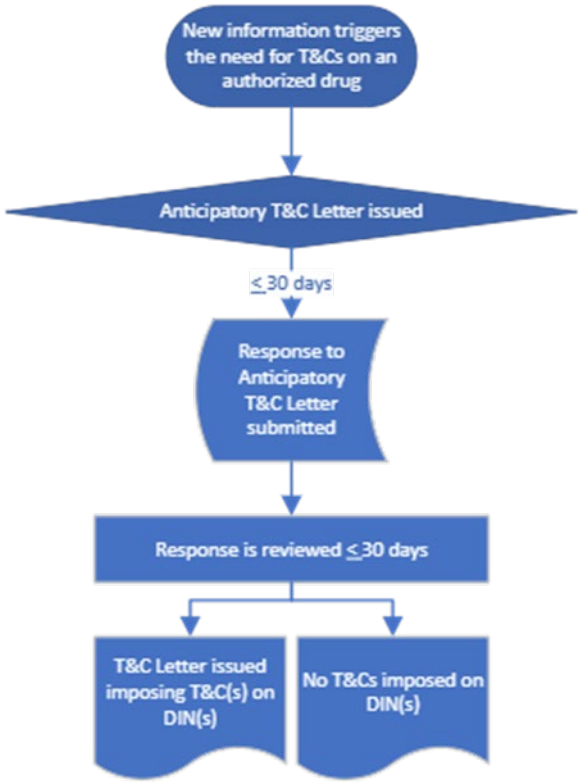


Figure 4: Anticipatory letter issued for an authorized product because of new information



Response to anticipatory terms and conditions letter

You should respond to the anticipatory letter in writing and include the details of a plan to fulfill the T&Cs. Generally, you should submit the response within 30 calendar days of receiving the anticipatory letter, or as specified in the letter. Should you fail to respond to the anticipatory letter, we may finalize the T&Cs based on the information available to us.

If a new risk or uncertainty is identified that requires urgent attention for an authorized and marketed drug, the time to respond may be reduced.

If the T&Cs are the result of pre-market submission review, your response to an anticipatory letter should:

- include the submission control number of the drug submission,
- be submitted using the regulatory enrolment process (REP) **and**
- use “response to anticipatory T&C letter” as the regulatory transaction description

If the proposed T&Cs require you to conduct more studies or activities, you will have an opportunity to provide:

- a brief description of the methodology, logistics, or study design of the proposed activity
- a description of the anticipated timeframes for starting and completing these activities
- any other details necessary to demonstrate how the conditions in the letter will be met

If you object to the proposed T&Cs, you may provide reasons for your objections. You may:

- suggest an alternative proposal with a supporting rationale
- comment on the technical feasibility of the T&Cs
- propose less burdensome means of achieving the objectives

You may also request to meet with us to discuss your objections.

Terms and conditions letter

We will review your response within 30 calendar days of receiving it. We will review information you provide and refer to any other information that could inform the review. During this review, we may request clarification in accordance with the following guidance documents:

- For human drugs: Guidance on management of drug submissions and applications
- For veterinary drugs: Management of regulatory submissions guidance

Following the review, if T&Cs are still needed, we will finalize the T&Cs in a letter that will specify the:

- applicable DINs on which the T&Cs will be imposed
- T&Cs to be fulfilled
- information to be submitted
- timeframe for fulfilling the T&Cs

As per subsection C.01.014.21(2), we will notify you of the final T&Cs by sending you the final T&C letter. For drug submissions based on promising evidence of efficacy and within the scope of C.08.003.2, the T&Cs will be considered during review. The “terms and

conditions letter" will be issued to the manufacturer with the notice of compliance (NOC) at the end of review.

For more information on drug submissions based on promising evidence of efficacy, refer to:

- Draft guidance on human and veterinary drug submissions based on promising evidence and terms and conditions

Transparency

After issuing a T&Cs letter, we'll post information related to the T&Cs on the Health Canada website. Details will include statements on the T&Cs imposed and their timelines. We'll update this information as T&Cs are fulfilled or amended. The information posted will not contain any confidential business information. It's imperative to the safe and effective use of a drug that information concerning T&Cs be readily available to patient groups, health care providers and other interested stakeholders.

