Draft guidance on human and veterinary drug submissions based on promising evidence and terms and conditions

This guidance document is being distributed for comment purposes only.

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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.

Table of Contents

Overview

Purpose

This guidance document outlines the:

- requirements for human and veterinary drug submissions that are based on promising evidence of clinical efficacy
- terms and conditions (T&Cs) when issuing a notice of compliance (NOC) for drugs authorized based on promising evidence of clinical efficacy

Introduction

The Food and Drugs Act (FDA) and its regulations give Health Canada the authority to regulate food, drugs, medical devices and cosmetics. All drugs intended to be marketed for human and veterinary use in Canada are reviewed to ensure that they meet the requirements of the FDA and its regulations. As the federal regulator for drugs, Health Canada's role is to thoroughly evaluate the information supporting a drug submission. Through scientific assessments, the review process is to ensure a drug:

- is safe for human and veterinary use, with acceptable risks compared to benefits
- is effective for the intended treatment or condition
- meets quality standards in manufacturing, purity, and consistency

To be authorized for sale, drugs for human and veterinary use must meet all applicable requirements in Part C, Division 1 of the Food and Drug Regulations (regulations). Drugs that meet the definition of a new drug under Part C, Division 8 of the regulations must also satisfy the requirements of Division 8. If there is insufficient evidence to support the safety, effectiveness or quality of a new drug, Health Canada will not grant market authorization for the drug.

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

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

However, while the available data may be limited, it may provide promising evidence that the drug could help reduce or prevent serious signs, symptoms, or adverse clinical outcomes of a disease or condition. The evidence may demonstrate that the drug has a clinical benefit and that the benefits outweigh the known risks relating to the drug's use. New drugs that are supported by information that has demonstrated promising evidence of clinical efficacy should be made available to individuals who have serious or severely debilitating conditions where there is an unmet medical need. If the information supporting the drug demonstrates the benefits outweigh the known risks and if it satisfies the requirements of the FDA and the regulations, a NOC may be issued to allow market authorization of the drug. However, in the case of a drug supported by promising evidence of efficacy, significant uncertainties remain with the effectiveness of the drug. As such, the available evidence may satisfy the requirements of the FDA and the regulations if additional confirmatory studies are performed to verify the new drug's effectiveness for further assessment.

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 drug met the relevant requirements of the FDA and its regulations and the evidence demonstrated the drug has a favourable benefit-risk profile. To be considered for market authorization of new drugs that are supported by promising evidence of clinical efficacy, we will consider imposing terms and conditions (T&Cs) to address the significant uncertainties regarding the effectiveness of the drug. T&Cs may be imposed on the DIN of the drug when determining to issue the NOC. These T&Cs will require market authorization holders (MAHs) to conduct further studies to confirm the effectiveness of the new drug and further confirm that it maintains a favourable benefit-risk profile as was determined at the time of authorization.

Scope and application

This draft guidance document applies to new drug submissions (NDS) and supplements to new drug submissions (SNDS) for human or veterinary drugs that meet the following criteria:

- the submission is for a human or veterinary drug that meets the definition of a new drug under C.08.001 **and**
- the information supporting the new drug is based on promising evidence of efficacy

It explains the:

- process for filing a NDS or SNDS based on promising evidence of efficacy
- review of these drug submissions
- process for human drug manufacturers to apply for shortened screening and review targets
- application of the T&Cs and when the Minister may take these into account during the review of a submission based on promising evidence of efficacy

The focus of this guidance is on drug submissions based on promising evidence of clinical efficacy where T&Cs are considered by applying section C.08.003.2 of the FDR. For general information on T&Cs and its application, refer to:

- Draft guidance on terms and conditions for human and veterinary drugs

Policy objectives and statements

A NDS or SNDS must be supported by sufficient information as required by the regulations for a new drug to be considered for market authorization.

Drug submissions supported by clinical data demonstrating promising efficacy, supported by subsequent confirmatory evidence, may be sufficient to support regulatory decision-making. However, until confirmatory evidence is fully assessed, significant uncertainties about the drug's effectiveness remain. In such cases, early market access may be considered appropriate for drugs intended to treat serious or severely debilitating diseases.

To be considered for market authorization, T&Cs will be considered to address the significant uncertainties with the clinical effectiveness of the drug. Such considerations may be applied when the proposed use of the new drug is for serious or severely debilitating disease or condition and its recommended purpose and conditions of use do not fall within those of any other drug that has been assigned a DIN. Alternatively, it may apply if the new drug is significantly more effective or presents a significantly lower risk than an existing drug with an active DIN.

Our objective in considering drug submissions supported by promising evidence of clinical efficacy is to enable earlier access to promising new therapies while ensuring that the drug's overall benefit-risk profile remains favourable.

Potential sources of promising evidence of efficacy

We may accept data from clinical trials or veterinary studies that use surrogate markers. To be validated, a surrogate marker must undergo extensive testing to confirm that its effect accurately predicts clinical benefits. Data from non-validated surrogate markers cannot replace evidence showing a drug's impact on recognized clinical endpoints.

In any case, while the evidence for efficacy is promising, these new drugs must demonstrate that they meet safety and quality requirements as well as other requirements for a NDS or a SNDS.

For human drugs, relevant evidence may be derived from:

- acceptable surrogate markers from clinical studies that require confirmation in additional clinical studies
- Phase II clinical studies that require confirmation in one or more Phase III studies

    - this may include cases in which Phase II results are available for only a specific disease stage or patient subgroup
- one or more small or moderately sized Phase III clinical studies that require confirmation in at least one additional larger, adequately sized, Phase III and/or Phase IV study
    - this may include cases in which limited Phase III results are available for only a specific disease stage or patient subgroup and additional data are required to support use of the drug in other disease stages and/or a broader patient population

For veterinary drugs, relevant evidence may be derived from:

- pilot studies where more animal subjects are needed **or**
- interim analysis of pivotal efficacy study

Results obtained from studies are evaluated in the context of additional information, such as:

- advisory panels
- expert opinions
- literature reviews
- real world evidence **and**/**or**
- pharmacokinetic/pharmacodynamic studies

Definitions

Advance consideration of promising evidence (ACPE) status: A status granted to human new drug submissions (NDS) and supplements to new drug submissions (SNDS) resulting in reduced screening and review targets when certain criteria have been met.

Available therapies: Drugs for which a DIN has been assigned and has not been cancelled for a specified recommended purpose and conditions of use. Products available through the special access program (SAP), emergency drug release (EDR), or the urgent public health need (UPHN) list are not considered "available therapies" for drug submissions based on promising evidence of clinical efficacy.

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

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 clinical evidence: 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 intermediate clinical endpoint that is reasonably likely to predict clinical benefit.

Request for advance consideration of promising evidence (ACPE): A form for drug submissions with promising evidence of clinical efficacy that, once completed, is used to determine if a submission will meet the criteria for reduced screening and review targets.

