Health Canada Santé Canada

Draft guidance document on terms and conditions (T&Cs) for human and veterinary drugs

Canada

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This guidance document gives an overview of the regulatory requirements for terms and conditions (T&Cs). It also provides direction and guidance to authorization holders and Health Canada staff on the use of T&Cs 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), medical devices and cosmetics. As a drug regulator, Health Canada's role is to verify that regulatory requirements for the safety, efficacy and quality of human and veterinary drugs are met through scientific assessments. These include product and establishment licensing, monitoring and surveillance, as well as compliance and enforcement activities.

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 aimed to improve Health Canada's ability to collect post-market safety information and take appropriate action when a serious risk to health is identified. These amendments were introduced to better protect patient health and safety and increase consumer confidence in therapeutic products on the market.

Under the FDA, a therapeutic product is defined as a drug or device or any combination of drugs and devices. It does not include a natural health product as defined in the *Natural Health Products Regulations*.

Drugs for human and veterinary use in Canada must meet certain requirements under the *Food and Drug Regulations* (FDR). Drugs must satisfy all applicable requirements in Part C, Division 1 to be authorized for sale. 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.

When an authorization is issued, a unique drug identification number (DIN) is assigned to a drug. The DIN serves as a tool to help in the follow-up of products on the market, recall of products, inspections and quality monitoring.

For information on the DIN, refer to:

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

For Division 1 only drugs, information must be submitted to satisfy the requirements of subsection C.01.014.1(1). The Minister assigns a DIN to a drug, which permits the authorization holder to market the drug in Canada.

For Division 8 drugs, submissions must include evidence to support the safety and effectiveness of the drug for its indicated use and conditions of use. This is in accordance with sections C.08.002, C.08.002.01, C.08.002.1 and/or C.08.003 of the FDR. The issuance of a notice of compliance (NOC) to the manufacturer of a new drug, in addition to a DIN, allows the sale of that new drug in Canada.

The granting of an authorization to sell a drug in Canada is based on:

- Health Canada's review of information that has been provided to support a drug submission and application **and**
- our determination that the information has met the requirements of Division 1 or Division 1 and 8 of the FDR

The rapid pace of innovation in industry has led to uncertainties and risks for therapeutic products that may not be adequately managed through existing regulatory provisions. *Vanessa's Law* gave the Governor in Council the authority to make regulations under the FDR that would support Health Canada's goal of implementing a life-cycle approach to regulating drugs and medical devices.

This includes making regulations that give the Minister the authority to impose or amend T&Cs on a DIN or a medical device licence. A T&C is an obligation that would require the owner of a DIN, or holder of a medical device licence, to conduct an activity concerning the drug or medical device on which the T&C(s) has been imposed.

Scope and application

This guidance document applies to drugs regulated under Part C, Division 1 only, or Divisions 1 and 8 of the FDR that are issued a DIN.

For the purpose of this document, "drug" is for human and veterinary use and includes:

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

It excludes natural health products and biocides.

T&Cs may be imposed on a DIN, and can be amended, at any time. This means they may be imposed after authorization or when an authorization is issued for submissions or applications that were filed as a:

- new drug submission (NDS)
- supplement to a new drug submission (SNDS)
- extraordinary use new drug submission (EUNDS)
- supplement to an extraordinary use new drug submission (EUSNDS)
- abbreviated new drug submission (ANDS)
- supplement to an abbreviated new drug submission (SANDS)
- abbreviated extraordinary use new drug submission (EUANDS)
- supplement to an abbreviated extraordinary use new drug submission (EUSANDS)
- application for a DIN (includes non-prescription products), such as:
    - DINA/F for a pharmaceutical
    - DINB for a biologic product

T&Cs can also be imposed on a DIN following the review of a submission or application filed as a:

- post-authorization Division 1 Change (PDC)
- notifiable change (NC)

Policy objectives and statements

This guidance document explains the purpose of T&Cs and the processes that will be applied so that T&Cs are imposed fairly and consistently and give regulated parties an opportunity to be heard.

