Health Canada Santé Canada

Draft Guidance: Accelerated Review of Human Drug Submissions

This guidance document is being distributed for comment purposes only.

Draft date

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
XXXXXXXXXXXXXXXXXXXXXXXXX

To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications@hc-sc.gc.ca

Publication date: Month 2019

Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy, or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable Guidance documents.

Table of Contents

1. Introduction

1.1 Purpose/Overview

For some time, Health Canada has used two pathways, both defined by policy and not in regulation, to provide accelerated drug reviews for medicines for the treatment of serious or life-threatening diseases or conditions which meet specific criteria. The Priority Review of Drug Submissions policy provided a 180-day review time for drugs with significant evidence of safety and efficacy, while the Notice of Compliance with Conditions policy provided a 200-day review time for similar products for which there is promising evidence, allowing such products to conditionally come to market earlier with requirements for further data generation and submission to Health Canada.

For the purposes of this guidance document, an Accelerated Review will encompass both pathways, and will provide an overarching policy by which critical medicines can be reviewed on an accelerated basis. This guidance for industry will provide information for drug sponsors wishing to submit a request for Accelerated Review, including submission eligibility criteria and the undertakings expected of a sponsor for a submission that may be granted a Notice of Compliance with Conditions (NOC/c) following completion of review.

When finalized, this guidance document will supersede the *Guidance document: Notice of Compliance with Conditions (NOC/c)*, September, 2016 and both the *Priority Review of Drug Submissions Policy* and *Guidance for Industry: Priority Review of Drug Submissions*, December 18, 2008.

Effective Date: TBD, 2019

This guidance document, once finalized, will be effective on the date of posting.

1.2 Scope and Application

The *Accelerated Review of Human Drug Submissions* guidance document applies to a New Drug Submission (NDS) or Supplement to a New Drug Submission (SNDS) in support of a prescription pharmaceutical, biologic (excluding biosimilars) or radiopharmaceutical drug product for human use for a **serious**, **life-threatening** or **severely debilitating disease or condition** for which:

1. there is evidence of clinical effectiveness that the drug provides treatment, prevention or diagnosis of a disease or condition for which there is no available therapy or drug marketed in Canada; **or**
2. there is evidence of clinical effectiveness that the drug provides a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by an available therapy or drug marketed in Canada; **or**

3. there is evidence of clinical effectiveness that the drug provides treatment, prevention or diagnosis of a disease or condition for which an existing drug for the same indication has been on the Canadian market for 12 months or less; **or**,
4. there is evidence that the drug addresses a health care system need by delivering high clinical benefit for public health or high clinical benefit for patients.

Certain elements of this guidance are also applicable to generic pharmaceuticals where the innovator product has a conditional authorization.

For the purposes of this guidance document, "evidence of clinical effectiveness" means either substantial evidence (which could lead to a standard Notice of Compliance), or promising evidence (which could lead to a Notice of Compliance with conditions). What could constitute either substantial or promising evidence will be further described below.

"Available therapy" refers generally to the conditions of use reflected in the authorized Canadian labelling of products regulated under the *Food and Drug Act* and *Regulations*. In certain circumstances, therapies which do not have authorized indications, but which are considered standard-of-care or are well-supported by substantial literature evidence could also be considered available therapy. Available therapy could also include treatments which are not regulated by Health Canada, such as surgery or specific dietary interventions.

1.3 Policy objectives

While enabling sponsors to satisfy the information and regulatory requirements under the *Food and Drugs Act* and Part C of the *Food and Drug Regulations*, the objectives of the Accelerated Review policy are to:

- support earlier access by way of shortened review times, to new or promising new drugs for patients suffering from serious, life-threatening or severely debilitating diseases or conditions;
- better align Health Canada's prioritization of drug reviews with the needs of the Canadian health care system; and
- ensure transparency of any conditions that may be associated with a market authorization, as well as create mechanisms for the appropriate completion of confirmatory trials to verify the clinical benefit of a drug granted a NOC/c.

1.4 Background

Health Canada's Regulatory Review of Drugs and Devices (R2D2) initiative began in 2017 to improve access to prescription medicines. Under R2D2, a review of the existing Priority Review policy was undertaken, with the aim of incorporating a broader consideration of health care system needs when making decisions about which drug submissions should receive an accelerated review. During the course of this review, it was determined that any changes to Priority Review criteria should also be considered for the similar eligibility criteria for the Notice of Compliance with Conditions policy.

Early consultations included an online questionnaire that was administered to representatives of stakeholder groups from across the health care system, including provincial payers, health technology assessment organizations, patient groups, health care professionals, and industry. The questionnaire sought feedback on the existing Priority Review policy, and the best way to incorporate consideration of the needs of the health care system in a revised decision-making process.

Most respondents felt the Priority Review policy works well, but did not always agree that the policy addresses health care system needs in Canada. Feedback highlighted the need for prioritization of new products, with such examples given as treatments for chronic and degenerative conditions, for pain management, and for those producing improvements in quality of life for patients. In terms of how a revised policy could better address health care system needs, the dominant themes of responses included accelerating access to:

- lower cost drugs;
- drugs for special populations (with particular focus on the needs of seniors and children) and;
- drugs already approved by other regulators.

Although cost-effectiveness assessment and financial considerations lie outside of Health Canada's regulatory mandate, stakeholders stressed that reimbursement through public drug programs is vital to making a drug affordable and accessible. Respondents also expressed the need for Health Canada to maintain a robust evidentiary bar for drug approvals and to continue to support transparency and alignment in decision-making in drug submission review, health technology assessment and funding recommendations.

2. Guidance for Implementation

2.1 Criteria for Eligibility for Accelerated Review

As with similar programs in other international jurisdictions, Accelerated Review designation applies to a combination of the product and specific indication(s) for which it is being studied and not the product alone.

To be considered for Accelerated Review status, a request package must first meet eligibility criteria outlined in Section 1.2. For clarity, this means that the drug product must first be determined to be intended for the treatment of a serious condition (as described in section 2.1.1) **AND** must meet at least one of the eligibility criteria (as described in sections 2.1.2, 2.1.3, 2.1.4, and 2.1.5).

For the assessment of all criteria, discretion will be exercised by Health Canada, with consideration of the Canadian clinical context, which may include available treatment guidelines, external expert advice, and/or input from patients.

2.1.1 Definition of Serious, Life-Threatening or Severely Debilitating Disease

In this section, all references to serious conditions will include life-threatening diseases. In determining whether a condition is 'serious', factors such as survival, day-to-day functioning or the likelihood that the untreated disease will progress from a less severe condition to a more serious one will be taken into account.

'Serious' conditions are generally associated with morbidity with a substantial impact on day-to-day functioning. Reversible persistent or recurrent morbidity outcomes may also be sufficient to qualify a product for Accelerated Review status should all additional criteria be met. Alternatively, examples of insufficient morbidity would normally include short-lived and/or self-limiting morbidity.

Many chronic diseases that may be generally well-managed by available therapy may have severely debilitating outcomes and would qualify a product for Accelerated Review status. Examples include inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression and psychoses.

In order to qualify for Accelerated Review status, the drug product must not only be intended for patients suffering from a serious, life-threatening or severely debilitating disease or condition but must also be indicated to treat, prevent or diagnose a serious symptom or manifestation of the condition. For example, a product indicated for alleviating a minor skin irritation in a patient with cancer would not be eligible for Accelerated Review status although the condition (cancer) itself is clearly life-threatening.