SNDS-Confirmatory (SNDS-C): A supplement to a new drug submission (SNDS) - confirmatory is a submission of the results from the confirmatory clinical trials and/or veterinary studies specified in the 'Terms and conditions letter'.

Surrogate markers: 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

Significant uncertainties – Section C.08.003.2 of the Food and Drug Regulations for terms and conditions

A drug must demonstrate it is safe, effective and of high quality, even when the efficacy data supporting a drug submission is based on promising evidence. All requirements of the Food and Drugs Act (FDA) and regulations must be met to be considered for authorization.

However, as per section C.08.003.2 of the regulations, if there are significant uncertainties regarding a new drug's effectiveness, the Minister may, in examining the submission or the supplement, consider whether T&Cs under section C.01.014.21 could help provide additional information on these uncertainties when the criteria is met.

The Minister may take this approach if the new drug is intended for:

- patients suffering from serious or severely debilitating diseases or conditions, and no drug has been issued a DIN, or the DIN has not been cancelled **or**
- a condition where the drug shows a significant increase in efficacy or a significant decrease in risk, compared to an existing drug with a DIN that has not been cancelled

The criteria in the provisions of section C.08.003.2 of the FDR state:

> In cases where there are significant uncertainties respecting the evidence of the effectiveness of a new drug that was provided in a new drug submission or supplement to a new drug submission, the Minister may, in examining the submission or supplement, take into account whether terms and conditions that may be imposed or amended under section C.01.014.21 would enable the Minister to obtain additional information respecting the uncertainties, if
>
> **(a)** the new drug is intended to diagnose, treat, mitigate or prevent a disease, disorder or abnormal physical state, or symptom of a disease, disorder or abnormal physical state, that poses or may pose a serious risk of injury to human or animal health **and**
>
> **(b)** the recommended purpose and conditions of use of the drug either:
>
> (i) do not fall within the recommended purposes and conditions of use of any other drug for which a drug identification number has been assigned and not been cancelled **or**

(ii) do fall within the recommended purposes and conditions of use of any other drug for which a drug identification number has been assigned and has not been cancelled, but the Minister has reasonable grounds to believe that the new drug is significantly more effective, or poses a significantly lower risk than the other drug

Confirmatory studies and terms and conditions if criteria in section C.08.003.2 of the Food and Drug Regulations is met

Drug submissions that are supported by promising evidence of efficacy may have significant uncertainties with the drug's clinical effectiveness. Therefore, to be considered for market authorization, drugs that are supported by promising evidence of efficacy may have T&Cs imposed on the DIN of the drug to further characterize the benefit of the drug while monitoring the risk so as to ensure a favourable benefit-risk profile is maintained. Confirmatory trials generate statistically conclusive evidence of the drug's efficacy and safety by testing it in larger groups or for longer times. Generally, these confirmatory trials would be conducted in the same population for which an approval with promising evidence was given. There are some circumstances where flexibility may be considered with a strong rationale (for example, confirmatory trial conducted in a different line of therapy). T&Cs may also be imposed that require market authorisation holders (MAHs) to provide results from confirmatory trials submitted to a foreign jurisdiction.

Through the imposition of T&Cs, MAHs will be required to pursue confirmatory trials. MAHs will be required to design, carry out, and report on additional human or animal clinical trials to verify the anticipated benefit for the authorized indication within a specified time frame, when the data may have been limited, or surrogate markers were used in clinical trial studies. T&Cs may also be imposed to require MAHs to provide results from confirmatory trials submitted to a foreign jurisdiction.

During the review period, prior to issuing a notice of compliance (NOC), we will apply section C.08.003.2 of the Food and Drug Regulations (regulations) if the criteria are met, and evaluate the acceptability of the proposed confirmatory studies.

There may be cases where a new drug submission or supplement to a new drug submission was not filed with information based on promising evidence of clinical efficacy but the information supporting the drug submission is insufficient to recommend the issuance of a NOC. However, during the review, we could determine that there is promising evidence of clinical efficacy for an unmet medical need. In such cases, if the drug meets the criteria in the regulations (section C.08.003.2) we may contact the manufacturer to discuss the potential for imposing T&Cs to require confirmatory evidence of effectiveness for a drug to be considered for a NOC since the drug demonstrates there is promising evidence of clinical efficacy.

As per section C.08.003.2, 2 criteria must be met (criterion (a) and (b)) when taking T&Cs into account when examining a submission for a drug that was supported by promising

evidence of efficacy. Consideration is given to the following when assessing whether the 2 criteria are met:

For criterion (a), serious or severely debilitating diseases or conditions are generally associated with morbidity that causes a substantial impact on day-to-day functioning. We may accept promising evidence of efficacy for new drugs or new indications proposed to be for:

- use in the treatment, prevention, or diagnosis of reversible, but recurrent serious or severely debilitating diseases or conditions **or**
- non-serious conditions that, left untreated, could be expected to progress to a serious or severely debilitating condition or mortality

Promising evidence of efficacy would not be acceptable for new drugs or new indications proposed for use in the treatment, prevention, or diagnosis of a condition that is:

- self-limiting
- of short duration
- a non-serious condition in a patient with a serious disease or severely debilitating condition (for example, a minor skin irritation in a patient with cancer)

When considering criterion (b)(i), the proposed recommended purpose and condition of use of the drug should:

- seek to provide treatment, prevention or diagnosis of a disease or condition for which no drug has been assigned a DIN in Canada, for the same recommended purpose and condition of use intended by the new drug
- address a favourable effect on a serious symptom or manifestation of the condition for which no drug has been issued a DIN in Canada, for the same recommended purpose and condition of use intended by the new drug

For criterion (b)(ii), the proposed drug should have promising evidence of clinical efficacy to demonstrate in comparison to a drug that has been assigned a DIN for the same recommended purpose and condition of use that it has achieved at least one of the following:

- treatment has shown improvement in one or more of the serious outcomes of the condition
- treatment has shown a benefit for patients who are unable to tolerate, or are unresponsive to, available therapies

- the proposed drug has greater improvement in one or more of the serious outcomes of the condition when combined with one or more approved drug(s), compared to use of the authorized drug(s) alone
- the proposed drug should have promising evidence to show it has a benefit similar to that provided by currently available therapy(ies) but includes:

    a) avoidance of serious toxicity that is associated with currently available therapy(ies) **and/or**
    b) avoidance of toxicity that commonly results in the discontinuation of currently available therapy(ies) for a serious disease or severely debilitating condition **and/or**
    c) the ability to provide similar benefit to existing therapies while demonstrating improvement in some factor, such as compliance or convenience, shown to lead to improved effects on serious outcomes

In assessing criterion (b)(ii), statistically significant and/or clinically relevant benefit is expected to be identified through well-designed clinical trials and veterinary studies.

Intent to impose terms and conditions

T&Cs may be imposed to require MAHs to conduct confirmatory trials or veterinary studies within a specified timeframe, to verify the anticipated benefit of the drug over time for the authorized indication and to ensure that a favourable benefit-risk profile is maintained.