In addition to the T&C information, you can find the following information online:

Notice of compliance (NOC) database

Contains NOCs issued for drugs for human and veterinary use from January 1, 1994 to present, pursuant to Division 8 of the Food and Drug Regulations (FDR).

Drug product database

Contains information about drug identification numbers (DINs) assigned for drugs authorized for sale by Health Canada for human and veterinary use, such as the:

- product monograph for human drugs
- product labelling for veterinary drugs
- availability of a risk management plan for human drugs

Drug and health product portal

Contains multiple pieces of information such as regulatory decision summaries and summary basis of decision documents. These describe Health Canada's rationale for approving certain prescription drugs for human use.

Clinical information portal

Contains the clinical information filed by sponsors to seek approval of human drugs under Division 8 of the FDR.

The drug and health products inspections database (DHPID)

Gives information about each type of drug and health product inspection done by Health Canada.

Progress reporting

Progress reports

Although not required by regulation, we may request progress reports on the status of activities that are required by a term and condition (T&C). If requested, the progress report should include:

- the summary of outstanding conditions
- the status of the trial if applicable (pending, ongoing, delayed, terminated, submitted or fulfilled)
- details explaining the status **and**
- subsequent action taken to address the T&Cs

The progress report should be submitted by a date agreed upon at the time of the issuance of the T&Cs letter. If there are any questions regarding the content of the progress report, Health Canada will contact the MAH.

Progress reports will be requested on a case-by-case basis, and you will be informed directly if one is needed.

Sample report

This is a sample template that can be used to submit a report on the progress of ongoing trials.

Progress report: Submitted on [date]

Manufacturer or sponsor:

Product: [brand name] (active ingredients), route of administration, dosage form and strength, species (for veterinary drugs)

Submission and control number: NDS, SNDS, ANDS, SANDS (control number)

Terms and conditions letter date: Year/month/day

Description of trial:

Trial schedule (as applicable):
Protocol approval date; Trial enrollment start date and conclusion date; Last patient evaluation date; Health Canada submission date.

Current status:
Pending, Ongoing, Delayed, Terminated, Submitted, Fulfilled

Explanation of the status:
Brief description and action taken

Ongoing trial current status definitions:

- **Pending:** The trial has not been initiated by the market authorization holder (MAH).
- **Ongoing:** The trial is proceeding according to the original schedule or is ahead of schedule. The results of the trial have not been submitted to Health Canada.
- **Delayed:** The progress of the trial has fallen behind the original schedule. Examples of the delay status include difficulties in patient enrolment, delays in the analysis of the results, or delay in the filing of the submission to Health Canada.
- **Terminated:** The applicant ended the trial before completion, and has not yet submitted a final trial report to Health Canada. Examples of termination include termination of trial arms that are no longer feasible. For specific safety, efficacy or quality concerns related to the drug, Health Canada needs to be notified within 15 days.
- **Submitted:** The sponsor has submitted a final trial report to Health Canada, and the submission is currently in review.
- **Fulfilled:** Health Canada has conducted the review of the final trial report filed as a submission and has issued a notice of compliance to approve updated labelling indicating that the MAH has met the T&C.

Filing information and review

Filing information to fulfill terms and conditions indicates a change

The terms and conditions (T&Cs) letter may include several conditions, each with different timelines for completion. Where applicable, you, the market authorization holder (MAH), must submit the information required to fulfill the T&Cs by the date indicated in the letter.

In some cases, similar conditions may have been imposed in another country and the foreign regulator later removed these conditions. Regardless of the status of the conditions imposed in another country, you must fulfill your obligations under the Food and Drug Regulations (FDR) for the T&Cs imposed by Health Canada.

