Health Canada Santé Canada

Draft guidance on management of rolling reviews for drug submissions

Canada

Foreword

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

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

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

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Overview

Purpose

This guidance helps sponsors interpret amendments to the *Food and Drug Regulations* (regulations) that allow a sponsor to apply for rolling review status for a forthcoming drug submission that meets specific eligibility conditions. Guidance is also provided on the review process for these types of drug submissions.

Sponsors of drug submissions for certain vaccines are eligible for a rolling review without having to apply for rolling review status prior to filing. These vaccines are listed in the List of Influenza Vaccines for Which Supplements to New Drug Submissions Can Be Filed.

Rolling review status allows a sponsor to file a drug submission with some but not all of the information necessary for Health Canada to assess the proposed drug's safety, efficacy and quality. After filing the drug submission, the sponsor has a set period of time to provide the missing information.

Eligibility for rolling review does not change the safety, efficacy and quality requirements outlined in Part C of the regulations.

This guidance:

- outlines Health Canada's expectations for rolling review submissions
- provides a consistent interpretation of the provisions in the regulations that pertain to rolling reviews
- clarifies the process by which a sponsor may apply for rolling review status for a forthcoming drug submission
- gives information about the rolling review process and the requirements after an application has been approved and a drug submission has been filed

Background

Health Canada has previously used rolling reviews to support timely access to drugs that reduce the risk of certain significant infectious diseases.

Rolling reviews have been available by policy for annual strain updates of human influenza vaccines and for the simultaneous review of veterinary drugs with the United States under the Regulatory Cooperation Council. Rolling reviews are also available in law for new drug submissions for designated COVID-19 drugs.

Due to the time constraints associated with annual strain updates of influenza vaccines, Health Canada has allowed sponsors to provide the required information for these updates in a rolling manner after filing their drug submission. Filing is made in accordance with the Annual update of seasonal influenza vaccines guidance document.

During the COVID-19 pandemic, Health Canada amended the regulations to maintain some of the modified requirements introduced through the Interim order respecting the importation, sale and advertising of drugs for use in relation to COVID-19. This included enabling rolling reviews specifically for COVID-19 drugs.

Based on our experience with rolling reviews, we are now giving sponsors an option to submit some of the required information after the filing of an eligible drug submission. Sponsors must submit the missing information within a specified time period after filing their submission, provided Health Canada has granted rolling review status to that submission.

The required information that is outstanding at the time of filing is referred to as "missing information" in the regulations and in this guidance document.

Scope and application

This draft guidance document is for sponsors:

- who want to apply to Health Canada for rolling review status for a forthcoming drug submission
- who have filed a drug submission that has been granted rolling review status

The draft guidance document also applies to the rolling review of drug submissions related to vaccines listed in the List of Influenza Vaccines for Which Supplements to New Drug Submissions Can Be Filed. This type of review allows sponsors to provide some of the information required to assess the safety, efficacy and quality of the proposed drug after they have filed their submission.

The scope of this guidance document includes drugs for human and veterinary use. The Health Products and Food Branch regulates these in accordance with the *Food and Drugs Act* (act) and its regulations.

This guidance document does not apply to the following submissions:

- drug submissions eligible for a rolling review for a public health emergency drug for COVID-19 or a condition described in the List of conditions that threaten public health in Canada
    - for more information, please refer to the Guidance on the Food and Drug Regulations for public health emergency drugs
- veterinary drug submissions undergoing joint or simultaneous reviews with foreign regulatory authorities
    - for more information, please refer to the country-specific simultaneous review guidance for veterinary drug submissions

The rolling review option outlined in this guidance document does not apply to the following:

- abbreviated new drug submission (ANDS) pathway
- supplement to an abbreviated new drug submission (SANDS) pathway
- submission classes with a performance standard of 120 days or less

Policy objectives

The objectives are to:

- provide an option allowing for specified information required for an eligible new drug submission (NDS) or supplement to a new drug submission (SNDS) to be provided to Health Canada after the submission has been filed
- help resolve issues early during the rolling review process and provide more opportunities for interaction with the regulator about their submission
- facilitate access to the Canadian market earlier provided the evidence requirements for safety, efficacy and quality have been met

Transparency

Health Canada's transparency initiatives for human drugs remain in place for drug submissions eligible for a rolling review.