During the review of the drug submission, if the criteria are met, we will inform the manufacturer of our intent to impose T&Cs for confirmatory studies to obtain additional information to address significant uncertainties. We will send an “Anticipatory terms and conditions letter” to allow the manufacturer an opportunity to be heard.

Terms and conditions for notification on issues identified by foreign jurisdictions

If the new drug or indication under review has obtained a market authorization from a foreign regulator, in addition to imposing T&Cs for confirmatory trials, we may also impose T&Cs to require notifying and reporting on specific issues of concern that have been identified by a foreign jurisdiction as part of addressing the significant uncertainties a new drug with promising evidence may have. We may require the MAH to do both of the following actions:

a) Notify Health Canada within 15 calendar days of the date on which an expert panel or advisory committee has been struck in a foreign jurisdiction to address

an issue regarding the drug as it relates to safety, efficacy or quality. Alternatively, notify Health Canada within 15 calendar days of the date on which there has been significant regulatory action in another jurisdiction. This includes a direction to issue warnings, a health advisory or the removal of a product from the market.

b) Prepare and submit a report on the issue that prompted the action in the foreign jurisdiction. The report should be available to Health Canada within 30 calendar days of the notification. This timeframe may be subject to negotiation with Health Canada when the scope of the issue under investigation warrants additional time to gather the necessary information.

Notifications and reports should be directed to the relevant pre-market authorisation directorate, the Marketed Health Products Directorate for human drugs, or to the Veterinary Drugs Directorate for veterinary drugs.

Before filing a submission

Before filing a new drug submission or supplement to a new drug submission for human and veterinary drugs based on promising evidence of efficacy

We ask that manufacturers request a pre-submission meeting in advance of filing a new drug submission (NDS) or supplement to a new drug submission (SNDS) for human and veterinary drugs seeking market authorization of their drug, on the basis of promising evidence of clinical efficacy.

Pre-submission meeting

Manufacturers should submit a pre-submission/application meeting package in one of the acceptable file formats.

For more information on the pre-submission meeting process, refer to:

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

Veterinary drugs – Pre-submission

For veterinary drugs, manufacturers should submit a pre-submission meeting package at least one month in advance of the meeting. In addition to the information to be included in the pre-submission meeting package as per the Management of regulatory submissions guidance, the following information should be provided as an appendix to the pre-submission package:

- A summary of studies completed to support the promising evidence
- How the product meets the criteria for a serious or severely debilitating disease or condition
- The status of ongoing studies aimed to support clinical effectiveness of a drug product, including anticipated completion dates
- A plan for completing all ongoing studies
- A timeline for filing of the submission based on promising evidence

We will notify the manufacturer if a NDS or SNDS contains the necessary information to be considered as a submission based on promising evidence of efficacy within 14 calendar days after the pre-submission meeting minutes are finalized.

Unless otherwise agreed to in the pre-submission meeting, submissions should be filed within 6 months of receiving this confirmation, or a new pre-submission meeting may be required. A copy of this confirmation should be included in the submission.

Advance consideration of human drug submissions filed with promising evidence of efficacy

Manufacturers may seek a shorter screening and review target for their drug submission by requesting advance consideration of promising evidence (ACPE) status. ACPE status will be granted for submissions based on promising evidence if specific criteria are met. Refer to the following in this guidance:

- For human drug submissions granted advance consideration
- Request for advance consideration of promising evidence template for human drugs status

Manufacturers should state within their pre-submission meeting request that they are seeking ACPE status. The request for ACPE template is to be completed and filed at the same time as the filing of the pre-submission meeting package. We will use the completed request as part of the initial assessment to determine if the drug submission will be granted a reduced screening and review targets.

We will grant or deny a request for ACPE status based on the assessment of the information provided in the ACPE template, the pre-submission meeting package and the pre-submission meeting minutes. We will inform manufacturers of our decision within 14 calendar days of receipt of the final pre-submission meeting minutes by the review bureau. This will be communicated to manufacturers through the issuance of an acceptance or denial letter for ACPE.

If ACPE is granted, the drug submission will be referred to as a drug submission based on promising evidence and will be subject to reduced screening and review targets.

The sponsor should clearly state in their cover letter when filing the drug submission that it has been granted ACPE. A copy of the acceptance letter should be included. The submission should be filed within 60 calendar days of the date of the acceptance letter (Figure 1).

We encourage manufacturers who file drug submissions to work with us and the relevant health technology assessment organizations on an aligned review:

- Canada's Drug Agency (formerly Canadian Agency for Drugs and Technologies in Health or CADTH)
- Institut national d'excellence en sante et en services sociaux (INESSS)

For additional information related to the aligned review process, refer to:

- Notice to industry: Aligned reviews between Health Canada and health technology assessment organizations

Denial of a request for advance consideration of a human drug submission filed based on promising evidence of efficacy

We may deny a request for ACPE of a drug submission based on promising evidence of efficacy for reasons such as:

- the drug does not meet the criteria listed in the section C.08.003.2 of the Food and Drug Regulations (regulations)
- failure to provide a completed ACPE template
- failure to adhere to the required filing procedures listed in section on before filing a drug submission with promising evidence of efficacy in this guidance

If the request for ACPE status is denied and a submission is filed, the submission screening and review targets will not be reduced.

Revised request following denial of a request for advance consideration of promising evidence for a human drug submission

If we deny a request for ACPE, the manufacturer has 30 calendar days from the date of the decision letter to file a revised request for ACPE. The document must clearly denote the new information submitted (for example, new results for ongoing clinical studies). Failure to provide new information will result in denial of the request. Health Canada will review the revised request for ACPE within 30 calendar days and will communicate its decision through the issuance of an acceptance or denial letter.

If we deny the revised ACPE request, no further requests based upon the same proposed indication for the drug will be considered for an ACPE.

Assessment of information in pre-submission meeting package

We will consider the current standard of care, which may or may not be the same as that used in the relevant clinical study in the planned NDS or SNDS when assessing the pre-submission meeting package as well as the information presented at the pre-submission meeting, and the ACPE request in the case for human drugs. The onus is on the manufacturer to provide a robust rationale for the selection of the comparator and to analyze the comparative benefit-risk profiles in the context of the current standard of care.

Additional information to be provided

Following a pre-submission meeting, and if ACPE status is granted for human drugs, the manufacturer is asked to include the following in their NDS or SNDS submission package, if available:

For human and veterinary drugs:

- Annual Summary Report (or similar safety update report, such as PSUR [for human and veterinary drugs] or PBRERs [for human drugs])
- Copies of foreign review assessment reports
- Copies of labelling for the drug product approved in other regulatory jurisdictions
- A complete listing of ongoing additional clinical trials related to the proposed indication
- A summary of the international regulatory status of the drug, including:
    - ongoing requests for market authorization in other jurisdictions
    - market withdrawals in other jurisdictions, along with reasons (for example, serious safety concerns, commercial reasons)
- Any existing marketing authorizations for the drug under review in foreign regulatory jurisdictions

In addition to the above, for human drugs only:

- Periodic Benefit-Risk Evaluation Reports (PBRERs)
- Copies of approved Pediatric development plans from other regulatory jurisdictions
- Copies of approved Risk Management Plans (RMPs) from other regulatory jurisdictions, if applicable

For information on RMPs, refer to:

- Submitting risk management plans guidance document

Submission screening and review

Targets for human drug submissions granted advance consideration of promising evidence status

If we grant advance consideration promising evidence (ACPE) status for human drugs, reduced targets for the screening and review of the NDS or SNDS are as follows (Figure 1):

- 10 calendar days for administrative processing
- 25 calendar days for screening
- 200 calendar days for submission review (60 additional days will be added to the review target for review and finalization of T&Cs)

Response to notice of deficiency (NOD): The above-noted targets for the submission would also apply to screening and review of a response to a NOD.

