Health Canada Santé Canada

GUIDANCE DOCUMENT

Notice of Compliance with conditions (NOC/c)

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Minister of Health

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : Ligne directrice Avis de conformité avec conditions (AC-C)

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

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 scientific justification. Alternate approaches 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 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 guidance 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 guidances.

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1.0 INTRODUCTION

Health Canada issued its first *Notice of Compliance with Conditions (NOC/c)* Policy on May 1998. In November 2002, the policy was revised to enhance consistency of application in light of similarities to the Priority Review Policy. A guidance document was also released then to facilitate the consistent application of educational material for NOC/c products, through the creation of various templates. Since 2002, the Policy and Guidance documents have remained substantively unchanged except for consequential amendments to incorporate the 2006 Guidance on the *Reconsideration of Final Decisions Issued for Human Drug Submission* and 2007 administrative changes to correct translation inconsistencies.

This guidance document combines and supercedes the policy and guidance documents for Notices of Compliance with Conditions (NOC/c) dated June 12, 2007. The revisions to this document incorporate the provision for the filing of Abbreviated New Drug Submissions (ANDSs) or Supplement to an Abbreviated New Drug Submissions (SANDSs) that reference a Canadian Reference Product (CRP) with NOC/c indications. These provisions were communicated via two Notices to Stakeholders which are found in Appendix 7. The first, issued on April 2, 2008 informed stakeholders that such ANDSs would be accepted for review; the second, issued on March 17, 2009 provided early information regarding the minimum requirements for these types of submissions.

In addition, this guidance incorporates other significant changes, impacting both New Drug Submissions (NDSs) and ANDSs, including revisions to:

- Annual Progress Reports for Confirmatory Trials;
- Adverse Drug Reaction (ADR) reporting for both NDSs and ANDSs;
- Changes to the Labelling, Marketing and Educational Material sections.

EFFECTIVE DATE: June 30, 2011

This policy and guidance document, once finalized, will be effective on the date of posting. The policy announcements contained in the two Notices remain effective as of April 2, 2008 and March 17, 2009 respectively.

1.1 Policy Objective

The objective of the Notice of Compliance with Conditions policy is to:

(a) provide access to promising new drugs for patients suffering from serious, life-threatening or severely debilitating diseases or conditions for which no drug is presently marketed in Canada or for which a significant increase in efficacy or a

significant decrease in risk is demonstrated in relation to an existing drug marketed in Canada;

(b) create mechanisms for the appropriate completion of confirmatory trials to verify the clinical benefit of a drug authorized under this policy; and

(c) ensure transparency of the conditions associated with the market authorization.

The benefits of the NOC/c policy are twofold:

1. It facilitates earlier access to the drug by physicians and patients. The acceptance of promising evidence of clinical effectiveness allows for the filing of an eligible drug submission earlier than normally possible. Should the outcome of the review be positive, the time to approval and market for the drug may be shortened. It should be noted that the time to agreement on the acceptability of the contents of the "Letter of Undertaking" will affect the overall time to market.

2. It provides the means to effectively monitor, and report on, the safety and efficacy of promising new therapies through enhanced post-market surveillance initiatives.

1.2 Policy Statement

A Notice of Compliance issued under the NOC/c policy may be granted for a drug product with promising clinical benefit, providing that it possesses an acceptable safety profile based on a benefit/risk assessment, and is found to be of high quality.

Prior to authorization, the sponsor must submit[1] a “Letter of Undertaking” acceptable to Health Canada which includes:

1) Sponsors of an NDS or SNDS must undertake to design, carry out and report on well-designed confirmatory trials to verify the clinical benefit of the drug. The sponsor must undertake to carry out any such trials in accordance with established scientific standards.

2) Sponsors of an ANDS or SANDS that references a Canadian Reference Product (CRP) with NOC/c indications, must undertake to design, carry out and report on well designed

[1] As per Part C, Section C.08.002.(3)(d) (for the purpose of a New Drug Submission) and Section C.08.002.1(3)(d) (for the purpose of an Abbreviated New Drug Submission) of the *Food and Drug Regulations* the Minister may request “any additional information or Material respecting the safety and effectiveness of the new drug.”

confirmatory trials to verify the clinical benefit of the drug, if deemed necessary given the status of the molecule.

3) All sponsors must undertake to pursue enhanced post-market monitoring and report on the safety and effectiveness of the drug product.