2.1.2 Product Eligibility Criterion #1: Effective Treatment, Prevention or Diagnosis of a Disease for Which No Drug Is Marketed in Canada

Serious, life-threatening or severely debilitating diseases or conditions, for which there is no available therapy or drug marketed in Canada, represent an obvious medical need. A new therapy effective in the treatment, prevention or diagnosis of an eligible condition would therefore meet this criterion for Accelerated Review status.

The term 'marketed' implies that sale of the product has commenced, pursuant to Part C.01.014.3 of the *Food and Drug Regulations* and that the product continues to be available for sale (i.e., has not been discontinued or removed from the market). The above criterion does not provide for eligibility for Accelerated Review due to drug shortage scenarios.

2.1.3 Product Eligibility Criterion #2: Effective Treatment, Prevention or Diagnosis of a Disease for Which an Existing Drug Has Been on the Canadian Market for 12 Months or Less

While, as described in Section 2.1.2, the absence of a treatment for a serious condition represents one health care system need, another need is for access to alternative treatments.

Therefore, at the time a sponsor files a request for Accelerated Review status, should there be an existing drug marketed in Canada for the same indication, the request may be considered if the existing drug has been marketed for one year or less. Any drug product seeking the accelerated review must exhibit the same or better safety and efficacy profile as others on the market.

Should more than one subsequent product be submitted for the same indication, the request for accelerated review may still be considered, within the same one-year timeframe from the date of marketing of the first product.

2.1.4 Product Eligibility Criterion #3: Significant Increase in Efficacy and/or Significant Decrease in Risk

For this criterion to be met, the sponsor should be able to demonstrate that the therapy provides – or has the potential to provide - a statistically significant and clinically relevant improvement in efficacy or decrease in risk such that the overall benefit/risk profile is improved over any available therapy or drug marketed in Canada.

The benefit/risk evaluation may include any of the following aspects:

- improvement in one or more of the serious outcomes of the condition on which the effect is claimed
- a favourable effect on a serious symptom or manifestation of the condition for which there is no existing therapy
- a clinical benefit for individuals unable to tolerate, or unresponsive to, existing therapies
- demonstration of effectiveness in combination with other critical agents, where no information is available or where combined use with existing therapy(ies) is not feasible due to safety or efficacy considerations
- demonstration that the new agent is able to provide clinical benefits that are similar to existing therapies while a) avoiding serious toxicity present in existing therapies and/or b) avoiding less serious toxicity, common to the therapy, which results in the discontinuation of treatment of a serious disease; or,
- the ability to provide similar benefit to existing therapies while demonstrating improvement in a factor that has been shown to be significant during the conduct of the pivotal trial.

2.1.5 Product Eligibility Criterion #4: Evidence That the Drug Addresses a Health Care System Need by Delivering High Clinical Benefit for Public Health or Significantly High Clinical Benefit for Patients

Health care system needs vary among regions, populations and between countries. Additionally, these needs will change over time, as technologies advance and clinical practice evolves. Therefore, while some illustrative examples are provided below, each

application will be assessed on a case-by-case basis. In all cases, sponsors claiming that their product meets this criterion should provide information substantiating this claim for benefit to the current Canadian clinical context, including information based on consultation with relevant patient groups and clinical experts where applicable.

Public health needs can include urgent or immediate needs, as well as long term needs.

Examples of products which could provide a clinical benefit for an ongoing public health need could include new drug submissions in aid of combatting the opioid crisis, novel human products which target relevant pathogens, such as those on the *Pathogens of Interest List* or which otherwise aid in combatting antimicrobial resistance, or drugs made available through the *Access to Drugs in Exceptional Circumstances* regulatory pathway where the urgent public health need is ongoing.

With respect to significant high clinical benefit for patients (in addition to the existing requirements for treatment of serious disorders), both clinical and statistical significance of outcome measures should be demonstrated. Treatment outcomes providing benefit for patients may include reduction of treatment burden related to reduced hospitalization time or less invasive or less time-consuming treatment related to improvements in the mode of product administration. Drugs with an indication targeting certain populations such as pediatrics (especially formulations where available adult formulations are unsuitable for pediatric use) or treatments for rare diseases may also qualify under this criterion.

2.2 Substantial Evidence – Eligibility for Notice of Compliance (NOC)

In general, Health Canada views substantial evidence of clinical effectiveness as evidence consisting of at least two adequate and well-controlled clinical studies, each convincing on its own to establish effectiveness of the drug involved. The effectiveness of the therapy would be assessed by experts qualified by scientific training and experience to evaluate the effect of the drug in treating the represented indication under the conditions of use prescribed, recommended or suggested in the labelling or proposed labelling thereof.

In some instances, clinical evidence consisting of a single, large-scale, adequate and well-controlled study or one pivotal trial and additional clinical evidence may be deemed "substantial". Additional clinical evidence could include literature review, expert opinions, panels or pharmacokinetic/pharmacodynamic studies.

2.3 Promising Evidence - Eligibility for Conditional Approval (NOC/c)

For some serious conditions, available data on the efficacy of a product may be limited due to small numbers of patients who are eligible for participation in clinical trials, or due to incomplete data on final outcomes such as morbidity and mortality. In these cases, use of surrogate markers may be acceptable.

Surrogate markers or endpoints can be expected to predict an effect of a drug on recognized clinical outcomes such as morbidity and mortality. For example, in some oncology settings, progression-free survival may be considered sufficient evidence of

efficacy that may ultimately reflect overall survival. Similarly, the effectiveness of vaccines is premised on the production of antibodies to provide immunity against disease.

In some instances, sufficient cumulative testing has been done to substantiate that an effect on a surrogate marker is predictive of clinical benefit. However, until surrogate markers can be validated, evidence of the effect of a drug on non-validated surrogate markers cannot replace data that demonstrate an effect on recognized clinical endpoints.

Where acceptable promising evidence is available, a Notice of Compliance with conditions (NOC/c) provides a mechanism for early access to a drug product with promising clinical benefit, providing that it possesses an acceptable safety profile based on a benefit/risk assessment, is found to be of high quality with respect to chemistry and manufacturing data, and that commitments are made by the sponsor to conduct additional confirmatory trials. Longer term data or additional trials with more substantive clinical outcome data may be used to fulfil these commitments.

2.4 Accelerated Review Process

2.4.1 Pre-Submission Meeting

Prior to filing a request for Accelerated Review status, sponsors should notify Health Canada of their intent to request consideration to file under this pathway by contacting the appropriate Centre/Bureau of the appropriate Directorate, and are encouraged to request a pre-submission meeting, either face-to-face or via teleconference, to outline the evidence of effectiveness to be provided in the submission as well as discuss potential eligibility for Accelerated Review status.

Determination regarding eligibility for Accelerated Review status will not be made at the pre-submission meeting, as discussions that occur during this meeting will serve to inform Health Canada's decision.

Please refer to Health Canada's Guidance for Industry: Management of Drug Submissions for contact information for the Regulatory Division/Office of the appropriate review Directorate.