Health Canada will continue to communicate up-to-date information about drugs for human and veterinary use. You can find the following information online:

- Submissions with a rolling review status that have been issued a screening acceptance letter appear in the lists for drug and health product submissions under review.
- 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, including the product monograph for human drugs and the product labelling for veterinary drugs.
- Drug and Health Product Portal: contains regulatory decision summaries and summary basis of decision documents, which describe Health Canada's rationale for the approval of 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.

Rolling review process, eligibility

The rolling review process

Health Canada is offering an option for a rolling review of a new drug submission (NDS) or supplement to a new drug submission (SNDS) that meets specific eligibility conditions. Sponsors nearing the end of clinical development of a drug can apply to Health Canada for rolling review status for a forthcoming drug submission. The sponsor's Rolling Review Application Package (RRAP) must contain an eligibility assessment and a submission plan.

If Health Canada grants rolling review status after assessing the RRAP, we will provide the sponsor with a "notice of rolling review status". The notice indicates the sponsor may file the drug submission with some, but not all, of the information necessary for us to assess the safety, efficacy and quality of the proposed drug. The sponsor may then provide the missing information over time after filing their drug submission.

The notice outlines how and when to provide the missing information. The sponsor must provide the submission to us within 60 calendar days after Health Canada issues this notice.

Only the recommended purpose and conditions of use (referred to in this guidance document as the proposed indication) outlined in the RRAP are eligible for a rolling review. In the case of an emerging infectious disease, it is possible that both an adult and a pediatric indication could be included in the same RRAP. However, the sponsor may not seek approval for additional indications within the submission beyond the indications put forward in the RRAP.

Once Health Canada processes and screens the submission, we will issue a screening acceptance letter (SAL). The review 1 period will then begin. The submission is immediately placed on "rolling review" until we receive the missing information, as indicated in the notice. Refer to the page on performance targets and standards for more information.

Note that the intent is for Health Canada to begin reviewing any submission information that has been provided during the period the submission is in "rolling review". We may also issue clarification requests during this period.

Once Health Canada reviews all of the information required to assess the safety, efficacy and quality of the drug, we will issue a decision on whether a notice of compliance (NOC) will be granted.

Eligibility for rolling review status

The regulations outline conditions that an NDS or SNDS must meet in order to be eligible for rolling review. These conditions are outlined as follows.

Eligibility conditions: C.08.002(4) and (5), and C.08.003(5)

Subsections C.08.002(4) and (5) and C.08.003(5) of the regulations set out the conditions that must be met for a drug submission to be eligible for a rolling review. The proposed human or veterinary new drug must meet the conditions of paragraphs C.08.002(5)(a), (b) or (c) to diagnose, treat, mitigate or prevent:

a. an emerging infectious disease that poses, or may pose, a serious risk of injury to human or animal health, and the Minister considers the proposed drug is needed for such a purpose. Within this context, a need is generally considered to include situations where:
    - there is a pressing necessity for other options even if there are 1 or more other drugs with a drug identification number (DIN) that have the same recommended purpose and conditions of use

Within the context of condition a), a serious risk of injury to human or animal health is in relation to an emerging infectious disease, which is defined by the World Health Organization as "one that has appeared in a population for the first time, or that may have existed previously but is rapidly increasing in incidence or geographic range."

Sponsors of generic and biosimilar drugs **may seek** to establish eligibility for rolling review status on the basis of a).

b. a disease, disorder or abnormal physical state that poses or may pose a serious risk of injury to human or animal health where:
    - the recommended purpose and conditions of use do not fall within those of any other drug with a DIN that has been assigned and has not been cancelled

The condition in b) is intended for novel drugs to address an unmet medical need. Sponsors of generic and biosimilar drugs **are not intended** to establish eligibility for rolling review status on the basis of b). Comparison-based submissions are not meant to result in the approval of drugs that have conditions of use that are broader than the drug that they compare themselves to.

c. a disease, disorder or abnormal physical state that poses or may pose a serious risk of injury to human or animal health where:
    - the recommended purpose and conditions of use of the drug falls within the recommended purposes and conditions of use of 1 or more other drugs for which a DIN has been assigned and has not been cancelled, and
    - there are reasonable grounds to believe that the new drug is significantly more effective, or poses a significantly lower risk, than each of the other drugs

Sponsors of generic and biosimilar drugs **are not expected** to establish eligibility for rolling review status on the basis of c). Comparison-based submissions are not meant to result in the approval of clinically superior drugs.