Response to a notice of non-compliance (NON): The targets for screening and review of a response to a NON are as follows:

- 10 calendar days for administrative processing
- 25 calendar days for screening
- 90 calendar days for submission review (60 additional days will be added to the review timeline for review and finalization of T&Cs)

Targets for veterinary drug submissions

While every effort to expedite the submission will be made, it will be resource-dependent. As such, the screening and review targets for veterinary drugs are in accordance with the following:

- Veterinary drugs - Management of regulatory submissions guidance

For more information on performance standards refer to:

- Appendix A of the Management of regulatory submissions guidance

Advance consideration of a human drug submission supported by promising evidence of efficacy was not pursued or not granted

Manufacturers may have filed a drug submission that was:

- for a proposed indication that was supported by information not based on promising evidence of efficacy **or**
- denied advance consideration of promising evidence (ACPE)

These drug submissions usually follow the standard 300-day review target. However, during review, if promising efficacy data is found for a specific use but uncertainties remain, T&Cs may be imposed under section C.08.003.2 of the Food and Drug Regulations (regulations). In such cases, we will issue an anticipatory terms and conditions letter to give the manufacturer the opportunity to respond. The 300-day target remains unchanged, and the response is reviewed within that period (Figure 2).

A manufacturer may have requested a priority review for their drug submission and if granted, the submission follows a 180-day review target. "Promising" clinical evidence including the use of non-validated surrogate markers, do not fall within the scope of drug submissions that would be granted priority review.

However, during the priority review, we may find promising efficacy evidence but also significant uncertainties of effectiveness, requiring T&Cs under section C.08.003.2 of the regulations. In such cases, an anticipatory terms and conditions letter will be issued before the 180-day review target ends, extending the target date by 60 calendar days. This will allow the manufacturer an opportunity to be heard and will provide us with time to review the manufacturer's response (Figure 2).

For more information on priority review refer to:

- Guidance for Industry - Priority Review of Drug Submissions

Issuance and response to the anticipatory terms and conditions letter

For information on the issuance and response to the anticipatory terms and conditions letter, refer to:

- Draft guidance on terms and conditions for human and veterinary drugs

Human drug submissions that have been granted ACPE status will be subject to a 200-calendar day review target. However this review target date will be extended by 60 calendar days when the anticipatory terms and conditions letter is issued to allow time for the manufacturer to respond and for Health Canada to review the response (Figure 1).

Manufacturers should submit a response within 30 calendar days of receiving the Anticipatory Terms and Conditions Letter from Health Canada, outlining how the T&Cs will be fulfilled. If no response is received, we may contact the manufacturer to inform them that we will proceed with imposing the T&Cs based on available information.

The response should include details on the confirmatory trials intended to verify the drug's clinical efficacy, as well as timeframes for their initiation and completion. The nature and scope of the proposed confirmatory trials must be:

- feasible, well-designed and include an assessment of key clinically relevant efficacy and safety endpoints
- carried out in accordance with established scientific standards **and**
- initiated and completed in a timely fashion

It is recognized that when an authorization with imposed T&Cs is granted, confirmatory trials may already be underway in Canada or other jurisdictions. At our discretion, these trials that are already underway may be acceptable confirmatory trials for a T&C.

Factors for consideration of confirmatory trials that may already be underway include:

- trial design
- clinical endpoints
- safety measures

The manufacturer is responsible for bridging the outcomes from the ongoing trials to the outcomes of the anticipatory T&Cs from the Health Canada-requested confirmatory trials, with appropriate rationale.

If the manufacturer does not agree with the confirmatory trials requested in the anticipatory terms and conditions letter, they must provide a written response. This response should include:

- the reason for their objections
- an alternative proposal to confirm the drug’s efficacy

Additionally, the response should include a supporting rationale explaining why the proposed alternative is preferable. For example:

- improved technical feasibility
- a less burdensome way of achieving the objectives

Responses to an anticipatory terms and conditions letter should reference the submission control number and be provided through the common electronic submissions gateway (CESG).

Issuance of the "Terms and conditions letter"

Upon receipt of the manufacturer's response to the anticipatory terms and conditions letter, we will review the response within 30 calendar days. During this review, we may ask for clarification. This will be done 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

Should the information in the manufacturer's response be considered acceptable, we will finalize the terms and conditions and prepare the T&Cs Letter. The letter will specify the:

- applicable DIN(s) on which the T&Cs will be imposed for confirmatory studies for the target population for which the clinical benefit is to be confirmed
- T&Cs to be fulfilled
- information to be submitted by the market authorization holder **and**
- required timeframe for fulfilling the imposed T&Cs

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

Figure 1: Process flow for a human drug submission where a request for advance consideration based on promising evidence was filed