2.4.2 Submission of Clinical Assessment Package and Determination of Product Eligibility for Accelerated Review

For the purposes of this consultation, Health Canada is presenting two different processes (Option A and Option B) for consideration, involving the submission and review of the Clinical Assessment Package (CAP). Please provide feedback on these options, including operational and technical considerations. This feedback will be considered and reflected in the final Guidance Document: Accelerated Review of Human Drug Submissions. Related changes will be made to the Guidance for Industry: Management of Drug Submissions and

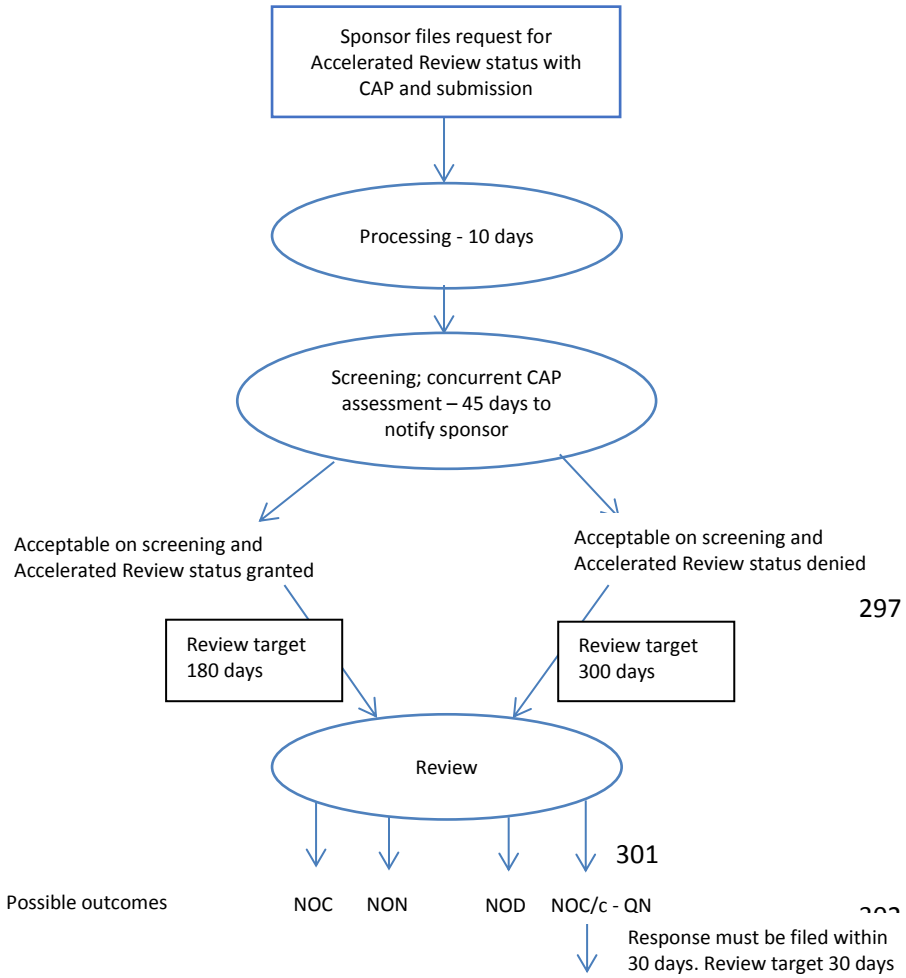
any other implicated documents at the time of finalization. Until that time, current processes apply.

Option A - Perform Concurrent Screening and CAP Assessment

In order to streamline submission timelines as much as possible, Health Canada will implement processes to conduct concurrent submission screening along with review of eligibility for Accelerated Review. Sponsors will file the drug submission and a clinical assessment package (CAP) simultaneously. Therefore, the review pathway will only be determined after the submission has been filed.

The timelines for the screening and review of the original submission is up to 235 calendar days: 10 days administrative processing; 45 days screening and concurrent determination of eligibility for Accelerated Review; 180 days submission review. These timelines would also apply for the subsequent screening and review of the response to a Notice of Deficiency (NOD).

The timeline for the subsequent screening and review of the response to a Notice of Non-compliance (NON) is up to 145 calendar days (10 days processing, 45 days screening, 90 days review).



The sponsor is required to submit a request for Accelerated Review status with a completed Clinical Assessment Package (CAP) in a format similar to that outlined in Appendix 1. The sponsor should clearly identify whether they are requesting eligibility for NOC or a NOC/c authorization. Incomplete packages or requests received in advance or subsequent to the arrival of the submission will not be accepted.

The sponsor will submit the Accelerated Review request and the full drug submission directly to OSIP or through the Common Electronic Submission Gateway.

Office of Submissions and Intellectual Property (OSIP)
E-mail: OSIP-BPPI@hc-sc.gc.ca

Accelerated Review requests and drug submissions should be filed in the eCTD format according to the *Guidance Document: Preparation of Drug Regulatory Activities in eCTD Format.* Accelerated Review requests will be assessed based on products and information available at the time the request is received and within the context of the disease for which the therapy is indicated. Packages will not be assessed based on comparator therapies at the time the pivotal trials were initiated.

The CAP and submission will be forwarded to the appropriate review Directorate where the CAP will be assigned to the relevant review division/bureau for assessment. This takes place while the submission undergoes screening. The evaluation team may, on occasion, request additional supporting information to support and clarify the information provided in the Accelerated Review request. The sponsor is required to submit, within two (2) business days of a request, any supplementary information needed to assist in the assessment. In the event that supplementary information is not received within the above period, the decision to grant or deny a request for Accelerated Review status will be based on the information provided in the original request, subject to the interpretation of Health Canada evaluators.

Health Canada will notify the sponsor of the decision to grant or deny Accelerated Review status within 45 calendar days following processing of the request. If granted, the Accelerated Review will commence following screening acceptance.