4) 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 Section and/or the labelling for that product.

5) The sponsor may be requested for an undertaking to comply with restrictions deemed appropriate by Health Canada on the advertising and/distribution of the drug product.

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 not be addressed through this policy, but through pharmacovigilance tools acceptable to Health Canada, such as Risk Management Plans or Risk Mitigation Plans (RMPs), prior to market authorization (see Health Canada's Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E, February 9, 2009).

1.3 Scope and Application

The Notice of Compliance with Conditions policy applies to:

1) NDS and SNDSs for a serious, life-threatening or severely debilitating disease or condition for which there is promising evidence of clinical effectiveness based on the available data that the drug has the potential to provide:

- effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada[2]; or
- 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 a drug marketed in Canada.

[2] An exemption to this criterion is outlined in Section 6.0 (Subsequent Submissions).

2) ANDS and SANDS in instances where the Canadian Reference Product still holds the NOC/c status.

In all cases, a prerequisite for issuance of an NOC, qualifying under the NOC/c policy, will be the sponsor's written commitment to pursue undertakings acceptable to Health Canada.

As with similar programs in other international jurisdictions, the NOC/c designation applies to the product's specific indication being studied, and not the drug product alone.

1.4 Background

There are a number of serious, life-threatening or severely debilitating diseases or conditions for which there are, as yet, no known cures. Examples of such diseases include Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS), Amyotrophic Lateral Sclerosis (ALS) and some cancers. Drugs are being developed that may alleviate or prevent some of the symptoms of such diseases and over time, these drugs may prove to be of significant clinical benefit with respect to improving survival of those suffering from these diseases. However, this development process is often very slow and expensive.

Initially, the data available on these types of drugs may be limited due to the small number of patients that are eligible for participation in clinical trials. Even with larger sample sizes, data on final outcomes such as morbidity and mortality may be lacking, and only data which measure the drug's effect on surrogate markers may be available.

Surrogate markers are parameters that when measured directly are reasonably likely, based on available evidence, to predict an effect of a drug on recognized clinical outcomes such as morbidity and mortality. For example, in HIV disease, drugs that elicit a durable virologic suppression are believed to confer a significant reduction in AIDS clinical progression and death. Therefore virologic endpoints may be indicative of efficacy. Similarly, the effectiveness of vaccines is premised on the production of antibodies to provide immunity against disease, and the reduction in tumour size in cancers may be a sign of an improved clinical prognosis.

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. In such instances, the Regulator may request additional confirmatory trials[3] to further verify the clinical benefit of the drug.

[3] May include extension studies.

Canadian authorities have been under increasing pressure to provide timely access to drugs for serious, life-threatening or severely debilitating diseases or conditions.

1.5 Definitions

AVAILABLE THERAPY: (also refers to "existing therapy" and "existing treatments"): Where the terms are not otherwise defined, available therapy is interpreted as therapy that is reflected in the authorized labelling of regulated products. In unusual circumstances, a treatment that is not labeled for use but is supported by substantial and compelling well-documented literature evidence as well as treatments not regulated by Health Canada (for example [e.g.], surgery) can be considered available therapy. Products available through the Special Access Programme (SAP) are not considered "available therapies" for the purposes of this guideline.

CLINICAL BENEFIT[4]: outcomes that have an overall positive impact on the treatment of a disease.

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

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

ENHANCED POST-MARKET SAFETY SURVEILLANCE: use of systematic surveillance to supplement or enhance the current spontaneous adverse reaction reporting system. This may include active surveillance activities (regular periodic collection of case reports from health care professionals and health facilities that are evidence-based) and targeted safety monitoring studies (Phase IV studies).

LETTER OF UNDERTAKING: a letter submitted to Health Canada by a sponsor of a drug submission prior to the issuance of a Notice of Compliance, qualifying under the NOC/c policy.

[4] Quality of Life (QOL) factors may be admissible in support of clinical outcomes, however QOL will not be considered sufficient on its own to establish clinical benefit.

The letter must be signed by the Chief Executive Officer, or designated signing authority of the sponsor and must outline commitments to pursue post-market activities satisfactory to Health Canada. The letter must also outline restrictions, if any, to be placed on the advertisement and/or distribution of the drug.

NOTICE OF COMPLIANCE WITH CONDITIONS (NOC/c): a Notice of Compliance that is issued with a notation relating to a Letter of Undertaking.