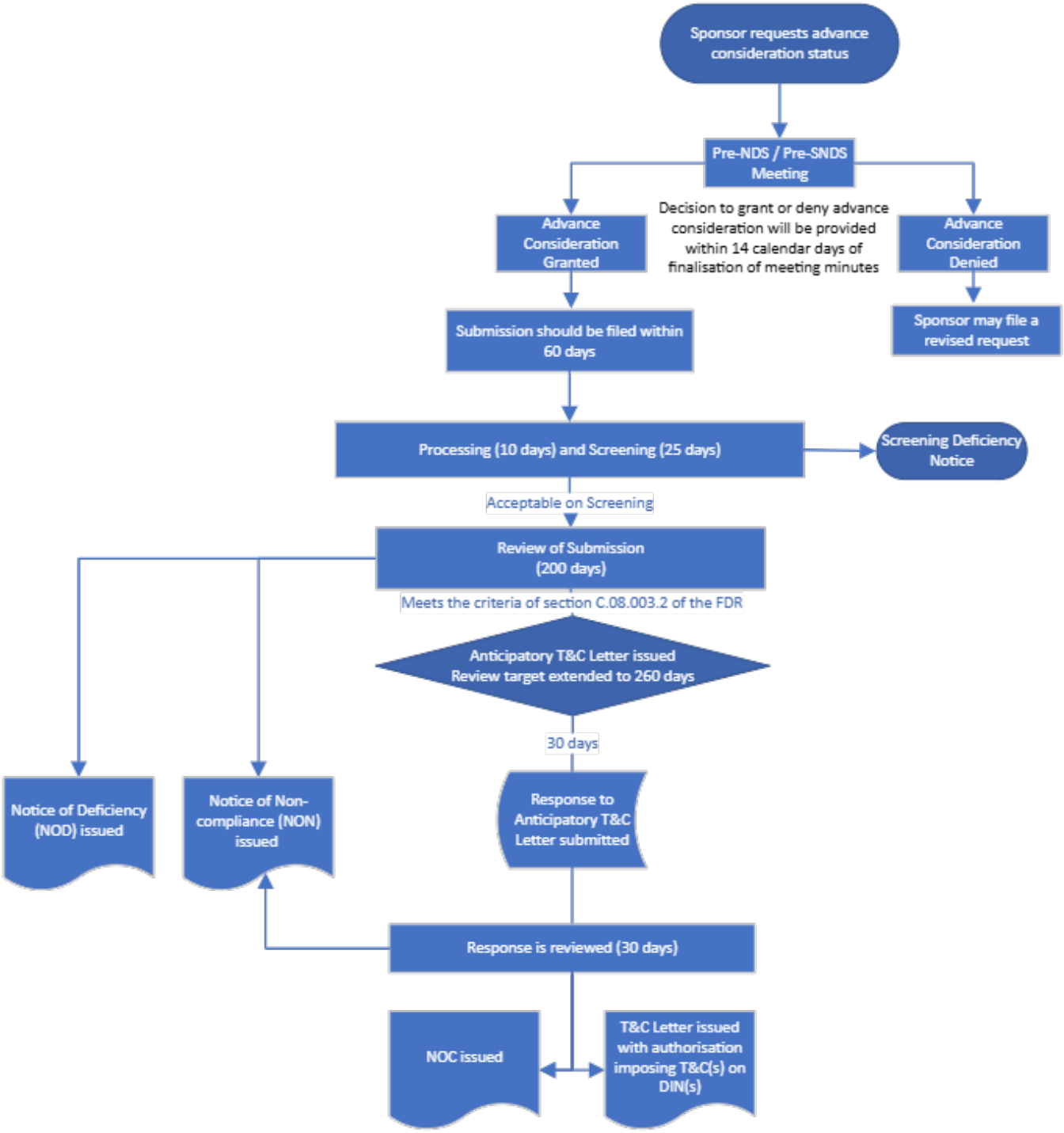


Figure 2: Process flow for a human drug submission where a request for advance consideration status was not filed or not granted

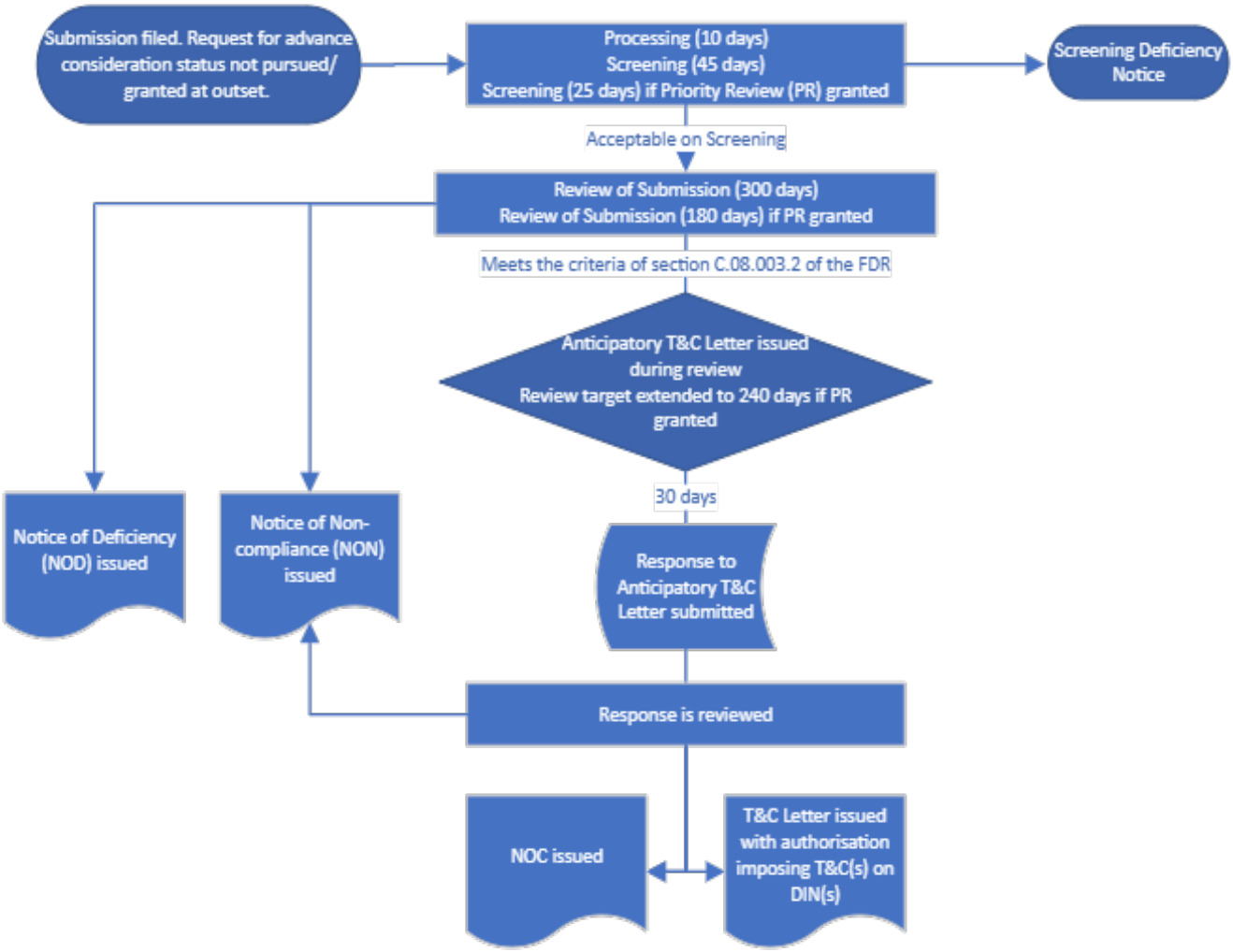
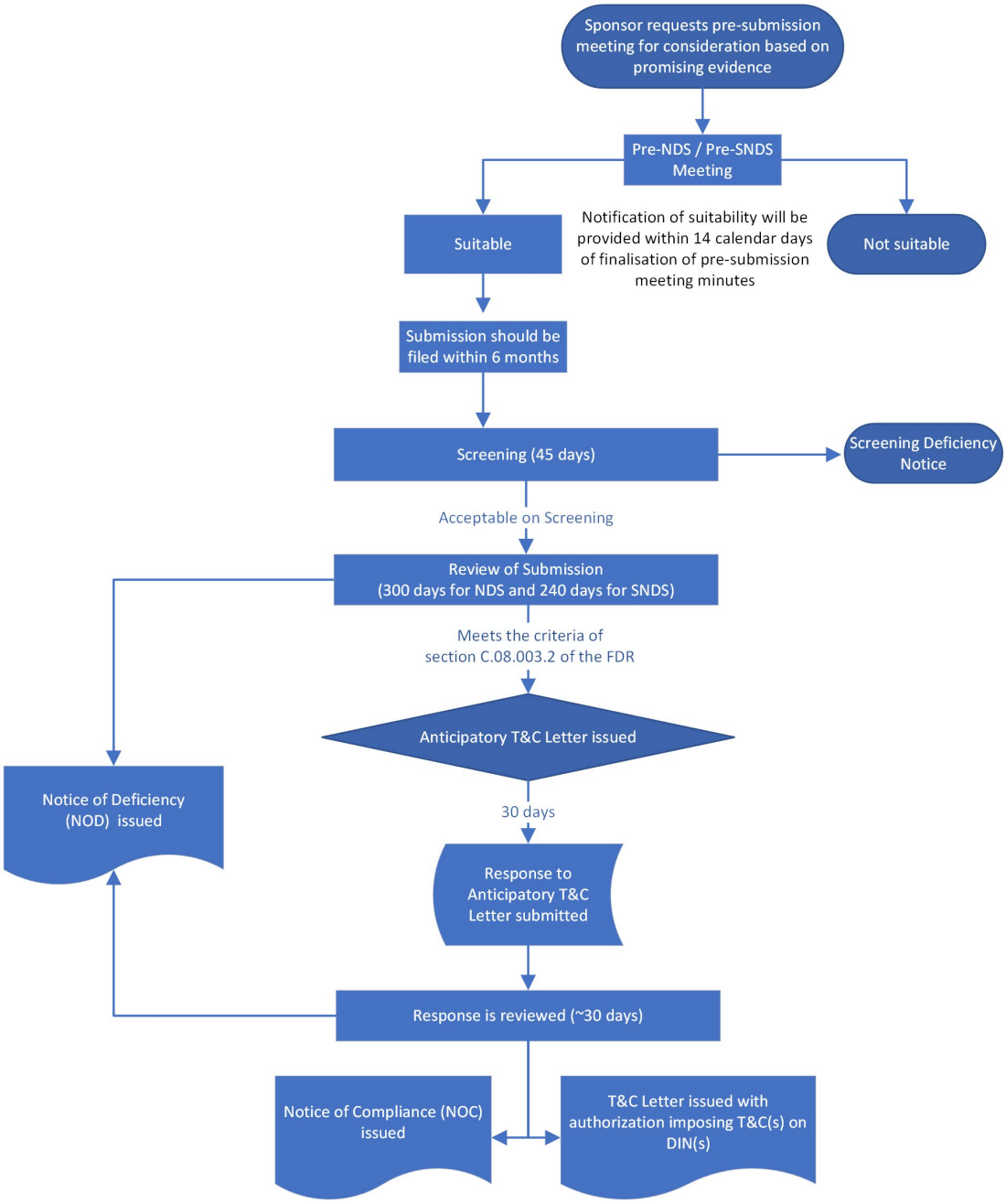