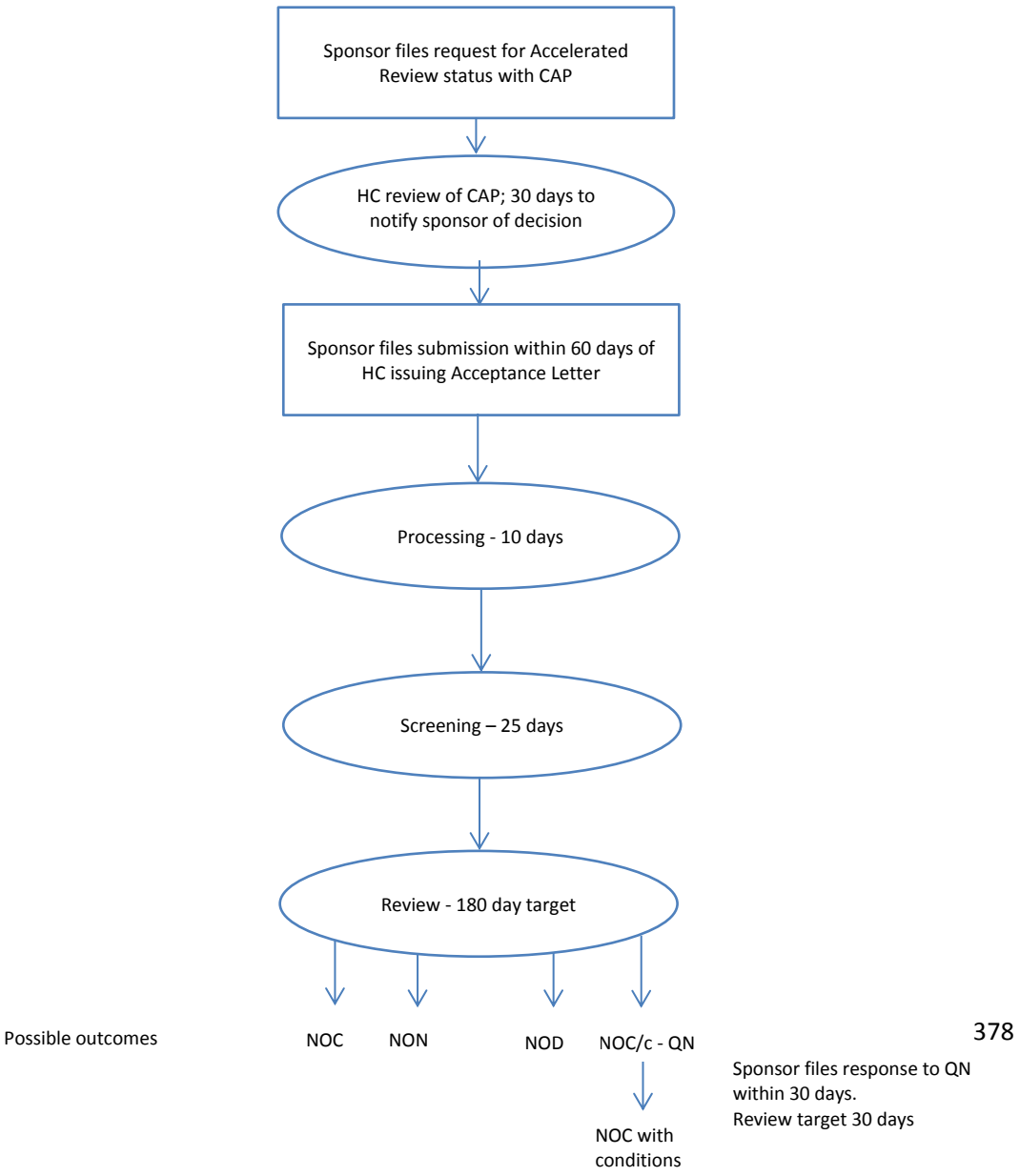
Option B – Use Current Priority Review Steps and Timelines for All Submissions

Accelerated review will be based on the processes used under the Priority Review policy, where determination of product eligibility for Accelerated Review is made prior to the submission being accepted into review, based on the review of a Clinical Assessment Package.

The timelines for the screening and review of the original submission is up to 305 calendar days: 30 day CAP assessment; 60 days for sponsor to file submission; 10 days administrative processing; 25 days screening; 180 days submission review.

The timelines for the subsequent screening and review of the response to an Accelerated Submission Notice of Deficiency (NOD) is up to 215 calendar days: 10 days administrative processing; 25 days screening; 180 days submission review.

The timelines for the subsequent screening and review of the response to an Accelerated Submission Notice of Non-compliance (NON) is up to 125 calendar days: 10 days administrative processing; 25 days screening; 90 days submission review.



The sponsor is required to submit a request for Accelerated Review status and a completed Clinical Assessment Package (CAP) containing all of the elements outlined in Appendix 1, in advance of filing of the drug submission. The sponsor should clearly identify whether they are requesting eligibility for NOC or a NOC/c approval. Incomplete packages or requests received subsequent to, or concurrent with the arrival of the submission will not be accepted.

The sponsor will submit the Accelerated Review request directly to OSIP or through the Common Electronic Submission Gateway within 60 calendar days of initial pre-submission meeting, if one is held.

Office of Submissions and Intellectual Property (OSIP)
E-mail: OSIP-BPPI@hc-sc.gc.ca

Accelerated Review requests should be filed in the eCTD format according to the *Guidance Document: Preparation of Drug Regulatory Activities in eCTD Format*. Accelerated Review requests will be assessed based on products and information available at the time the request is received and within the context of the disease for which the therapy is indicated. Packages will not be assessed based on comparator therapies at the time the pivotal trials were initiated.

The CAP is then forwarded to the appropriate review Directorate where it will be assigned to the relevant review division/bureau for assessment. The evaluation team may, on occasion, request additional supporting information to support and clarify the information provided in the Accelerated Review request. The sponsor is required to submit, within two (2) business days of a request, any supplementary information needed to assist in the assessment. In the event that supplementary information is not received within the above period, the decision to grant or deny a request for Accelerated Review status will be based on the information provided in the original request, subject to the interpretation of Health Canada evaluators.

Health Canada will notify the sponsor of the decision to grant or deny Accelerated Review status within 30 calendar days following processing of the request. If granted, the sponsor must submit the full drug submission to Health Canada within 60 calendar days of, but not prior to, the date of issuance of the Accelerated Review Status Granted Letter, in order to maintain Accelerated Review status.

Submissions received in advance of the Accelerated Review Status Granted Letter will undergo screening and, if found acceptable, shall enter the review queue as a non-accelerated submission. The ongoing review of an Accelerated Request (CAP) related to the submission shall cease immediately upon receipt of the submission.

2.4.3 Rejection/Reconsideration

A request for Accelerated Review status may be denied for reasons including, but not limited to, the following:

- failure to provide the information outlined in Sections 2.2.2 and Appendix 1;
- failure to demonstrate that the product satisfies the criteria outlined in Section 1.2;
- failure to adhere to request filing procedures outlined in section 2.4.2.

The following are not acceptable rationales for denial of an Accelerated Review request:

- the existence of a submission for a similar indication is undergoing review with Health Canada;
- approval of a product for the same indication, where the product is not available for sale in Canada, or has been available for sale in Canada for a year or less;

- off-label use of a product already marketed in Canada for the proposed indication; and,
- disclosure of a sponsor's inability to market the product in a timely manner following approval (refer to Section 2.4.4).

In the event that an initial Request for Accelerated Review status is denied, sponsors may file a Request for Reconsideration of the decision within 30 calendar days, in accordance with the procedure outlined in the Health Canada's *Guidance for Industry Reconsideration of Final Decisions Issued for Human Drug Submissions.*

As per section 5.1 of Health Canada's *Guidance for Industry Reconsideration of Final Decisions Issued for Human Drug Submissions*, the denial of either a first or second Accelerated Review request is eligible for Reconsideration. However, sponsors may only file a Request for Reconsideration of the first denial *or* file a second Request for Accelerated Review status - they may not file both.

Option A - Perform Concurrent Screening and CAP Assessment:
The submission review will commence while the Reconsideration of a denial is underway. In the event that Accelerated Review status is granted as a result of a Request for Reconsideration, the review target will be adjusted accordingly from the date upon which screening acceptance was issued.

Option B – Use Current Priority Review Steps and Timelines for All Submissions:
A submission may be filed with the appropriate review Directorate and undergo screening while the Reconsideration of a denial is underway. In the event that Accelerated Review status is granted as a result of a Request for Reconsideration, the review target will be adjusted accordingly from the date upon which screening acceptance was issued.

Instead of filing a Request for Reconsideration, sponsors may choose to file a second request for Accelerated Review, for additional consideration for the same indication, following a period of 60 days from the date of the original request, providing the submission has not yet been filed. New information in support of the Accelerated Review status of the submission must be evident, i.e. results of ongoing clinical trials. Failure to provide new information will result in denial of the request. Re-analysis of data to address reasons for the denial of the original request falls within the scope of the Reconsideration procedure and may not be used as the basis for a second request.

In the event that the second request for Accelerated Review Status is denied, for the same indication, no further requests will be accepted. In the event that the second Request for Accelerated Review status is denied, sponsors may appeal the decision and file a Request for Reconsideration of the second decision.