With regard to b) and c), a serious risk of injury to human or animal health refers to a **disease, disorder or abnormal physical state** generally associated with clinically meaningful morbidity that causes a substantial impact on day-to-day functioning. In determining whether a disease, disorder or abnormal physical state is serious, Health Canada will consider factors such as:

- survival
- day-to-day functioning
- the likelihood that the untreated disease, disorder or abnormal physical state will progress from a less severe to a more severe state

Diseases, disorders or abnormal physical states where there is a serious risk to health are generally associated with morbidity, which causes a substantial impact on day-to-day functioning.

The regulations do not enable a rolling review under the ANDS/SANDS pathway. Therefore, any submission based on a direct or indirect comparison that meets the eligibility condition in C.08.002(5) must be provided as an NDS/SNDS.

Note that the terms "recommended purpose and conditions of use", both in the regulations and in this guidance document, should be understood as the proposed indication of the drug.

List of influenza vaccines for which an SNDS can be filed

A sponsor of an influenza vaccine listed in the List of Influenza Vaccines for Which Supplements to New Drug Submissions Can Be Filed specified in C.08.003(2)(b.1) may file an SNDS that does not yet include all of the information and material required under C.08.003 **without submitting an RRAP** if that submission only seeks

to update the strains of the influenza vaccine. This is outlined in sections C.08.003(2)(b.1) and C.08.003(10) of the regulations.

Within this context, an influenza vaccine submission eligible for a rolling review without an RRAP is expected to only include information on:

- changes to the virus strain(s)
- changes to the seed banks that are required to produce vaccine for the upcoming influenza season

All other changes require a separate submission. In this case, all information required to assess the safety, efficacy and quality of the drug must be provided at the time the submission is filed in the normal course.

Please refer to the following for more information and guidance:

List of Influenza Vaccines for Which Supplements to New Drug Submissions Can Be Filed, as amended from time to time

- Guidance document: Annual update of seasonal influenza vaccines

Missing information that can "roll"

If the drug submission meets all eligibility conditions, a sponsor may:

- file an NDS without some of the information required in paragraphs C.08.002 (2)(g) to (i), (m), (n) and (p) of the regulations at the time the submission is filed and, if applicable, corresponding information that is required to be included under section C.08.005.1
- provide to Health Canada the missing information in accordance with the notice of rolling review status after the submission has been filed

Only the information in C.08.002(2)(g) to (i), (m), (n) and (p) is permitted to be provided after the NDS has been filed.

Similarly, a sponsor may file an SNDS without some of the information that is required to be included in a supplement under C.08.003(3) and, if applicable, corresponding information that is required to be included in the supplement under section C.08.005.1. The sponsor may provide the missing information in accordance with the notice of rolling review status after filing the submission if the proposed drug meets any of the conditions in C.08.002(5).

In all cases, the sponsor must provide information on the medicinal ingredient, formulation, dosage form, use and route of administration for which authorization is sought at the time the submission is filed. These elements cannot be part of the missing information and are not expected to significantly change over the course of the review. Any significant changes to the formulation (including strengths), dosage form or use must be sought through a separate supplement rather than as part of the missing information provided after the submission has been filed.

For veterinary drugs, the sponsor must provide the following information when the drug submission is filed:

- the species and sub-type
- if the drug will be used to treat food-producing animals

For human drugs, from the clinical perspective, it is very likely that **a pivotal or supportive clinical study** may be nearly complete at the time the submission is filed. Depending on the progress of the ongoing clinical trial, the following documents may need updating after the clinical trial is completed:

- product monograph
- risk management plan
- clinical overview and clinical summary
- final version of clinical study report for the ongoing study
- for vaccines, process validation data including a data package that shows comparability of commercial lots to the clinical lots, including drug substance and/or drug product tests, additional characterization data and analytical procedures, with particular attention to potency and safety

For veterinary drugs, note that if an interim analysis is submitted with the submission, the final analysis may affect other aspects of the submission (for example, labelling).

For both human and veterinary drugs, please refer to the eligibility assessment template for more details about information requirements.

Pre-submission meeting

Before submitting an RRAP, the sponsor is encouraged to request a pre-submission meeting to:

- discuss potential eligibility
    - to help sponsors decide if their forthcoming drug submission may be suitable for rolling review
    - Health Canada will not determine the eligibility of the forthcoming drug submission for rolling review status at the pre-submission meeting
- discuss the proposed plan for providing the missing information after the submission has been filed
- provide guidance on the process involved in applying for rolling review status through an RRAP
- outline the evidence describing the benefits, risks and uncertainties of the proposed drug

If a pre-submission meeting is to take place, Health Canada recommends that a relevant Canadian health care professional participate. For example, a practising clinical specialist who has expertise on the disease and available treatments in Canada, particularly in the case of an unmet medical need. The health care professional should disclose any potential conflict of interest before the meeting takes place.