For subsequent-entry drugs, you are responsible to fulfill your T&Cs even if the reference product is no longer marketed. Reference product includes Canadian reference product (CRP) or Canadian reference biologic drug (CRBD). If you reference a CRP or CRBD with T&Cs imposed on its DIN, you should monitor the:

- Notice of Compliance Database
- Drug and Health Product Portal
- Drug Product Database
- product monograph brand safety updates (for human drugs only) **and**
- most recent labels

If the information being filed indicates a change that may impact the drug's benefit-risk profile, labelling, or the drug's safety, efficacy or quality, file it using the appropriate submission type. Examples include:

- supplemental new drug submission (SNDS)
- drug identification number application (DINA)

For **human** subsequent-entry drugs comparing to a CRP, if the information being filed indicates changes that may impact the drug's labelling based on the CRP's fulfilling T&Cs, file it using an SANDS labelling only and not SANDS labelling only (generic drug).

For **veterinary** subsequent-entry drugs comparing to a CRP, if the information being filed indicates changes that may impact the drug's labelling based on the CRP's fulfilling T&Cs, file it using an SANDS.

In the case of drugs that have been authorized based on promising evidence of efficacy, final results from confirmatory trials should be filed in the form of an SNDS-confirmatory (SNDS-C) according to the individual deadlines outlined in the T&Cs letter. For more information on drug submissions based on promising evidence of efficacy, refer to:

- Draft guidance on human and veterinary drug submissions based on promising evidence and terms and conditions

You should file quality changes with a substantial or moderate potential to adversely affect the identity, strength, quality, purity or potency of a drug product as the appropriate post-authorization submission type. These factors may relate to the safety or effectiveness of the drug product.

You should still submit quality changes with minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency (level III changes).

For more information on determining which post-authorization submission type to use, consult the relevant guidance documents:

- Post-NOC changes: Quality
- Post-NOC changes: Safety and efficacy
- Post-drug identification number changes
- Post-notice of compliance (NOC) changes: Framework
- Post-NOC changes: Guidance for quality of veterinary drugs
- Post-NOC changes: Framework document for veterinary drugs
- Post-NOC changes: Guidance for safety and efficacy of veterinary drugs

Filings may be subject to applicable fees. We will handle submissions in accordance with the following guidance documents:

- For human drugs: Guidance on management of drug submissions and applications
- For veterinary drugs: Management of regulatory submissions guidance
- Regulatory Enrolment Process (REP) for Drugs for Human and Veterinary Drugs and Disinfectants

For post-market-related activities only, you can file as:

- For human drugs:
  - risk communication – pharmacovigilance (RC-PV)
  - risk management plan – pharmacovigilance (RMP-PV)
  - post-authorization commitments – pharmacovigilance (PA-PV)
  - post-authorization act and regulations – pharmacovigilance (REG-PV)
  - periodic benefit-risk evaluation report – pharmacovigilance (PBRER-PV)
  - periodic safety update report – confirmatory (PSUR-C)
  - periodic benefit-risk evaluation report – confirmatory (PBRER-C) **or**
  - patient safety/advertising ad-hoc post-market request – pharmacovigilance (PSA-PV)
- For both human and veterinary drugs:
  - periodic safety update report (PSUR-PV)

The T&C letter may include more detailed instructions on how to file the information. Information filed to fulfill T&Cs should only address the T&Cs. It should not be filed as additional information to support an expanded indication or another significant change to the information in the original submission that is outside the scope of the T&Cs.

Filing information to fulfill terms and conditions does not indicate a change

You must file information to fulfill a T&C. This applies even if results from studies or information required by the T&C do not indicate a change to the safety, efficacy or quality since authorization that may impact the drug's benefit-risk profile or product labelling. Product labelling includes the product monograph (for human drugs) and package insert as well as package labelling.