2.4.4 Submission and Review

When received, it is expected that the submission will contain the information and material for the purposes of Division 8, Part C of the *Food and Drug Regulations* and be subject to the *Guidance Document: Management of Drug Submissions and Applications*.

Option A - Perform Concurrent Screening and CAP Assessment:
The submission will be screened as per usual practice. Sponsors will be requested to remove any information not pertaining to the indication(s) for which Accelerated Review was granted within 15 days of the submission being accepted in to review.

Option B – Use Current Priority Review Steps and Timelines for All Submissions:
The submission will be screened as per usual practice. A Screening Deficiency Notice (SDN) may be issued to request the removal of any information not pertaining to the indication(s) for which Accelerated Review was granted.

Sponsors are strongly encouraged to consider participating in an aligned review between Health Canada and health technology assessment organizations. For additional information related to this process, please refer to Health Canada's *Notice to industry: Aligned reviews between Health Canada and health technology assessment organizations*

As indicated in the policy statement, the intent of an Accelerated Review is to expedite availability of critical drugs needed by Canadian patients and the health care system, and this process relies on intensive use of Health Canada resources which are also responsible for the review of other products. It is therefore also expected that sponsors intend and will be capable of marketing the product in a timely fashion (e.g., 30 - 60 days) after Notice of Compliance (NOC) or Notice of Compliance with Conditions (NOC/c) is granted, and sponsors are requested to indicate this in their CAP. However, Health Canada acknowledges that occasional delays in marketing, particularly for biological products, may result from sourcing delays, lot release issues and other legitimate circumstances.

Although every attempt is made to commence review of the Accelerated submission in an expedited manner, the policy does not preclude staff from working on other projects.

2.4.5 Discontinuation

Accelerated Review status will be re-evaluated upon issuance of a Notice of Deficiency (NOD) or Notice of Non-Compliance (NON). Sponsors will receive formal notification should Health Canada decide to revoke Accelerated Review status based on whether the conditions precedent for Accelerated Review status still apply.

Due to the impractical nature of ceasing a review once initiated, and in the interests of enhanced transparency, submission review will continue until such time as a NOD/NON is issued, regardless of the issuance of a NOC and subsequent marketing for a product with the same indication.

2.5 Conditional Authorization (Notice of Compliance with Conditions)

2.5.1 Notice of Compliance with Conditions - Qualifying Notice (NOC/c - QN)

When the data submitted have been reviewed and are determined to qualify for a NOC/c authorization, the appropriate Directorate will contact the sponsor to discuss particulars of the submission, commitments and potential considerations. Following discussions with the sponsor, Health Canada will issue a Notice of Compliance with Conditions Qualifying Notice (NOC/c - QN). The NOC/c - QN will indicate that the submission qualifies for a NOC, with conditions, and outline the additional clinical evidence to be provided in confirmatory trials, post-market surveillance responsibilities and any requirements related to advertising, labelling, and distribution. Submission review will cease upon issuance of the NOC/c - QN.

Responses to a NOC/c - QN must be sent to the appropriate Directorate within 30 calendar days of NOC/c - QN issuance, and must include the following:

a. *A letter signed by the Chief Executive Officer, or designated signing authority, indicating if the sponsor agrees to have the submission considered under a NOC/c authorization. In agreeing to accept a Notice of Compliance with Conditions (NOC/c) the sponsor consents to the posting of the NOC/c-QN on Health Canada's website once market authorization has been received. *Note: In the event that the sponsor does not wish to have the submission considered for a NOC/c, a Notice of Non-Compliance (NON) may be issued*

   Additional post-market surveillance commitments, requirements on advertising and distribution, and a commitment to carry out any requested clinical trials to confirm the clinical benefit of the product are requirements associated with a NOC qualifying under the NOC/c policy. As such, in order to proceed with further consideration, the sponsor must first provide a letter indicating agreement to have the submission considered as such. Submissions will also be subject to applicable fee regulations.

b. *A draft Letter of Undertaking signed by the Chief Executive Officer of the sponsor, or designated signing authority*

   Prior to authorization of the submission, sponsors must submit a draft Letter of Undertaking signed by the Chief Executive Officer, or designated signing authority, with the required content and in a format that is satisfactory to Health Canada. The intent of the undertakings is to further characterize the benefit of the drug while monitoring the risk so as to ensure a favourable benefit-risk profile. Any outstanding known or potential risks identified in the pre-market assessment should be addressed through pharmacovigilance tools acceptable to Health Canada, such as the Risk Management Plan. A sample template for a Letter of Undertaking is provided in Appendix 2.

c. *If applicable, an initial outline of proposed confirmatory trials and a rationale bridging the "Promising Clinical Evidence" with the proposed confirmatory trials. Similarly, an initial outline of any agreed-upon safety monitoring trials*

The sponsor is required to provide a synopsis/outline of confirmatory trials (design, population, etc.) to verify the drug's clinical benefit as well as a rationale linking the anticipated outcome of the confirmatory trial with the indication and effectiveness claims for which "promising clinical evidence" was received. Anticipated timeframes for initiation and completion of confirmatory trials should also be included. Inclusion of this information in the initial submission is beneficial, when a sponsor considers that their product might qualify for NOC/c.

It is recognized that when authorization by way of NOC/c is granted, confirmatory trials may already be underway in Canada or other jurisdictions. Such trials may be accepted at the discretion of Health Canada. Factors for consideration include trial design, clinical endpoints and safety measures. Where ongoing trials do not directly correspond to confirmatory trials requested in the NOC/c - QN, the ongoing trials must be bridged, with accompanying rationale, to the anticipated outcomes of the requested confirmatory trials.

It should be noted that requirements for confirmatory trials may also apply to Abbreviated New Drug Submissions or Supplement to an Abbreviated New Drug Submissions where Health Canada has determined that confirmatory trials are appropriate.

2.5.2 Agreement of Conditions and Issuance of the NOC/c

Upon receipt of the sponsor's response to the NOC/c – QN, Health Canada will commence a review of the additional information provided, which is subject to a 30 day calendar review target. Should the information be considered acceptable, Health Canada will finalize, with the sponsor, the conditions associated with issuance of the NOC as well as the Letter of Undertaking.

Upon authorization, the NOC/c – QN posted to the Health Canada website will have all proprietary information redacted.

For NDSs or SNDSs reviewed and receiving a NOC/c authorization, or for ANDSs or SANDSs where confirmatory trials are required, the NOC will be issued with the notation:

You have undertaken to conduct timely, well designed studies to verify the clinical benefit of this drug. You have also undertaken to provide appropriate educational material and comply with any post-market surveillance commitments and advertising, labelling and distribution requirements placed on the drug. Failure to comply with any one or all of these undertakings may be interpreted as suggesting, inter alia, the possibility of insufficient evidence, at that time, to establish the effectiveness of the drug for the purposes recommended. Accordingly, consideration will be given to regulatory

action, removing the product from the market under the authority of the Food and Drug Regulations.

For ANDSs or SANDSs reviewed and granted NOC/c authorization where no confirmatory trials are required, the NOC will be issued with the following notation:

You have undertaken to provide appropriate educational material and comply with any post-market surveillance commitments and advertising, labelling and distribution requirements placed on the drug. Failure to comply with any one or all of these undertakings can result in potential regulatory action in order remove the product from the market under the authority of the Food and Drug Regulations.