Sponsors should include the pre-submission meeting minutes with their RRAP.

For more information on pre-submission meetings, refer to the following guidance documents:

- Management of drug submissions and applications
- Veterinary drugs - Management of regulatory submissions guidance
- Preparation of regulatory activities in the eCTD format
- Preparation of regulatory activities in non-eCTD format

Eligibility assessment template

The eligibility assessment should be no longer than 25 pages (excluding references) and must include the elements outlined as follows, with headings in bold text. Explanatory text is provided for context and should be removed from the completed document before submitting it to Health Canada.

Date of application for rolling review status:

Sponsor name:

Contact information:

Product information:

- Proposed dosage, formulation and route of administration. Confirm that the same dosage was used in the clinical trial or veterinary pivotal study.
    - Is this a combination product?
- Drug class:
    - Is this a first-in-class drug?
- If a comparator (for example, placebo, standard of care therapy) was used in the clinical trial or veterinary clinical study for a new drug, confirm that the recommended dose for the indication was used in the trial. In addition, provide the role of the comparator (for example, Canadian clinical guidelines) in the current Canadian setting.

If the forthcoming drug submission will be made on the basis of a direct or indirect comparison with another drug for which a DIN is assigned:

A notice of compliance will be sought on the basis of a direct or indirect comparison to a drug for which a DIN is assigned. Refer to C.08.002(4)(v) or C.08.003(5)(iv):

Yes □ No □

- **If Yes, provide the DIN(s) here: _____**

Proper or common name of product and proposed brand name (if known)

Specific proposed indication

- Only the proposed recommended purpose and conditions of use (indication) sought for rolling review should be provided

Patient population

- Describe the patient population for this new drug
- For veterinary drugs, include:
    - species and subtypes
        - multiple species, if for 1 indication
    - If they are used for the treatment of food-producing animals

Regulator decision or application status in foreign jurisdictions:

The sponsor should provide information about the application status in foreign jurisdictions:

- Is the new drug under review in another jurisdiction and, if so, is this review being conducted by that jurisdiction's regulatory authority under an accelerated timeline?

- Was the new drug approved or denied approval in another jurisdiction? If denied approval, include details of the proposed indication and rationale for denial, including date of denial.
- Is the sponsor now seeking a review of the new drug with new clinical data in Canada?
- In the case of human drugs, if the drug is authorized in another regulatory jurisdiction based on interim data or phase 1 or 2 study results, provide prescribing information.
- In the case of veterinary drugs, if the drug is conditionally approved in other regulatory jurisdictions, please provide the conditionally approved labelling.

Health Canada requests the sponsor's authorization to allow Health Canada to discuss all information included and related to the submission with the foreign jurisdiction.

Complete eligibility condition (a) **or** (b) **or** (c) [Select 1 only.]

Eligibility condition (a)

The new drug is needed to diagnose, treat, mitigate or prevent an emerging infectious disease that poses or may pose a serious risk to human or animal health.

- Provide an overview of the emerging infectious disease and treatment options, if any
- Provide the clinical context within which the drug will be used to support the request

Eligibility condition (b)

The new drug is intended to diagnose, treat, mitigate or prevent a disease, disorder or abnormal physical state that poses or may pose a serious risk of injury to human or animal health, and

The recommended purpose and conditions of use of the drug do not fall within the recommended purposes and conditions of use of any other drug for which a DIN has been assigned and has not been cancelled.

- Provide an overview of the disease, disorder or abnormal physical state and treatment options, if any
- Provide the clinical context within which the drug will be used to support the request
- Demonstrate the recommended purposes and conditions of use do not fall within those of any other drug with a DIN that has been assigned and has not been cancelled

Eligibility condition (c)

The new drug is intended to diagnose, treat, mitigate or prevent a disease, disorder or abnormal physical state that poses or may pose a serious risk of injury to human or animal health, and

There are reasonable grounds to believe that the new drug is significantly more effective or poses a significantly lower risk than 1 or more other drugs for which a DIN has been assigned and has not been cancelled.