If you submit information to fulfill a T&C but we determine that it **does** affect the information on which the authorization was based, we'll ask you to file the appropriate submission or application type. We'll do this if it might:

- require a labelling change
- impact the benefit-risk profile **or**
- indicate a change in the quality of the product

Review of information filed

Once you file the information to fulfill the T&Cs, we will review the submitted information as per the performance standards in the applicable guidance documents:

- For human drugs: Guidance on management of drug submissions and applications
- For veterinary drugs: Management of regulatory submissions guidance

After reviewing the information submitted, we will inform you of the results. We will remove any T&Cs that are fulfilled, unless further conditions are imposed or existing conditions need to be amended. If further conditions are to be imposed, we will inform you through another anticipatory letter of what actions must be taken. You will be given up to 30 days to respond, unless specified otherwise.

New conditions may be imposed if, for example:

- new risks or significant uncertainties are identified
- more studies or activities are needed to address or manage the uncertainties
- the existing T&Cs have not been adequately addressed or have not managed the identified or potential risks

We will consider other regulatory tools to address any identified issues. Depending on the nature of the issue, rather than imposing T&Cs we may, for example, request that you submit:

- for human drugs:
    - an annual summary report (ASR)
    - an updated risk management plan (RMP)
    - labelling updates to reflect new information
    - a periodic safety update report (PSUR) **or**
    - periodic benefit risk evaluation report (PBRER)
- for veterinary drugs:
    - labelling updates to reflect new information
    - that you submit a PSUR

If the information or data you filed demonstrates an unfavourable change to the benefit-risk profile, we may take other regulatory actions such as cancelling a DIN. Examples of reasons for doing so include:

- the drug is considered unsafe for the authorized indications
- there isn't enough evidence to demonstrate that the drug will be effective under the conditions of use

Amending terms and conditions

The T&C letter will be amended as T&Cs are fulfilled, indicating the date on which the T&Cs were met. It will also be amended if T&Cs need to be modified, or additional T&Cs are to be imposed as a result of new information.

You may request an amendment to a T&C. Amendments may be requested if, for example, you conclude that a study imposed through a T&C cannot be completed for technical or scientific reasons. For example, if the date of submission of clinical trial results needs to be extended due to slower than anticipated enrollment or challenges with recruitment, or because a particular methodology is no longer feasible. If you request an amendment to a T&C, you must provide the basis for requesting an amendment with supporting rationale and documentation.

For changes related to technical or scientific issues, you may also be required to provide a scientific rationale. In such cases, you must include the proposed alternatives for fulfilling the T&Cs, including the proposed alternative methodology or study. We will review the information you provide and amend the T&C as appropriate.

To request an amendment, you may file details of the request with the rational to the appropriate directorate as indicated in the following guidance documents:

- For human drugs: Guidance on management of drug submissions and applications
- For veterinary drugs: Management of regulatory submissions guidance

Subsequent submissions for reasons other than to fulfill terms and conditions

Unfulfilled T&Cs continue to apply even if a new DIN is assigned as a result of subsequent submissions through post-authorization changes. Existing T&Cs may apply to the new DIN if:

- the drug is authorized and a new DIN is assigned as a result of the subsequent submission **or**
- the existing DIN is re-assigned under a new MAH or new brand name

This will depend on the nature of the new authorization and whether the T&Cs have yet to be fulfilled. In any case, if a new DIN is assigned, we will re-issue a T&C letter for unfulfilled T&Cs that will apply to the new DIN.

For more information on post-authorization changes, refer to:

- Post-NOC changes: Quality
- Post-NOC changes: Safety and efficacy
- Post-drug identification number changes
- Post-notice of compliance (NOC) changes: Framework Document (Pharmaceutical, biologic and radiopharmaceutical drugs for human use only)
- Administrative processing of submissions and applications involving human or disinfectant drugs
- Post-NOC changes: Framework document for veterinary drugs
- Post-NOC changes: Guidance for safety and efficacy of veterinary drugs
- Post-NOC changes: Guidance for quality of veterinary drugs

Subsequent entry drug submissions may reference drugs that have T&Cs imposed on its DIN. We will treat these subsequent entry submissions as follows:

- Supplemental (Level 1) changes that rely on the safety and efficacy data of the original submission (for which authorization was granted with T&Cs) will be treated as SNDSs, SANDS or DIN applications. If a new DIN is assigned, T&Cs may be imposed if prior DINs for that drug had T&Cs. An example would be a submission for a change in strength or formulation. The imposition of T&Cs on the new DIN will be decided following consideration of the following factors if:
    - the T&Cs are technically feasible
    - there is a less burdensome way of meeting the objectives of T&Cs **and**
    - another regulatory mechanism could address the issues identified
- T&Cs will remain in place if a product undergoes an administrative change (such as a change in product name or manufacturer name) but continues to rely on the safety, efficacy and quality data of the original submission.
- Administrative changes to subsequent-entry drugs which rely on the safety and efficacy data of the original submission will carry over any unfulfilled T&Cs from the original submission. In such cases, if a new DIN is assigned, we will re-issue a T&Cs letter for the appropriate DIN.

- T&Cs will continue to apply, even if subsequent changes (through supplements to drug submissions and applications) that are filed and authorized don't result in new T&Cs. Depending on the outcome of the review, subsequent submissions may qualify for authorization, with or without new T&Cs.
- If we revoke or suspend the original NOC for a drug with T&Cs, including for drugs that used a reference product with T&Cs, we may take appropriate action for all subsequent submissions. Additional T&Cs that have been imposed specifically on the subsequent-entry drugs (that is, in addition to the conditions of the original drug), will continue to apply and must be fulfilled (unless they are otherwise amended or removed).

If you need clarification on filing and processing subsequent submissions, contact the appropriate review area listed within the following guidance documents:

- For human drugs: Guidance on management of drug submissions and applications
- For veterinary drugs: Management of regulatory submissions guidance

T&Cs may apply to the DIN of a cross-licensed product if the licensor's drug had T&Cs imposed on its DIN. For more information on administrative processing of drug submissions, refer to:

- Guidance document: Administrative Processing of Submissions and Applications Involving Human or Disinfectant Drugs (while veterinary drugs are not in the scope of this document, it can be used as a reference)

When all conditions are fulfilled

Once you've provided satisfactory evidence that all the objectives of the T&Cs in the original (or amended) T&C letter have been met, Health Canada will issue a final letter. It will reference the DINs on which the T&Cs were imposed and:

- indicate that the T&Cs have been fulfilled **and**
- state that the T&Cs are removed

In the case of subsequent-entry drugs for which the T&Cs of the CRP or CRBD have been fulfilled, the T&Cs for the subsequent-entry drug will usually be considered fulfilled if the generic or biosimilar drug had similar T&Cs imposed depending on the nature of the T&C.

Compliance and enforcement

Market authorization holder does not comply with terms and conditions

All terms and conditions (T&Cs) are enforceable under section 21.7 of the Food and Drugs Act (FDA). MAHs may be held criminally liable for not fulfilling or complying with T&Cs, including failing to submit trials and studies as per their deadlines outlined in the T&Cs letter.

Health Canada may also take compliance and enforcement actions as outlined within the policy:

- Compliance and enforcement policy (POL-0001)

We will apply a risk-based approach when taking regulatory actions related to information generated by the T&Cs, indicating that the:

- drug poses a risk to people in Canada
- veterinary drug poses a risk to animal health **or**
- predicted efficacy or quality of the drug has changed

Regulatory actions may result in:

- stop-sale
- ordering label changes
- ordering additional studies
- suspending a notice of compliance (NOC) **or**
- cancelling a drug identification number (DIN)

For subsequent-entry drugs, sometimes the MAH of a CRP or CRBP fails to fulfill their T&Cs or discontinues their DIN, and the CRP or CRBP or any indications of these products are then withdrawn. In such cases, further regulatory action with the MAH of the subsequent-entry drug may be required. For example, in cases where the MAH of the subsequent-entry drug wishes to continue marketing the drug, they may be required to provide evidence to support continued approval of the subsequent-entry drug. We will decide whether that evidence is sufficient to support continued approval.