PROMISING[5] CLINICAL EVIDENCE: evidence based on well-controlled and well-conducted clinical trials establishing that the drug product has an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit.

Periodic Safety Update Report- confirmatory (PSUR-c): For this guideline PSUR reporting is the same as described in the International Conference on Harmonization (ICH) E2C guideline. For products approved under NOC/c, the ending "-c" is used for internal tracking.

SIGNIFICANT IMPROVEMENT: statistically significant and clinically relevant improvement identified through well-controlled clinical trials.

SNDS-'c': a Supplement to a New Drug Submission (SNDS) consisting of results of confirmatory clinical trials specified in either the innovator's or subsequent-entry drug manufacturer's Letter of Undertaking.

SANDS-'c': a Supplement to an Abbreviated New Drug Submission (SANDS), label only, submitted by the subsequent-entry drug manufacturer to remove the conditions. SANDS-'c' will be submitted once the clinical benefit has been confirmed and the conditions are removed for the CRP.

SURROGATE MARKERS: parameters that when measured directly are reasonably likely, based on available evidence, to predict an effect of a drug on recognized clinical outcomes such as morbidity and mortality. A validated surrogate marker is predictive of the clinical benefit of a drug.

[5] The use of this term does not suggest the application of a standard lesser than "substantial" evidence of clinical effectiveness. Health Canada acknowledges the importance of flexibility in assessing whether promising evidence presented, in the context of such diseases and current scientific knowledge, is viewed as substantial.

2.0 GUIDANCE FOR IMPLEMENTATION

2.1 Determining the Notice of Compliance with Conditions (NOC/c) Eligibility for a New Drug Submission (NDS) or Supplement to a New Drug Submission (SNDS)

Authorization under the Notice of Compliance with Conditions policy may be granted for a drug product with promising evidence of clinical effectiveness providing it possesses an acceptable safety profile based on a benefit/risk assessment, and is found to be of high quality[6].

Prior to authorization, the sponsor must undertake in writing to design, carry out and report on confirmatory trials to verify the clinical benefit of the drug. The "Letter of Undertaking" must meet the satisfaction of Health Canada. 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.

For the purposes of monitoring the safety of the drug product, sponsors must agree to enhanced post-market surveillance and reporting requirements to be outlined in the Letter of Undertaking.

For the purposes of assuring the safe use of the drug product, the conditions under which the drug product is authorized must be clearly reflected and highlighted in the Product Monograph, Consumer Information Section/Patient Medication Section (Part III of the Product Monograph) and/or labelling for that 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.

Prior to authorization, the sponsor must prepare for distribution educational material including the Consumer Information Section/Patient Medication Section (Part III of the Product Monograph) for patients/caregivers.

The NOC/c policy applies to drug submissions intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease or condition for which there is no existing therapy available on the Canadian market which possesses a similar therapeutic profile or for which the new submission demonstrates a significant improvement in the benefit/risk profile over alternate available products.

In order to qualify for eligibility under the NOC/c policy, the product 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 NOC/c policy although the condition (cancer) itself is clearly life-threatening.

[6] Chemistry and manufacturing data found acceptable upon review.

For the purposes of establishing eligibility, the section to follow provides guidance regarding how Health Canada determines whether a condition meets the 'serious' criterion. All life-threatening conditions would also be considered 'serious' diseases and as such, separate distinction will not be provided. In the following discussion, all references to serious conditions will include life-threatening diseases.

2.1.1 Serious/Life-Threatening Disease

To determine if a condition is considered "serious", factors such as survival, day-to-day functioning or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one are all 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 for consideration under the NOC/c policy should all additional criteria be met. Alternatively, examples of insufficient morbidity would normally include short-lived and self-limiting morbidity.

Serious conditions include, but are not limited to:

- Acquired immunodeficiency syndrome (AIDS);
- All other stages of human immunodeficiency virus (HIV) infection;
- Alzheimer's dementia;
- Amyotrophic Lateral Sclerosis (ALS);
- Angina Pectoris;
- Heart Failure;
- Cancer; and
- other diseases that are clearly serious in their full manifestations.