- Describe how the new drug is significantly more effective or poses a significantly lower risk relative to available drugs with a DIN in Canada (for example, current standard of care)
- Provide the clinical context within which the drug will be used to support the request and indicate how the drug will provide additional benefits over the available clinical management of the disease or condition in Canada

Clinical evidence

Include the following:

1. Concise information about the study(ies) to be submitted including design, enrolled patient population, inclusion and exclusion criteria, primary and key secondary endpoints, key safety findings (if available) and so on. This information may be presented in point form or in a table.
2. For the study(ies) to be provided at the time the forthcoming drug submission is filed, describe the efficacy results and discuss statistical significance and clinical meaningfulness in support of the efficacy conclusions. If the results are based on an interim analysis, provide anticipated completion dates. For human drugs, provide the data from phase 2 proof of concept trials and the available data from phase 3 trials. For veterinary drugs, provide data from completed dose determination and dose confirmation studies.
3. Provide the status of any relevant ongoing study(ies) and indicate if any of these study(ies) are intended to verify the favourable benefit-risk profile of the drug. For each such study, include a brief outline of the design. The sponsor must indicate the timeframe for the provision of these outstanding studies in the submission plan.

References

An appendix can provide all references supporting these data/the indication as cross-referenced in the eligibility assessment. A sponsor can designate up to 12 **key** references to facilitate the review.

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Applying for rolling review status

The Rolling Review Application Package

Sponsors who wish to apply for rolling review status for a forthcoming drug submission must do so **before** they file their submission.

To apply for rolling review status for a forthcoming new drug submission (NDS) or supplement to a new drug submission (SNDS), sponsors must provide a Rolling Review Application Package (RRAP). The RRAP is forwarded to the appropriate directorate and assessed within 45 calendar days.

The RRAP has 2 components:

1. an eligibility assessment
2. a submission plan

Both components must meet the requirements set out in the regulations. If a pre-submission meeting has taken place, the RRAP should also include the minutes of the pre-submission meeting.

For relevant contact information, refer to the following guidance documents:

- Management of drug submissions and applications
- Veterinary drugs - Management of regulatory submissions guidance

Eligibility assessment

The eligibility assessment must include information for clinical review that demonstrates the proposed drug meets the eligibility conditions for a rolling review. The eligibility assessment should be no longer than 25 pages (excluding references). Refer to the eligibility assessment template.

During the process of demonstrating that a forthcoming NDS meets the eligibility conditions, sponsors must also demonstrate that they possess a significant amount of the evidence to establish the safety and efficacy of the proposed drug. This is in line with the requirements under C.08.002(4)(a) (iii) and (iv) of the regulations.

For an SNDS, sponsors must demonstrate that they possess a significant amount of the information and material required under C.08.003(3). This is in line with the requirement under C.08.003(5)(a)(iii).

The eligibility assessment for submissions for veterinary drugs should also include:

- a summary of dose determination studies, target animal safety studies and laboratory animal studies conducted
- a summary of completed dose confirmation studies and interim analyses or study outlines of any pivotal efficacy studies

Sponsors who wish to seek an NOC for a drug on the basis of a direct or indirect comparison to a drug that has a drug identification number (DIN) must provide the DIN of the drug to which the comparison will be made (C.08.002(4)(a)(v) and C.08.003(5)(a)(iv) in the regulations). Failure to accurately identify the DIN will result in the submission being considered cancelled by the sponsor after it has been filed.

Conditions to be met

The sponsor must be able to demonstrate that the proposed drug meets the eligibility conditions outlined in C.08.002(4)(a)(iii) and (iv) or C.08.003(5)(a)(iii) and C.08.002(5) based on the available information that they have.

For human drug submissions, sponsors should be nearing the end of clinical development. They should have collected significant evidence to establish the safety and clinical effectiveness of the proposed drug for the recommended purpose and conditions of use.

For veterinary drug submissions, these would be final studies conducted to demonstrate efficacy and safety under the proposed conditions of use of the drug in the target population.

To meet the condition of C.08.002(5)(a), the sponsor must provide:

- an overview of the emerging infectious disease that poses or may pose a serious risk of injury to human or animal health
- a description of the treatment options, if available
- the clinical context within which the drug is proposed to be used

To meet the condition of C.08.002(5)(b), the sponsor must provide:

- an overview of the serious disease, disorder or abnormal physical state and treatment options, if any
- information establishing that the disease, disorder or abnormal physical state poses or may pose a serious risk of injury to human or animal health
- the clinical context within which the drug is proposed to be used

The sponsor must be able to demonstrate that the recommended purposes and conditions of use of the proposed drug do not fall within the recommended purposes and conditions of use of any other drug with an assigned DIN that has not been cancelled. Note that the market status of all drugs assigned a DIN can be found in the Drug Product Database.