Figure 3: Process flow for a new drug submission or a supplement to a new drug submission based on promising evidence for veterinary drugs



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Labelling and advertising

Labelling of human and veterinary drugs

On a case-by-case basis, we will assess the labelling of drugs that may be granted market authorization based on promising evidence of clinical efficacy that meet the requirements of the Food and Drugs Act (FDA) and the regulations. This evaluation will help determine if enhanced labelling requirements are necessary. This assessment is based on:

- proposed conditions of use (for example, hospital setting, physician or veterinarian administered)
- indication (multiple or singular) **and**
- other potential considerations

For veterinary drugs, package inserts (PI) should include, at a minimum, the sections necessary to ensure veterinarians, producers, and animal owners are properly informed about the imposed T&Cs.

For human and veterinary drugs, manufacturers should refer to sections 3, 9 and 10 of the FDA, as well as related provisions of the Food and Drug Regulations, to ensure compliance with labelling requirements.

For more information on labelling requirements, refer to:

- Guidance on veterinary drug labelling
- Guidance document: Labelling of pharmaceutical drugs for human use

Product monograph for human drugs

The product monograph (PM) should contain the standard information as outlined in the product monograph guidance document. It should also include additional information in specific sections, clearly stating that the:

- DIN for the drug was assigned with imposed terms and conditions (T&C)s **and**
- information presented in the PM is based on promising evidence of clinical efficacy

It should also include an instruction for health care providers to notify the patient that the drug's market authorization was granted based on promising evidence of clinical effectiveness.

Each drug product authorized based on promising evidence of effectiveness should include a PI in its packaging. The PI should include, at a minimum, the sections necessary to ensure health care providers and patients are properly informed about the imposed T&Cs.

For additional information on labelling and PI, refer to:

- Questions and Answers: Plain Language Labelling Regulations for Prescription Drugs - document

Generic or biosimilar products that compare to a Canadian reference product (CRP) or Canadian reference biologic drug (CRBD) with T&Cs to confirm clinical benefit may have T&Cs imposed on their DINs. Manufacturers of generic or biosimilar products may be required to reflect the promising nature of efficacy in their product monograph. They may also be required to include a copy of the PI within the product packaging.

For specific wording for subsequent entry products, refer to:

- Guidance document: Product monograph

Transparency measures for veterinary drugs

After issuing a T&C letter, we will post information related to the T&Cs on the Health Canada website as outlined in the Draft guidance on terms and conditions for human and veterinary drugs.

Additional transparency measures for human drugs

Once a T&C letter is issued, in addition to publishing relevant T&Cs information on our website, as outlined in the Draft guidance on terms and conditions for human and veterinary drugs. We will also include details about those issued a notice of compliance (NOC) based on promising evidence of effectiveness with T&Cs imposed on their DIN.

This will be done by posting a "Notice of market authorization based on promising evidence of effectiveness with imposed terms and conditions" on Health product InfoWatch. The notice will also be shared with key health care groups to highlight that the

drug was authorized with imposed T&Cs supporting approval came from promising evidence of efficacy.

We will not include any confidential business information in the notice. However, we will provide relevant links to the PM and MAH contact information.

We will send a copy of the notice to the MAH 2 business days before posting the notice on the Health Product InfoWatch web page. During this time, the MAH will be able to verify that the information is accurate.

Since the Health product InfoWatch is a monthly publication, the notice of market authorization with imposed T&Cs will be published in the month following the assignment of the DIN and issuance of the NOC, or soon after.

Learn more:

- Health Product InfoWatch
- Draft guidance on terms and conditions for human and veterinary drugs

Advertising requirements and pre-clearance of all promotional materials

Manufacturers of human and veterinary drugs must comply with all advertising requirements outlined in the FDA, the Controlled Drugs and Substances Act (CDSA) and the associated regulations regarding the advertising of drug products.