Before T&Cs are imposed, consideration will be given as to whether the obligations under the T&Cs are technically feasible and can be reasonably expected to achieve their objectives. Health Canada will consider whether the T&Cs imposed will:

- reduce the risks and/or uncertainties associated with the potential to cause injury to health
- address significant uncertainties
- manage risks and uncertainties and/or
- confirm a drug's benefit-risk profile for the indicated use

Drug submissions and applications must be supported by the necessary information and must meet all requirements of the FDR to be authorized for sale in Canada. Data establishing the safety, efficacy and quality of a drug must demonstrate a favourable benefit-risk profile.

If the Minister identifies risks and/or uncertainties related to a human or veterinary drug, T&Cs can be imposed on its DIN at the time of authorization or after authorization when risks and/or uncertainties are identified for the authorized indication. T&Cs are a regulatory tool giving Health Canada oversight of an authorized drug's safety, efficacy and/or quality throughout its life cycle. This tool will also be used to reduce the risks and/or uncertainties associated with the potential to cause injury to health after the drug's authorization.

T&Cs can also be amended throughout the life cycle of a drug.

The main objective of imposing T&Cs is to ensure a drug maintains a favourable benefit-risk profile throughout its life cycle. In other words, its safety, efficacy and/or quality are retained.

Before we impose T&Cs, Health Canada will consider if other regulatory mechanisms are available to address the risks and/or uncertainties that we have identified.

Note about guidance documents in general

Guidance documents provide assistance to industry with the 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 accompanying notice and the relevant sections of other applicable guidance documents.

Overview of the regulatory provision in section C.01.014.21

We will impose T&Cs when we need to manage risks or address uncertainties. We will also impose T&Cs when new or additional information becomes known that may affect the drug's benefit-risk profile for its indicated use.

As per the proposed section C.01.014.21, the provision states:

The Minister may, at any time, impose terms and conditions on a drug identification number assigned for a drug, or amend those terms and conditions, after considering the following factors:

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 to:
    i. optimize the benefits and manage the risks associated with the drug
    ii. manage the uncertainties relating to the benefits and risks and
    iii. collect information to be able to continuously assess the benefits and risks, identify any changes to them and manage the uncertainties
c. whether the proposed terms and conditions may contribute to meeting the objectives set out in subparagraphs (b)(i) to (iii)
d. whether compliance with the proposed terms and conditions is technically feasible and
e. whether there are less burdensome ways to meet the objectives of the proposed terms and conditions

Implementation of terms and conditions

T&Cs may be imposed on a DIN for several reasons, including when there is a significant uncertainty about the drug's safety, efficacy and/or quality for its indicated use. They may also be imposed to:

- manage risks and uncertainties
- gather further information that could affect the drug's benefit-risk profile or
- address uncertainties that could potentially cause injury to health

T&Cs may also be imposed or amended after authorization has been given. We will do so when new information for the drug's indicated use suggests that the initial benefit-risk profile that was concluded to be favourable may have significantly changed.

The Minister must consider if the T&Cs are technically feasible. Consideration must also be given to less burdensome ways to meet the objectives of the T&Cs.

Imposing terms and conditions at issuance of market authorization

To be considered for a market authorization, all drugs must be supported by information required by the FDR. A drug must have a favourable benefit-risk profile for the intended use at the time an authorization is issued.

Health Canada reviews the submitted information. We may ask for further information during this process. Following our review of the submitted information, the drug may have a favourable benefit-risk profile for the indication being sought, but risks and/or uncertainties about the drug may be identified. In such cases, the drug may receive authorization for a specific indication. To manage or address the risks and/or uncertainties that have been identified, Health Canada may impose T&Cs on the DIN.