To meet the condition of C.08.002(5)(c), the sponsor must provide:

- an overview of the serious disease, disorder or abnormal physical state and treatment options, if any
- information establishing that the disease, disorder or abnormal physical state poses or may pose a serious risk of injury to human or animal health
- the clinical context within which the drug is proposed to be used
- information to show that the proposed drug falls within the recommended purpose and conditions of use of any other drug with an assigned DIN that has not been cancelled and that the proposed new drug is
    - significantly more effective or
    - poses a significantly lower risk

The sponsor must be able to show that the drug provides a clinically meaningful improvement in effectiveness and/or safety compared to available therapies in Canada. Health Canada would accept a comparison to the current standard of care. If multiple therapies are available in Canada, consider what constitutes the best available treatment for comparison (for example, current standard of care).

In demonstrating that a drug meets condition C.08.002(5)(c), the eligibility assessment should address the following aspects where relevant:

- a clinically meaningful improvement in 1 or more of the serious outcomes, symptoms or manifestations of the disease, disorder or abnormal physical state on which the effect is claimed, while maintaining an acceptable safety profile
- a clinically meaningful benefit for individuals unable to tolerate or who are unresponsive to available therapies
- a demonstration that the drug provides clinically meaningful benefit that is consistent with available therapies while also demonstrating a more favourable safety profile than existing therapies by:
    - avoiding serious toxicity present in existing therapies **and/or**
    - avoiding less serious toxicity, common to the therapy, which results in the discontinuation of treatment of a serious disease, disorder or abnormal physical state

Clarification requests related to an eligibility assessment

If Health Canada requests clarification on information provided in the eligibility assessment, the sponsor must respond within 2 business days. If we do not receive supplementary information within this time, we will make a decision on the request for rolling review status based on the information provided at the time we received the RRAP.

Submission plan for rolling review

A sponsor applying for rolling review status for a forthcoming NDS or SNDS must provide a submission plan. This plan is part of the RRAP. It must outline what information the sponsor proposes to provide to Health Canada after the drug submission has been filed and when this information will be provided. (Refer to C.08.002(4)(a)(ii) or C.08.003(5)(a)(ii) of the regulations.)

Submission plan

When developing a submission plan, sponsors should keep in mind that:

- the plan outlines what missing information the sponsor expects to provide Health Canada after it has filed its forthcoming drug submission and when it expects to provide this missing information
- the missing information should be provided to the Minister through a small number of regulatory transactions (up to 3) after the submission has been filed
- the timeline and milestones outlined in the plan should be realistic and credible
- missing information should only be provided after a screening acceptance letter (SAL) has been issued for the submission
- new data/information provided in each transaction should be clearly identified to help Health Canada reviewers easily distinguish new information to be evaluated
- the data/information provided in each transaction should be substantial so that the reviewers can reach a conclusion from the information provided

As outlined in the regulations, the submission plan must provide details on how all required information supporting the safety, efficacy and quality assessment of the drug submission will be provided to Health Canada by the 155th day after the submission has been filed. In some circumstances, we will expect sponsors to provide the remainder of the missing information in less than 155 days. This 155-day period reflects a standard administrative processing period of 10 days, a screening period of 25 days and the first 120 days of the review 1 period. The plan should be in calendar days.

Preparing the submission plan

The sponsor should aim to provide the forthcoming drug submission's missing information in an efficient and complete manner and consider the following:

- Only information and studies that are not final at the time the submission is filed may be provided after the filing date. All finalized data or information and any available interim data related to the missing information is expected to be provided when the submission is filed.
- The sponsor must provide draft summary documents at the time the submission is filed (for example, module 2 for human drugs). The sponsor should provide an annotated update later, if there are additions to the summary in subsequent transactions.