2.5.3 Health Product InfoWatch Communication

For products issued a NOC/c, a Notice of Market Authorization with Conditions will be communicated in Health Canada's Health Product InfoWatch in the month following issuance of the NOC/c. The InfoWatch communication will be posted on the Health Canada website and will be disseminated to key health care groups.

The Notice of Market Authorization with Conditions will be completed by Health Canada and a copy will be sent to the sponsor two business days prior to publication. The sponsor will have the opportunity to verify the accuracy of the information in the Notice during this two day period.

2.6 Post-Market Commitments Under Conditional Authorization

2.6.1 Confirmatory Trials

Sponsors must undertake to design and carry out confirmatory trials to verify the clinical benefit of the drug. The nature and scope of the confirmatory trials must be acceptable to Health Canada. Details pertaining to the above will be agreed upon in discussions between Health Canada and the sponsors during review of the initial submission and/or the response to the NOC/c - QN. The sponsor must also undertake to carry out any such trials in accordance with established scientific standards and the trials must be well designed as well as initiated in a timely fashion.

Requirements for confirmatory trials may also apply to Abbreviated New Drug Submissions or Supplement to an Abbreviated New Drug Submissions where Health Canada has determined that confirmatory trials are appropriate.

2.6.2 Providing Annual Progress Reports of Confirmatory Trials and Other Ongoing Trials

Sponsors will be required to submit to Health Canada, on an annual basis, status reports on the progress of ongoing confirmatory trials. The annual status report should be submitted

within 60 calendar days of the market authorization anniversary or a date agreed upon at the time of the issuance of the market authorization. The details of the requirements for filing and termination of the annual status report will be outlined in the Letter of Undertaking.

A sample template for the status report for ongoing confirmatory trials is provided in Appendix 3.

2.6.3 Advertising and Labelling Material

Products authorized with conditions are subject to enhanced advertising and labelling requirements. The term advertising includes promotional labelling and advertisements. Examples include, but are not limited to, brochures, booklets, detailing pieces, bulletins, calendars, motion pictures and slides, materials published in journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, the internet and telephone communication systems. The term label is defined in the *Food and Drugs Act* as: "*… any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic device or package*".

Sponsors are requested to receive pre-clearance by an Advertising Preclearance Agency recognized by Health Canada for advertising material for all health products directed to health professionals. For further information, refer to Health Canada's *List of Canadian Advertising Preclearance Agencies*.

The display portion of all advertising material, as well as all labelling material, for products authorized with conditions must contain boxed text with prominent disclosure of the nature of the market authorization granted and the need to conduct trials to confirm its clinical benefit.
Example:

> *"<Brand name>, indicated for <...>, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization."*

Advertising material must be consistent with the specific restrictions or conditions specified in the Canadian product monograph. Clear disclosure of any statements in the product monograph or labelling that the indication is based on surrogate endpoints and that the clinical benefit has not been confirmed is required. At the discretion of Health Canada, sponsors may also be required to commit to individual labelling restrictions on a case-by-case basis. For additional information refer to the *Guidance Document: Product Monograph* and the accompanying *Product Monograph Template: Notice of Compliance with Conditions*.

Additionally, package labelling requirements will be assessed based on their use (e.g., hospital setting, physician administered), indication (multiple or singular) and other potential considerations.

2.6.4 Subsequent Submissions

The conditions associated with authorization of a product, for a particular indication, will remain until the commitments have been fulfilled and authorized by Health Canada. Prior to the removal of conditions from the NOC, subsequent submissions will be managed as follows:

i. Supplemental changes that rely on the safety and efficacy data of the original submission, for which conditional authorization was granted will be processed as SNDSs and if authorized, will receive a NOC/c. Examples include, but are not limited to, submissions for a new strength or formulation;

ii. Administrative changes in product and/or manufacturer name which therefore rely on the safety and efficacy data of the original submission, will receive a NOC/c if authorized; and

iii. Subsequent submissions for a new indication must demonstrate efficacy, safety and clinical pharmacology independent of the original submission. As such, upon outcome of a review of the data provided, such submissions may qualify for a NOC, with or without conditions. Submissions should be filed as Supplement to a New Drug Submissions (SNDSs) cross-referencing the chemistry and manufacturing, pre-clinical and clinical pharmacology (if appropriate) data from the original submission.

Sponsors must clearly indicate, upon filing, the NOC/c status of an originating submission (if applicable).

In the event of revocation or suspension of the original NOC, appropriate action will be taken for all subsequent submissions which rely on efficacy and safety information provided in the original application.

Sponsors wishing additional clarification on filing and processing of subsequent submissions are advised to contact the Regulatory Division/Office of the appropriate review Directorate.

2.6.5 Providing the Results of the Confirmatory Trials

Results from confirmatory trials must be submitted in the form of a SNDS-c within the agreed-upon timeframe, as indicated in the Letter of Undertaking. In the event that there is more than one confirmatory trial underway, results of the trials may be submitted individually. Submissions will be handled in accordance with standard submission target timelines as outlined in the *Guidance to Industry: Management of Drug Submissions* and will be subject to applicable fees. Sponsors will receive notification regarding the outcome of

each SNDS-c, however conditions associated with the NOC will remain until such time as all components outlined in the Letter of Undertaking are determined to be acceptable to Health Canada.

Information contained within a SNDS-c must only address the original indication or condition of use for which the NOC/c was issued. Additional information, as well as revisions or expansions to the indication(s), are not acceptable and must be submitted within a separate SNDS, or a separate NDS with cross-reference to the chemistry and manufacturing information contained within the original application.

Additional trials related to safety as well as other remaining trials should be submitted as the appropriate submission type in accordance with the *Food and Drug Regulations* and the *Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document.*

A sponsor must also file a submission with Health Canada if wanting to seek authorization for changes to any of the representations made with respect to the drug. In accordance with the *Food and Drug Regulations* Section C.08.003(2)(h) data that would enhance the safe use of the drug resulting in an amendment to the wordings in the Contraindications, Warnings and Precautions and/or Adverse Reactions sections of the Product Monograph should be submitted to Health Canada as soon as the data are available.

Submissions should be directed according to the *Guidance Document: Management of Drug Submissions and Applications*.

2.6.6 Overseeing Commitments

Terminating Conditions or Restrictions

NDS / SNDS or ANDS / SANDS where confirmatory trials were requested:

As outlined in their Letter of Undertaking, sponsors must submit the results from confirmatory trials to Health Canada for review. The Directorate(s) may determine, on the basis of a comprehensive review of the information submitted by the sponsor, that any one or all of the undertakings have been satisfied. In instances where all the undertakings have been satisfied, and the clinical benefit of the drug has been confirmed, conditions associated with the NOC will be removed by Health Canada.

ANDS / SANDS where confirmatory trials were not requested:

Conditions associated with the NOC for a generic pharmaceutical will be removed by Health Canada once the clinical benefit has been confirmed for the Canadian Reference Product (CRP) and the conditions associated with the NOC for the CRP are also removed. The sponsor must submit a SANDS-c (labelling only) to remove the conditions within 90 calendar days. Sponsors are responsible to monitor the NOC database and most recent Product Monographs for any updates posted for the Canadian Reference Product.

Negotiating a New Letter of Undertaking

If, based on the outcome of a review, not all undertakings have been satisfied, or, in the event that sponsors foresee an inability to adhere to the agreed upon trials or timelines for commencement or completion of confirmatory trials (as outlined in the Letter of Undertaking), the sponsor will be required to submit a new Letter of Undertaking to Health Canada for review and approval. The sponsor must also submit an accompanying cover letter to the Director of the appropriate review area requesting a change in the agreed-upon confirmatory trials and/or an extension to the timelines, along with a rationale for the request.