The term “advertising” includes any representation by any means whatever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device. It includes:

- brochures, booklets, detailing pieces, bulletins, calendars, videos and slides
- materials published in journals, magazines, other periodicals, and newspapers
- materials presented at healthcare professional conferences, continuing medical education activities and other learning activities (OLAs)
- advertisements broadcast through media such as radio, television, the internet, social media and telephone communication systems

Advertising material must abide by the restrictions or conditions specified on the labels for human and veterinary drugs and the PM for drugs intended for human use.

If T&Cs require confirmatory trials, advertising material must clearly state that the authorized indication(s) is based on promising evidence of efficacy and that additional studies are being conducted to confirm the clinical benefit.

If the approved labelling and PM include statements about promising evidence of efficacy, the display portion of all advertising material for these drugs must contain boxed text. This boxed text must disclose that the market authorization was granted based on promising evidence of clinical effectiveness. It must also state that T&Cs have been imposed to confirm the drug's clinical benefit.

For human drugs, manufacturers must submit all healthcare professional directed promotional material related to products authorized based on promising evidence of clinical effectiveness to an independent advertising preclearance agency (APA) recognized by Health Canada. Refer to:

List of Canadian advertising preclearance agencies

Post-market safety

Post-market safety monitoring

For human drugs only, risks and uncertainties may need to be addressed through Risk Management Plans (RMPs).

For more information on requirements for RMPs, refer to:

- Submitting risk management plans guidance document

All drugs that have been authorized based on promising evidence of efficacy, or subsequent-entry drugs (generic drugs and biosimilars) that compare to such a drug, may be subject to enhanced post-market safety monitoring, reporting and active surveillance.

For more information on post-market safety monitoring, reporting and surveillance, refer to:

- Reporting adverse reactions to marketed health products
- Preparing and submitting summary reports for marketed drugs and natural health products - Guidance document for industry
- Notifying Health Canada of foreign actions - Guidance document for industry
- Adverse veterinary drug reactions

Adverse reaction reporting

For human drugs

Adverse events (AE) and adverse reaction (AR) reports from confirmatory trials must follow clinical trial application requirements if conducted in Canada.

These reports, outlined in the terms and conditions letter for drugs with marketing authorization based on promising evidence of clinical effectiveness, must be reported to Health Canada. These reports should be submitted electronically whenever possible.

Sponsors are strongly encouraged to use the electronic reporting gateway to improve efficiency. We support the submission of clinical trial AR reports following international standards outlined in ICH E2B (R2). Manufacturers interested in setting up electronic reporting should contact the trading partner management office at tpmo-bgpc@hc-sc.gc.ca for assistance.

For manufacturers not yet connected to the electronic reporting gateway, reports can still be submitted by fax to the following Canada vigilance program fax lines:

- Pharmaceutical drugs directorate for pharmaceutical drugs: 613-941-2121
- Biologic and radiopharmaceutical drugs directorate for biologic and radiopharmaceutical drugs: 613-957-0364

As a reminder, market authorization holders (MAHs) of marketed human drugs must report post-market ARs to Health Canada as required by the Food and Drugs Act (FDA) and its regulations, and as explained in the Canada vigilance program's Overview of the reporting adverse reactions to marketed health products - Guidance document for industry.

On a case-by-case basis, we may ask manufacturers to update the drug labels, the human drug PM and RMP if:

- new safety concerns have been identified that were not a concern at the time of authorization
- new information has been obtained as a result of additional data obtained on the clinical benefit from the confirmatory studies

For veterinary drugs

For all veterinary drugs marketed in Canada, every MAH is required to report ARs known to them involving their marketed health products in accordance with the requirements of the FDA and its regulations. Serious adverse events occurring as part of confirmatory trials should be reported to the Veterinary Drugs Directorate (VDD) pharmacovigilance (PV) program by:

- telephone: 1-877-838-7322
- the electronic PV works gateway **or**
- completing the Adverse Event Reporting Form Veterinary Drugs Directorate (VDD) and submitting it by email to pv-vet@hc-sc.gc.ca

Manufacturers wanting to set up electronic reporting should contact the PV program at pv-vet@hc-sc.gc.ca for assistance.

Compliance and enforcement

Annual progress reports of confirmatory trials for human drugs

Although not required by the regulations, we ask that market authorization holders (MAHs) submit reports on the progress of ongoing confirmatory trials to Health Canada on an annual basis. The annual progress report should be submitted through the Common Electronic Submissions Gateway (CESG) for eCTD submissions.

The report should be submitted within 60 calendar days of the market authorization anniversary. Alternatively, it can be submitted by the agreed-upon date set by Health Canada and the MAH at the time of the market authorization issuance.

The annual progress report should be brief and include the following:

- a summary of the conditions outlined in the terms and conditions (T&Cs) letter and their outcomes
- the current status of the confirmatory trial(s), which may be pending, ongoing, delayed, terminated, submitted or fulfilled
- explanatory comments regarding the status of the confirmatory trials
- any actions taken by the MAH, for example, if the:
    - status is “pending, delayed or terminated”, the explanatory comments should indicate any other actions taken by the MAH
    - trial was terminated, the explanatory comments should indicate the next steps by the MAH to confirm efficacy of the drug
    - trial is delayed, the explanatory comments should indicate the actions that are being taken to mitigate the delay

If we have any questions regarding the content of the annual progress report, we will contact the MAH within 90 calendar days of receipt of the report by the relevant review bureau.

Progress reports for veterinary drugs

We may request a progress report on the status of ongoing trials on a case-by-case basis. If requested, the brief progress report should include:

- the summary of outstanding conditions
- the status of the trial (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 an agreed-upon date at the time of the issuance of the market authorization. If there are any questions regarding the content, Health Canada will contact the MAH.

Sample progress report

Progress Report: Submitted on DATE (to be submitted annually for human drugs)

Manufacturer/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 Confirmatory Trial:

Confirmatory Trial Schedule:
Protocol approval date; Confirmatory trial enrollment start date and conclusion date; Last patient evaluation date; Health Canada submission date.

Current Status:
Pending, Ongoing, Delayed, Terminated, Submitted or Fulfilled

Explanation of the Status:
Brief description and action taken.

The following are definitions that apply when providing the status of confirmatory trials:

- **Pending:** The confirmatory trial has not been initiated by the MAH.
- **Ongoing:** The confirmatory trial is proceeding according to the original schedule or is ahead of the schedule. The results of the confirmatory trial have not been submitted to Health Canada.
- **Delayed:** The progress of the confirmatory 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 confirmatory 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 should be notified within 15 days.

- **Submitted:** The MAH 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 (NOC) indicating that the MAH has met the T&C.

Process for fulfillment of terms and conditions – Confirmatory trials

Results from confirmatory trials must be submitted as a SNDS-Confirmatory (SNDS-C) according to the individual deadlines outlined in the terms and conditions letter. If multiple confirmatory trials are underway, the final results must be submitted by their respective target dates. It is acceptable to combine results from multiple trials into one SNDS-C, provided the submission is filed by the earliest requested deadline.