When imposing T&Cs, Health Canada will consider the factors listed in the proposed section C.01.014.21 of the FDR. The Minister may impose T&Cs on a DIN to manage risks or address uncertainties relating to its risks

and benefits for the indicated use and/or the quality of the drug. In the case of a generic drug or a subsequent entry drug (biosimilar) where the Canadian Reference Product (CRP) or reference biologic drug has imposed T&Cs, the Minister will determine on a case-by-case basis which T&Cs will be imposed on the generic or subsequent entry drug.

Health Canada will inform the manufacturer of our intent to impose T&Cs on the DIN before we do so.

T&Cs can be imposed a DIN for many reasons depending on the information provided in the drug submission or application. The following lists give some examples of when T&Cs may be imposed on a DIN at the time an authorization is issued.

T&Cs may be imposed to manage and/or address:

- uncertainties with the use of the drug by assessing the effective use of a drug, and the food safety for certain veterinary drugs
- uncertainties of identified and/or potential risks after long-term use of a drug
- uncertainties in a specific patient population using the drug when safety and/or efficacy information is limited
    - specific patient populations could be pregnant women, certain age groups or patients with renal or hepatic impairment
- uncertainties of a drug's known risks to verify the worldwide safety experience of the drug by requiring more frequent submission (rather than yearly) of the following:
    - periodic safety update report (PSUR)
    - periodic benefit-risk evaluation report (PBRER) and/or
    - annual summary report (ASR)

T&Cs may also be imposed to:

- address uncertainties of a drug through confirmatory studies on safety and efficacy when surrogate markers were used in clinical trial studies to support an authorization
    - surrogate markers are parameters that when measured directly are reasonably likely, based on available evidence, to predict an effect of a drug on recognized clinical outcomes such as morbidity and mortality
- collect information to continuously assess the benefits and risks, identify any changes to them and manage the uncertainties
- implement an ongoing monitoring program to detect trends in quality, for example:
    - verifying impurities identified in a drug through additional specific testing and investigational requirements for impurities
- request results from confirmatory trials submitted to a foreign jurisdiction

Imposing or amending terms and conditions after authorization

The Minister may impose or amend T&Cs at any time after issuing an authorization. The Minister will do so if new information about the drug's safety, efficacy and/or quality could affect the product's benefit-risk profile, which was established at the time of authorization.

New risks or uncertainties about a drug's safety, effectiveness or quality for the authorized indication(s) may be identified through:

- post-market assessments of real world evidence or
- new evidence from studies or reports

Post-NOC or post-DIN changes may also reveal:

- new uncertainties related to safety, efficacy or quality or
- new risks that require additional assessment or mitigation

These could lead to the imposition of T&Cs

Examples of T&Cs that may be imposed after authorization include the following:

- conditions that manage and/or address:
  - uncertainties by evaluating the effectiveness of risk mitigation measures
  - uncertainties with the safety of a drug following the review of safety ASRs, PSURs and/or PBRERs
  - risks or uncertainties about risks and/or the drug's efficacy identified following a review of submissions filed for new indications
  - new risks, uncertainties and/or emerging issues that were not known at the time of the drug's market authorization through specific risk mitigation measures
  - uncertainties identified following the review of initial T&Cs imposed, which may have potential impacts on the benefit-risk of the drug for its indicated use
  - new risks or uncertainties identified as a result of new information obtained from markets outside Canada or from published evidence in scientific journals as it relates to our authorization of the indication
  - new risks and uncertainties resulting from outcomes from studies conducted under risk management plans (RMPs), which may have impacts on the benefit-risk profile of the approved drug
- conditions that:
  - implement an ongoing monitoring program to detect trends in quality such as verifying impurities identified in a drug through additional specific testing and investigational requirements for impurities

Anticipatory terms and conditions

Anticipatory terms and conditions letter

Health Canada will inform the manufacturer of its intent to impose T&Cs by issuing an 'Anticipatory Terms and Conditions Letter'. The anticipatory letter will:

- explain the risk(s) and/or uncertainties that we have identified
- outline the objectives for imposing T&Cs and
- describe the expected outcome from the specific T&Cs imposed

Response to letter

Manufacturers should provide a response to the Anticipatory Terms and Conditions Letter and, as applicable, include information on how they will fulfill the T&Cs.