The submission plan for human drugs should follow the common technical document (CTD) structure and have the following fields:

- CTD module and section/subsections
- description
- content type
- anticipated transaction date(s)

The plan for veterinary drugs should follow the structure outlined in Appendix V: "Master Index" of the Guidance for industry: Preparation of veterinary new drug submissions. It should also have the following fields:

- prescribed structure parts and subparts
- description
- content type
- anticipated transaction date(s)

The plan should be in either MS Word, MS Excel or PDF format. Refer to the relevant eCTD or non-eCTD guidance document:

- Preparation of regulatory activities in the eCTD format
- Preparation of regulatory activities in non-eCTD format

Clarification requests related to a submission plan

Health Canada may request clarification on information provided in the submission plan. The sponsor must respond within 2 business days. If we do not receive supplementary information within the noted time, we will make a decision on the request for the rolling review status based on the information provided at the time we received the RRAP.

During the assessment process, Health Canada may contact the sponsor to discuss and negotiate:

- the nature and extent of the missing information to be provided after the drug submission has been filed
- the date(s) by which the missing information will be provided
- any changes proposed by us in this regard

A request for rolling review status can be rejected on the basis of an unrealistic plan.

Notice from the Minister of rolling review status

If Health Canada finds that the forthcoming drug submission meets the eligibility conditions for a rolling review, we will issue a notice of rolling review status. The notice will confirm this status. It will also state the manner and the dates by which the sponsor must provide the missing information (C.08.002(4)(b) and C.08.003(5)(b) of the regulations). The sponsor is responsible for providing the missing information.

Health Canada will indicate in the notice if the forthcoming drug submission will seek a notice of compliance (NOC) on the basis of a direct or indirect comparison to another drug, as well as the other drug's DIN. The Minister will rely on the sponsor's obligation in C.08.002(4)(a)(v) and C.08.003 (5)(a)(iv) to support the determination of whether the forthcoming drug submission will be sought on the basis of a direct or indirect comparison to a drug for which a DIN has been assigned.

If the forthcoming drug submission does not meet the eligibility conditions for a rolling review, Health Canada will inform the sponsor in writing that the RRAP has been rejected. In this case, the sponsor may refer to other guidance documents and file a submission when all of the information is ready:

- Management of drug submissions and applications (MDSA)
- Veterinary drugs - Management of regulatory submissions guidance
- Guidance for industry – Priority review of drug submissions

Filing a submission

Filing and content of the submission

The filing date is established according to the following:

- MDSA guidance document for human drug submissions
- Veterinary drugs - Management of regulatory submissions guidance for veterinary drug submissions

Data or information provided after the submission is filed in accordance with the notice of rolling review status will not change the filing date of the submission.

For a submission that is granted rolling review status, the sponsor must provide a new drug submission (NDS) or supplement to a new drug submission (SNDS) for which the rolling review status was granted within 60 calendar days after the day that Health Canada provides the notice to the sponsor.

Failure to do so within this 60-day period will make the submission ineligible for a rolling review. In this case, the sponsor would have to provide a submission with all information required to assess the safety, efficacy and quality at the time the submission is filed.

To meet C.08.002(4)(c) or C.08.003(5)(c), the drug submission must contain:

- all of the information and material required under C.08.002 or C.08.003 except for the missing information as indicated in the notice

At the time it is filed, the submission must contain a significant amount of information to establish the safety and efficacy of the proposed new drug. This is the information that the sponsor indicated it had in its possession to form the basis of the eligibility assessment. Please refer to C.08.002(4)(a)(iii), (iv) and (c).

Health Canada expects the sponsor to provide the following when they file their submission:

- a statement in the cover letter that declares the date on which the submission was granted rolling review status in order to facilitate processing
- a copy of the notice of rolling review status referred to in C.08.002(4)(b) or C.08.003(5)(b)
- the submission certificate certifying that the missing information will be provided
- foreign questions and answers related to the drug submission in a foreign jurisdiction (when available)

Format and structure for filing

For general procedures on how to file drug submissions, please also refer to the following guidance documents:

- Management of drug submissions and applications for human drugs
- Management of regulatory submissions guidance for veterinary drugs

Screening for rolling review

The drug submission is screened:

- using the notice of rolling review status to determine if the sponsor has submitted the required information under C.08.002 or C.08.003, except for the missing information to be provided later, in accordance with the notice
    - if the drug submission contains less information than what was outlined in the notice, Health Canada may issue a screening deficiency notice (SDN)
- following the regular process in the MDSA guidance document for human drugs or Management of regulatory submissions guidance for veterinary drugs

Once the screening requirements are met, the sponsor is issued a screening acceptance letter (SAL) and the review 1 period begins. However, the submission will be placed in "rolling review" on the first day of the review 1 period until all missing information is provided in accordance with the notice. Please refer to Performance targets and performance standards.