Failure to Satisfy Conditions

All authorized products, including those with conditions, are subject to the provisions within the *Food and Drugs Act and Regulations*. For products granted a NOC/c, failure to comply with any of the undertakings contained within the Letter of Undertaking may result in the issuance of a C.01.013 letter or Health Canada advising that the drug or the indication authorized under the NOC/c be removed from the market. Enforcement capabilities outlined within the *Food and Drug Regulations* include the following:

i. Failure of a sponsor to undertake or complete a confirmatory trial may provide Health Canada with reason to suspect the product is unsafe or ineffective at that time. Failure to provide results of a confirmatory trial by a specified date may also be interpreted as suggesting the possibility of insufficient evidence, at the time, for establishing the effectiveness of the drug for the purposes recommended. In either case, consideration will then be given to the Director to invoke section C.01.013 of the *Food and Drug Regulations*;

ii. Failure of confirmatory trials to demonstrate clinical benefit and/or if such trials raise safety concerns about the drug, may result in the regulator exercising section C.08.006(2)

At the discretion of Health Canada and consistent with the regulation of all marketed products, the following may be discussed with the sponsor and evaluated on a case-by-case basis:

- restriction of patient population or distribution for which the drug was authorized (i.e., limiting prescribing information);
- dissemination of further educational material for informed use; or
- enhanced post-market surveillance analysis.

Where a decision is taken by Health Canada to request a stop sale for an indication authorized with a NOC/c, or when the sponsor recalls the drug from the market, a SNDS-c will only be accepted by Health Canada for review if data are presented that support all outstanding conditions as specified in the Letter of Undertaking from the original NOC with conditions.

2.7 Determining Conditional Eligibility for an Abbreviated New Drug Submission (ANDS) or Supplement to an Abbreviated New Drug Submission (SANDS) Where the Innovator Has Conditional Authorization

A NOC/c authorization may be issued for an ANDS or SANDS if the innovative drug has been issued a NOC/c, and its sponsor has yet to fulfill the conditions outlined in their Letter of Undertaking. In these situations, the innovative drug may be used as a Canadian Reference Product (CRP). ANDSs or SANDSs that reference a CRP with NOC/c status will be subject to the standard review timeline of 180 calendar days.

In circumstances where an ANDS or SANDS submission references a CRP, and the confirmatory trial(s) are ongoing or have not yet been submitted or reviewed by Health Canada, the subsequent-entry drug submission shall:

a. contain all the information and material to comply with the requirements of sections C.08.002.1 and C.08.005.1, pursuant to section C.08.004 of the *Food and Drug Regulations*; and

b. pursuant to section C.08.002.1(3)(d) of the *Food and Drug Regulations*, the sponsor for the ANDS or SANDS will be requested to provide undertakings similar, but not necessarily identical, to those required for the sponsor of the CRP.

Prior to authorization, undertakings for the sponsor of an ANDS or SANDS will, at minimum, include:

- enhanced post-market surveillance and reporting for the purposes of monitoring the safety of the drug product;
- a Product Monograph, Consumer Information Section/Patient Medication Information Section and labelling that clearly highlights the conditions under which the drug product is authorized, thus assuring the safe use of the drug product. The sponsor may also be requested to undertake to comply with restrictions imposed by Health Canada on the advertisement and/or distribution of the drug; and
- preparation of educational material including the Consumer Information Section/Patient Medication Information Section for distribution to patients/caregivers.

The sponsor for an ANDS or SANDS may also be requested to undertake in writing to design, carry out and report on confirmatory trials to verify the clinical benefit of the drug. The necessity to conduct confirmatory trials by generic pharmaceutical sponsors will be decided on a case-by-case basis through an appropriate review area evaluation. An example of the necessity to conduct a confirmatory trial by a generic pharmaceutical sponsor includes a circumstance where the sponsor for the CRP withdraws their drug from the market prior to completing and/or submitting the confirmatory trial(s). In this instance the sponsor may be requested to provide data to verify the clinical benefit. The need and content of the trial would be re-assessed as per C.08.002.1(3)(d). Similar to the CRP, the details of the undertakings to confirm the clinical benefit will be detailed by the sponsor in their Letter of

Undertaking or amendment to the Letter of Undertaking. The Letter of Undertaking must meet the satisfaction of Health Canada prior to approval.

Generic pharmaceutical sponsors will not automatically be requested to complete the confirmatory trials. Consideration will be given to such factors as the status of the original confirmatory trial(s); the potential to affect subject recruitment in both the original and subsequent confirmatory trials; potential competition for the same and possibly limited human and material research resources needed to conduct the trial; and ethical considerations for requesting a duplicative trial. Health Canada's goal in these considerations is to avoid unnecessary delay of the completion of confirmatory trials, and to avoid possibly undermining the objective to create mechanisms for the appropriate completion of confirmatory trials to verify the clinical benefit of a drug.

2.8 Post-Market Safety Monitoring for All Products

Regardless of whether a product qualifies for NOC or NOC/c, sponsors are required to meet all post-market safety monitoring responsibilities under the *Food and Drug Regulations*, including preparation of annual summary reports and adverse reaction reporting. Additional reporting may be required for products receiving a NOC/c; these requirements will be specified in the Letter of Undertaking.

Appendices

Appendix 1 – Template - Clinical Assessment Package

The Clinical Assessment Package (CAP) should be no longer than 20 pages in length and should include the following elements (headings in bold text). Text in italics is provided as guidance for content and should be removed from completed document.

Date of request for Accelerated Review:
Sponsor: **Contact Information:**
Section 1: Product Information:
Proper or Common Name of product and proposed Brand Name (if known):
Regulatory Status of the Drug Worldwide: *Indicate whether product is authorized in other jurisdictions, including date of authorizations and whether any conditional authorizations have been granted. Include details of authorized indications.* *Indicate whether product is currently under review in other jurisdictions.*
Specific Indication(s) Sought: *In many instances numerous indications for one drug are presented, however Accelerated status will only be granted on the basis of applicable indications. Sponsors are requested to present the strongest case for Accelerated Review status and no others, e.g., for antibiotic therapies, the nature of the microorganism and/or disease site against which the antibiotic provides resistance should be indicated. Do not list all indications (e.g. all microorganisms). List only the indication for which Accelerated Review status is warranted.* *Sponsors filing submissions containing multiple related indications or uses should contact the Submission Management Division /Unit of the appropriate review Directorate to discuss the submission filing.* *Sponsors of submissions with multiple unrelated indications are required to submit an Accelerated Review Request for each indication. Sponsors will be requested to remove non-accelerated indications from the package and submit as a separate NDS, including complete chemistry and manufacturing information.*
Request Type: ☐ Eligibility for Accelerated Review for Notice of Compliance (NOC) ☐ Eligibility for Accelerated Review for Notice of Compliance with Conditions (NOC/c)