If the T&Cs require the manufacturer to conduct more studies for the indicated use, the manufacturer should provide:

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

If confirmatory studies are one of the T&Cs being imposed, such studies may already be under way in Canada or other jurisdictions. Health Canada will consider accepting these studies if they meet the objective of the T&C.

In general and depending on the nature of the issues raised, the manufacturer will be given up to 30 calendar days from the date specified on the letter to respond. If a new risk and/or uncertainty identified requires urgent attention, the time to respond may be reduced.

We will review a manufacturer's response within 30 calendar days upon receiving the manufacturer's response. During this review, we may ask for clarification. This will be done in accordance with the following guidance documents:

- Guidance document: The management of drug submissions and applications for human drugs
- Veterinary drugs – Management of regulatory submissions: Updated guidance for industry for veterinary drugs

Manufacturers who object to the proposed T&Cs may provide reasons for their objections. They may:

- suggest an alternative proposal with a supporting rationale as to why the alternative is preferable
- comment on the technical feasibility of the T&Cs and/or
- propose less burdensome means of achieving the objectives

Terms and conditions letter

Once we have reviewed the response to the Anticipatory Terms and Conditions Letter, we will finalize the conditions following review of the information provided by the manufacturer.

We will prepare the final 'Terms and Conditions Letter'. The letter will specify the:

- applicable DIN(s) for the authorized indication on which the T&Cs will be imposed
- conditions to be fulfilled
- information to be submitted and
- timeframe for fulfilling the T&Cs, as applicable

Amending terms and conditions

An amendment to a T&C includes adding, modifying or removing a T&C(s) on the DIN of a drug for its authorized indication. The T&C letter is updated as individual conditions are fulfilled, to reflect the date the condition(s) was fulfilled, where applicable.

Although the Minister initiates amendments, a DIN owner may request an amendment to a T&C(s) by filing an undefined regulatory activity (UDRA).

For more information on this submission type for human drugs, you may consult the following guidance document:

- Guidance document: The management of drug submissions and applications

When doing so, the DIN owner must provide a rationale as to why they are asking for the amendment. Depending on the type of amendment, they would also have to provide the scientific basis to support the reason for the requested amendment.

If the amendment request concerns changing a study methodology to meet the main objective of the T&C, the DIN owner should provide the proposed methodology. For example, if during an ongoing study, the DIN owner concludes that the study cannot be completed for technical or scientific reasons, they must include

the proposed alternative methodology or study to fulfill the T&C(s). The Minister would review the information provided and make a decision to amend the T&C(s) accordingly.

Filing information to fulfill terms and conditions

The 'Terms and Conditions Letter' may include several conditions. Each condition may have a different timeline for completion or no timeline for conditions imposed that are ongoing.

Where applicable, a DIN owner must submit the information required to fulfill the T&C(s) by the date indicated in the letter. Some DIN owners may have had similar conditions imposed in another jurisdiction and the foreign regulator may have removed these conditions. Regardless of the status of the conditions imposed in another jurisdiction, a DIN owner must fulfill their obligations under the FDR for the T&Cs imposed in Canada by filing the relevant information for Health Canada's review.

The DIN owner should file information to fulfill the T&Cs using the appropriate submission type (detailed in this section). For more information, you may also consult the following guidance documents:

- Guidance document: The management of drug submissions and applications for human drugs
- Veterinary drugs – Management of regulatory submissions: Updated guidance for industry for veterinary drugs

If results from studies or information required by the T&C:

- indicate the benefit-risk profile has changed since the submission or an application was reviewed and issued an authorization, the DIN owner should file this information as an appropriate post-authorization submission type
- do not indicate that the safety, efficacy and/or quality has changed, a UDRA may be filed
    - if we determine that the evidence filed as a UDRA affects the information on which the authorization was based, we will ask the DIN owner to file the appropriate submission or application type