Providing missing information

As specified in the regulations, sponsors must provide all missing information in accordance with the notice of rolling review status. When providing the balance of the remaining missing information, the sponsor should confirm that it considers all missing information to have been provided.

Failure to adhere to the time and manner for providing the missing information, as specified in the notice, may result in the cancellation of the submission.

Risk management plan

As specified in C.08.002(4), the sponsor may provide the risk management plan (RMP) required under section C.08.002(2) of the regulations to Health Canada after the submission has been filed, as per the notice of rolling review status. The sponsor should submit the RMP either before or when they submit the final version of the clinical study report (CSR) for the pivotal or supportive clinical study or clinical evidence.

For details on the format of RMPs accepted by Health Canada, please refer to the following guidance document:

- Submitting risk management plans guidance document

Also refer to the section on missing information that can "roll".

Note: The provisions related to RMPs do not apply to veterinary drugs.

Performance targets and standards, cancellation

Performance targets and standards

The time to complete the screening of a drug submission with a rolling review is 25 days. Once the screening acceptance letter is issued, the review 1 period would begin. The submission would immediately be placed on "rolling review" until Health Canada receives all of the missing information, as indicated in the notice.

Once all of the missing information has been received, Health Canada would plan to complete the review of the submission within 180 days (that is, within a 180-day rolling review performance target). This 180-day period, combined with the period the submission is under "rolling review", would not exceed the 300-day review 1 performance standard for cost recovery purposes.

During the review 1 period, while Health Canada waits to receive the missing information, the submission is considered to be in "rolling review". Our intent is to start reviewing the drug submission during this period.

During rolling review, Health Canada may request clarification on any of the information or data we have received. Sponsors may ask for an extension for any clarification requests, as indicated in the "pause the clock" process. The processes are outlined as follows:

- for human drugs, in the MDSA guidance document
- for veterinary drugs, in the Management of regulatory submissions guidance

Extensions granted for sponsors to respond to clarification requests do not change the timelines indicated in the notice of rolling review status for the sponsor to provide missing information. The timeline(s) for providing this missing information is independent from, and not affected by, timelines related to any responses to clarification requests.

The performance standard for cost-recovery purposes for a submission with a rolling review is not changed. The performance standard for that class of submission (for example, 300 days for a "new active substance" submission) is outlined in the following order:

- Performance standards for fees in respect of drugs and medical devices order

Should a submission with rolling review status fall under a submission class with a performance standard below 300 days, the shorter performance standard would apply. For example, the review of a submission with comparative data as well as chemistry and manufacturing information would be completed within the 180-day cost recovery performance standard. This includes the period during which the submission is in rolling review.

Submission classes with a performance standard of 120 days or less (for example, chemistry and manufacturing data only, labelling only) are not expected to be able to meet the eligibility conditions for a rolling review.

Cancellation (C.08.002(7) or C.08.003(7))

A new drug submission or supplement is considered to be cancelled by the sponsor if the sponsor:

- failed or is not able to provide the missing information in accordance with the notice within 10 days after the relevant date specified in the notice or a longer period of time specified by the Minister, or
- did not identify as part of the eligibility assessment that the submission or supplement will be made on the basis of a direct or indirect comparison to a drug that has a drug identification number (DIN) or did not identify the appropriate DIN(s)

Before cancelling the submission or supplement, the sponsor may speak to the issue.

On an exceptional basis, Health Canada may extend the timeline for providing the missing information beyond 10 days after the dates contemplated in the notice. The sponsor must request an extension in advance and provide a robust justification.

If the submission is considered cancelled, Health Canada will notify the sponsor in writing.

If the submission or supplement is cancelled, the sponsor can file a new submission that includes all of the information required to assess safety, efficacy and quality at the time the submission is filed.

Fees

As with other drug submissions, sponsors of a new drug submission (NDS) or supplement to a new drug submission (SNDS) that has been granted rolling review status must comply with either of the following:

- Guidance on evaluation fees for human drugs and disinfectants: Invoicing, fee payment and mitigation
- Guidance document: Fees for the review of veterinary drug submissions and applications

Sponsors will be issued an invoice for the full fee related to examining the NDS or SNDS once Health Canada has accepted the submission for review and issued the screening acceptance letter.

Payment of the fee in full is required even if the missing information is not provided and the submission is cancelled or withdrawn.