Refer to Sections 2.2 and 2.3 this guidance document for further information
Product Eligibility: Treatment of a Serious, Life-threatening, or Severely Debilitating Disease or Condition *Provide a brief description of the disease or condition and the clinical context within which the product will be used to support the request. Indicate briefly how the product will add to the clinical management of the disease or condition.*
Product Eligibility Criterion #1: Effective treatment, prevention or diagnosis of a disease for which no drug is marketed in Canada *Describe how the drug satisfies an unmet medical need for treatment, prevention or diagnosis of the disease state as outlined in Section 2.1.2. It must be clearly indicated that no other drug which provides the same therapeutic profile is available on the Canadian market and, where applicable, that there are no available non-drug therapies.*
Product Eligibility Criterion #2: Effective treatment, prevention or diagnosis of a disease for which an existing drug has been on the Canadian market for 12 months or less *Discuss the marketing status of any existing drugs on the Canadian market with the same indication. Any drug product seeking the accelerated review must exhibit the same or better safety and efficacy profile as others on the market.*
Product Eligibility Criterion #3: Significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada *Provide a rationale for the overall improvement in benefit/risk profile over therapies currently available on the Canadian market.*
Product Eligibility Criterion #4: Evidence that the drug addresses a health care system need by delivering high clinical benefit for public health or significantly high clinical benefit for patients *Provide information relevant to the Canadian context, with appropriate references or data, including patient and clinician input. Clinical and statistical significance should be demonstrated to substantiate significant high clinical benefit for patients.*
Clinical Evidence: *Include the following:* 1. *Concise information about the studies to be submitted including design, patient population, number of patients withdrawn due to safety concerns or lack of efficacy, etc. This information may be presented in point form or in a tabular format;* 2. *Properly tabulated results demonstrating statistically significant and clinically relevant data in support of the claim, including brief discussion and comments on the results* 3. *The status of ongoing studies. Should they be interim results (e.g. oncology products based on surrogate markers), provide anticipated completion dates.*

The status of evidence (substantial vs promising) supporting the proposed indication to be included in the submission should be clearly discussed. Does the sponsor believe a Notice of Compliance with Conditions may be appropriate?
References: *Up to twelve key references supporting the data/indication as cross-referenced in the Clinical Assessment Package should be provided. Any remaining references must be available on request within one business day.*
Additional Information (for information purposes only): *Do you intend to, and are you capable of, marketing the above product within 30-60 calendar days of authorization?* *Will this submission also be made through the aligned review process with CADTH/INESSS?*

Appendix 2 – Template - Letter of Undertaking for NOC/c

Prior to authorization, the sponsor is to submit a Letter of Undertaking which should include the following elements (headings in bold text). Text in italics is provided as guidance for content and should be removed from completed document.

Sponsor: **Contact Information:**
Date:
Listing of Confirmatory Trials *Provide a list of confirmatory trials. The following phrase, or an acceptable alternate, must appear before the list:* "As per the Notice of Compliance with Conditions (NOC/c), we hereby agree to accept a NOC for <product name>, indicated for use in/as <...>. We also agree, as the condition for authorization of <product name> to submit to Health Canada, a Supplement to a New Drug Submission - Confirmatory (SNDS-C) which will include:" *Sponsors must provide an outline of confirmatory trials intended to verify the drug's clinical benefit including an indication of timeframes. Details pertaining to the above will be agreed upon in discussions between Health Canada and the sponsors. The sponsor must undertake to carry out any such trials in accordance with established scientific standards. The trials must be well designed and initiated in a timely fashion. Sponsors must also agree to submit an annual progress report.* *Requirements for confirmatory trials may also apply to an ANDS or SANDS where the CRP is authorized with conditions.*

Post-market Surveillance Commitments *A paragraph must be provided wherein the sponsor shall include the provision to submit to Health Canada in writing a summary of significant change(s) or no change to the risk/benefit profile of the drug on an annual basis, until such time as the conditions have been fulfilled and removed from the NOC by Health Canada. In addition, the paragraph should include commitments regarding any enhanced post-market surveillance, as determined on a case-by-case basis following discussions between Health Canada and the sponsor.*
Advertising, Distribution and Labelling Requirements *A paragraph outlining agreed-upon advertising, labelling or distribution requirements imposed on the product must be included. All sponsors must clearly reflect and highlight the conditions under which the drug product is authorized in the Product Monograph, the Consumer Information Section/Patient Medication Information Section and/or the labelling for that product.*
Other Ongoing Clinical Trials *A complete listing of ongoing additional clinical trials related to the product should be provided in brief as an appendix to the Letter of Undertaking. All ongoing trials, apart from agreed-upon confirmatory trials, are to be filed to the appropriate review bureau/centre and classified in accordance with the Food and Drug Regulations and the Post Notice of Compliance (NOC) Changes Guidance documents.* *Ongoing clinical trials are not necessarily linked to the conditions of the NOC/c submission. In all cases, safety aspects of ongoing trials cannot be excluded from the assessment of the submission.*
Regulatory Status of the Drug Worldwide: *Indicate whether product is authorized in other jurisdictions, including date of authorizations and whether any conditional authorizations have been granted. Include details of authorized indications.* *Indicate whether product is currently under review in other jurisdictions.*

Appendix 3- Template - Progress of Ongoing Confirmatory Trials Report

Sponsor: **Contact Information:**
Annual Status Report: *Indicated the date this report is submitted.*
Product: *BRAND NAME (active ingredients), oral, dosage form and strength*
Submission and Control Number: *NDS, SNDS, ANDS, SANDS (control number)*

Letter of Undertaking Date:
Description of Confirmatory Trial: **Trial Schedule:** *Provide the following dates: Protocol approval date; Trial enrollment start date and conclusion date; Last patient evaluation date; Health Canada submission date.* **Current Status:** *Indicate the current status of the confirmatory trial(s) using to the terminology listed below; explain status changes and subsequent action taken, as applicable.* • *Pending (the confirmatory trial has not been initiated by the sponsor)* • *Ongoing (the confirmatory trial is proceeding according to the original schedule or is ahead of the schedule. The results of the confirmatory trials 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 (SNDS-c) to Health Canada)* • *Terminated (the applicant ended the trial before completion, and has not yet submitted a final trial report to Health Canada. Examples of termination include termination of trial arms that are no longer feasible.* • *Submitted (the sponsor has submitted a final trial report to Health Canada, and the submission is currently in review)* • *Fulfilled (Health Canada has conducted the review of the final trial report filed as a SNDS-C and has issued a Notice of Compliance indicating the sponsor has met the commitment)*

Appendix 4 - References

1. Government of Canada, Food and Drugs Act, R.S.C., 1985, c. F-27, Act current to 2018-12-12 and last amended on 2018-05-23
2. Government of Canada, Food and Drug Regulations
3. Health Canada, Access to Drugs in Exceptional Circumstances
4. Health Canada, Pathogens of Interest List
5. Health Canada, Guidance for Industry: Management of Drug Submissions
6. Health Canada, Guidance for Industry Reconsideration of Final Decisions Issued for Human Drug Submissions
7. Health Canada, Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Guidance Document, 2018
8. Health Canada, Guidance Document Product Monograph, 2016

9. Health Canada, Product Monograph Template: Notice of Compliance with Conditions, 2016
10. Health Canada, Guidance Document - Submission of Risk Management Plans and Follow-up Commitments, 2015
11. Health Canada, List of Canadian Advertising Preclearance Agencies
12. Health Canada, Notice to industry: Aligned reviews between Health Canada and health technology assessment organizations
13. Health Canada, Guidance Document: Preparation of Drug Regulatory Activities in eCTD Format
14. Government of Canada, Notice: Vanessa's Law
15. Reporting Adverse Reactions to Marketed Health Products - Guidance Document for Industry, 2018