For more information on determining which post-authorization submission type is most appropriate, please consult the relevant post-authorization changes guidance documents:

- Post-notice of compliance (NOC) changes: Safety and efficacy document
- Post-notice of compliance (NOC) changes: Quality document
- Post-drug identification number changes

Once a DIN owner files the information to fulfill the T&C(s), we will review the submitted information as per the performance standards outlined in the applicable guidance documents:

- Guidance document: The management of drug submissions and applications for human drugs
- Veterinary drugs – Management of regulatory submissions: Updated guidance for industry for veterinary drugs

Once we have reviewed the information filed, we will inform the DIN owner of the results of the review.

If the condition(s) is fulfilled and a favourable benefit-risk profile is maintained, the Minister will amend the Terms and Conditions Letter to indicate the date by which the T&C(s) was fulfilled.

If further conditions are to be imposed or existing conditions need to be amended, the Minister will inform the DIN owner of what actions must be taken through another Anticipatory Terms and Conditions Letter.

If other regulatory tools can be used to address the identified issues, additional T&Cs may not be imposed. Depending on the nature of the issue, rather than imposing T&Cs, we may, for example:

- require that the labelling in the product monograph be updated to reflect new information
- request an updated RMP
- ask the DIN owner to submit a PSUR, PBRER or ASR

We may impose new conditions if, for example:

- the identified and/or potential risks, and/or uncertainties for which the T&Cs were initially imposed have not adequately addressed or managed the risks and/or uncertainties
- new risks and/or uncertainties have been identified
- additional studies or trials can be conducted to address or manage the uncertainties

In such cases, the Minister will issue a new Anticipatory Terms and Conditions Letter to the DIN owner. This letter will indicate the new T&C(s). The DIN owner will have up to 30 days to respond from the date of the letter.

Health Canada may take other regulatory actions if the information or data demonstrates an unfavourable change to the benefit-risk profile. Reasons for doing so include, for example:

- the drug is considered unsafe for the authorized indication(s)
- there is insufficient evidence to demonstrate that the drug will have the effect and/or benefit under the conditions of use prescribed, recommended or proposed

All conditions are fulfilled

Once a DIN owner provides satisfactory evidence that all the T&Cs of the original (or amended) Terms and Conditions Letter have been met, we will issue a final letter. This letter will:

- indicate that the DIN owner has met all the conditions
- reference the DIN(s) on which the T&Cs were imposed
- state that the T&Cs will be removed

Compliance and enforcement of terms and conditions

All T&Cs will be enforceable under section 21.7 of the FDA. Under section 31.2 of the FDA, it is an offence if a DIN owner does not comply with the T&Cs imposed (for example, fails to submit a confirmatory study within the specified time outlined in the Terms and Conditions Letter).

If a DIN owner were not to comply with the T&Cs imposed, Health Canada may take compliance and enforcement actions.

Learn more:

- Compliance and enforcement policy (POL-0001)

Health Canada 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 or
- efficacy or quality of the drug has changed

Regulatory actions may result in stop-sale, ordering additional studies, ordering label changes, suspending an NOC or cancelling a DIN.

Transparency

Health Canada will continue to communicate up-to-date information about drugs for human and veterinary use.

You can find the following information online:

- NOC database: contains NOCs issued for drugs for human and veterinary use
- Drug product database: contains information about DINs issued for drugs for human and veterinary use, such as:
    - the product monograph for human drugs
    - the product labelling for veterinary drugs
- Drug and Health Product Register: contains regulatory decision summaries and summary basis of decision documents
    - these describe our rationale for approving 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
- Drug Product Inspection Database (DHPID): The drug and health products inspections database (DHPID) gives information about each type of drug and health product inspection done by Health Canada

We will also post information on the Drug and Health Product Register about T&Cs that have been imposed on the DIN of a drug for its authorized indication(s), including statements on the T&Cs imposed and their timelines. We will update these as T&Cs are fulfilled and amended. The information we post will not contain any confidential business information.