The SNDS-C must focus only on the original indication or condition of use for which the authorization was issued. Typically, additional information supporting a new or expanded indication cannot be included and must be submitted separately as a NDS or SNDS.

However, in some cases, the same submitted information may support both the confirmation of the clinical effectiveness and a proposed new indication. In these situations, MAHs may discuss with Health Canada the feasibility of a combined submission.

Once Health Canada has determined that the T&Cs for confirmatory trials have been satisfied, the SNDS-C must also be found to be acceptable. At that point, notations regarding T&Cs may be removed from the product monograph (PM) and product labelling. The T&Cs may also be removed from the drug identification number (DIN).

A NOC will be issued to confirm the acceptability of the SNDS-C and authorize updates to the labelling with the confirmatory trial results.

Amending terms and conditions

The T&C letter will be amended as T&Cs are fulfilled, indicating the date at 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. For more information on amending T&Cs, refer to:

- Draft guidance on terms and conditions for human and veterinary drugs

Failure to undertake, complete, and/or provide results of confirmatory trial(s) for a drug product

MAHs may be held criminally liable for not fulfilling T&Cs, including failing to submit confirmatory trials as per their deadlines outlined in the terms and conditions letter.

Failure of a MAH to undertake or complete a confirmatory trial listed in the T&Cs imposed on the DIN of a drug may give us a reason to reassess the drug's benefit-risk profile. This assessment will be based on all available information known about the drug. Relevant information may include post-market data, such as adverse drug reaction reports and information from foreign regulators.

Failure to provide results of a confirmatory trial by a specified date may provide us with a reason to assess the clinical effectiveness of the drug, which could result in consideration being given to invoking subsection C.01.013(1) of the regulations, that is, the manufacturer shall make no further sales of that drug unless the manufacturer has submitted the evidence requested.

For more information on failing to comply with T&Cs, refer to:

- Draft guidance on terms and conditions for human and veterinary drugs

Failure of confirmatory trial(s) to demonstrate clinical benefit of the drug product

If one or more confirmatory trials for drug products that were market-authorized based on promising evidence of clinical efficacy fail to demonstrate clinical benefit, we may request withdrawal of the authorized indication(s). Depending on the context, this could also lead to a recommendation for complete market withdrawal of the drug product.

Unfavourable change to the benefit-risk profile of the drug product

We will contact the MAH to discuss next steps if there is an unfavourable change to the benefit-risk profile of the drug. An unfavourable change to the benefit-risk profile of a drug may occur if new information becomes available. For example, information from another regulatory jurisdiction may indicate that the anticipated benefits no longer outweigh the identified risks.

Template

Request for advance consideration of promising evidence status template for human drug submissions

The advance consideration of promising evidence (ACPE) status request should be no longer than 25 pages (excluding references) and should be submitted along with the pre-submission meeting package. Sample text is provided as guidance for content and should be removed from the completed document before filing along with this introductory text. The headings should be kept in bold text.

Date of request for advance consideration of promising evidence:

Sponsor:

Contact information:

Product information:

- Dose / route / strength:
- Is this a combination product? Y / N
- Drug class:
- Is this a first-in-class drug? Y / N

Proposed brand name (if known) (Proper or common name of product):

Specific indication(s) sought:

In many instances, a single drug may be authorized for many indications. ACPE status, however, will only be granted on the basis of an applicable indication(s). The sponsor is requested to present only the most compelling rationale for Advance Consideration. List only the indication(s) for which ACPE status is being sought. If ACPE status is granted, only the indication(s) for which Advance Consideration has been granted should be included within the submission.

Regulatory decision or application status in foreign jurisdictions:

In a tabular format, indicate if the drug is authorized in other jurisdictions, including date of authorizations, and if any accelerated approval or conditional authorizations have been granted. Include details of authorized indications.

Indicate if the drug was denied authorization in other jurisdictions, including date of denial. Include details of the proposed indication and reasons for denial.

Indicate whether the product is currently under review for the proposed indication in other jurisdictions and the anticipated decision date, if known.

If meetings were held in other jurisdictions, provide a summary of the advice or discussion as an appendix.

Proposed patient population:

Eligibility criteria:

Complete criterion A and at least 1 of criterion Bi or Bii.

To avoid duplication, hyperlinking to relevant sections of the pre-submission package is recommended.

Criterion A: The drug submission being filed for review is for a drug intended to diagnose, treat, mitigate or prevent a serious or severely debilitating disease or condition.

Provide an overview of the disease or condition and therapeutic options available in Canada. Discuss the clinical context within which the drug will be used to support the request. Describe how the drug will contribute to the clinical management of the disease or condition.

Criterion B(i): The available data demonstrate the drug has the potential to provide effective treatment, prevention or diagnosis of a disease or condition for which no other drug has been assigned a Drug Identification Number (DIN) that has not been cancelled.

Describe how the drug fulfills an unmet medical need for treatment, prevention, or diagnosis of the disease or condition. Clearly indicate that no other drug in Canada which has been assigned a DIN that has not been cancelled is approved for the same conditions of use.

Criterion B(ii): The available data demonstrate the drug has the potential to provide a clinically meaningful improvement in benefit and/or reduction in risk, such that the overall benefit-risk profile is improved over that of existing drugs that have been assigned a DIN

that has not been cancelled in Canada, that are currently available to manage the serious or severely debilitating disease or condition.

Describe how the drug provides a clinically meaningful improvement in efficacy or safety, such that the overall benefit-risk profile is more favourable than other drugs for which a DIN has been assigned but not cancelled in Canada.

Clinical evidence:

Include the following:

1. Description of the study to be submitted including, but not limited to: design, enrolled population, primary and key secondary endpoints, key safety findings, and the number of patients withdrawn due to safety concerns or lack of efficacy. If evidence is derived from a surrogate endpoint(s), provide justification and validation as to how it predicts a meaningful clinical outcome. Where applicable, it is recommended that references be included to support the validation of surrogate endpoints and their relationship to clinical outcomes.
2. Description of findings demonstrating statistically significant and/or clinically meaningful results to support the claim for efficacy and/or safety. If results are based on interim analyses, provide anticipated dates for availability of the final results.

Confirmatory studies:

Include the following:

1. The status of any relevant ongoing and planned studies, and indicate if any of these studies are intended to verify the benefit-risk profile of the drug for the proposed indication.
2. Provide justification on why these studies are considered confirmatory for the proposed indication.
3. For each such study, include a brief outline of the design and anticipated timing of study completion.

References:

Generally, up to 12 supporting **key** references may be included as part of this ACPE request to facilitate the review. However, this will be assessed on a case-by-case basis. All references should be provided as an appendix to the ACPE request.

Additional Information:

- Anticipated timeline for drug submission and then marketing in Canada if authorized:

Note: An aligned review process with health technology assessment (HTA) agencies (for example, Canada's Drug Agency [formerly CADTH] and Institut national d'excellence en santé et services sociaux [INESSS]) is available as a tool to reduce the time between authorization and HTA reimbursement recommendations.

Aligned reviews between Health Canada and health technology assessment organizations