2.1.2 Severely Debilitating Disease

NOC/c eligibility extends to drugs indicated for the treatment of a severely debilitating disease or condition wherein there exists an unmet medical need or for which a substantial improvement in the benefit/risk profile of the therapy is demonstrated. Many chronic diseases that may be generally well-managed by available therapy may have severely debilitating outcomes. Examples of the above include inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses. Once again, discretion on the part of Health Canada will be exercised. Sponsors seeking consideration under the NOC/c policy on the basis of promising clinical evidence are required to deliver a brief presentation to Health Canada staff at which time additional clarification may be provided (refer to section 2.3 for details).

2.1.3 Effective Treatment, Prevention or Diagnosis of a Disease

Serious, life-threatening or severely debilitating diseases or conditions, for which no therapy is presently marketed in Canada, represent an obvious medical need. A new therapy effective in the treatment, prevention or diagnosis of that condition would therefore meet this criterion for eligibility under the NOC/c policy.

The term 'marketed' implies that sale of the product has commenced, pursuant to C.01.014 and that the product continues to be available for sale (that is [i.e.,] it has not been discontinued or removed from the market).

*Note: The above criterion does not provide for eligibility due to drug shortage scenarios.

2.1.4 Significant Increase in Efficacy and/or Significant Decrease in Risk

For the above NOC/c criterion to be met, the sponsor should be able to demonstrate that the therapy has the potential to provide a statistically significant and clinically relevant improvement in benefit/risk profile, over existing therapies on the Canadian market.

The potential of the therapy can be construed from:

- Trials with surrogate markers that require validation;
- Phase II trials that would require confirmation with Phase III trials consistent with the normal course of development of a therapeutic entity; or
- Phase III trials where a single small to moderately sized trial would require confirmation of either the efficacy or safety of the agent under question. These trials should be replicates of the pivotal trials or trials of different design where the outcomes are congruent with, and complimentary to, those of the original trial.

In some instances, clinical evidence consisting of a single, large-scale, adequate and well controlled trial or one pivotal trial and additional clinical evidence may be deemed sufficient for NOC authorization without conditions. Furthermore, there are multiple ways whereby clinical evidence may be established including literature review, expert opinions, panels or pharmacokinetic/pharmacodynamic studies.

Sponsors preparing to file a drug submission for NOC/c consideration are required to deliver a brief presentation to Health Canada review staff, prior to submitting the application, at which time additional clarification may be provided.

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 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 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; and
- The ability to provide similar benefit to existing therapies while demonstrating improvement in some factor, such as compliance or convenience, shown to lead to improved effects on serious outcomes.

The following source may be consulted for additional guidance:

"Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", Food and Drug Administration, May 1998.

2.2 Determining the Notice of Compliance with Conditions (NOC/c) Eligibility for an Abbreviated New Drug Submission (ANDS) or Supplement to an Abbreviated New Drug Submission (SANDS)

Notice of Compliance under the NOC/c policy may be granted for ANDS and SANDS. Innovative drugs that have been issued an NOC under the NOC/c policy and for which the brand name sponsor has yet to fulfill the conditions outlined in the Letter of Undertaking may be used as a Canadian Reference Product (CRP).

In circumstances where an ANDS or SANDS submission references a CRP where the confirmatory trial(s) are ongoing or have not been submitted or reviewed by Health Canada, the second-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 (FDR)*; and

b) pursuant to section C.08.002.1(3)(d) of the *FDR*, the ANDS or SANDS sponsor will be requested to provide undertakings similar, but not necessarily identical, to those provided by the CRP sponsor.

Prior to authorization, undertakings for an ANDS or SANDS for the second-entry drug sponsor 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 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 Section for distribution to patients/caregivers.

The ANDS or SANDS sponsor 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 ANDS sponsors will be decided on a case-by-case basis through an appropriate clinical bureau evaluation. An example of the necessity to conduct a confirmatory trial by an ANDS sponsor includes a circumstance where the CRP sponsor withdraws their drug from the market prior to completing and/or submitting the confirmatory trial(s). In this instance the ANDS 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.

ANDS 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 possibly undermining the objective of the NOC/c policy 'to create mechanisms for the appropriate completion of confirmatory trials to verify the clinical benefit of a drug'.

2.3 Consideration for Market Authorization under the Notice of Compliance with Conditions (NOC/c) policy and Review

For consideration under the NOC/c policy, NDSs/SNDSs and ANDSs/SANDSs must first meet the criteria outlined in Scope and Application section of this document.

NDS or SNDS

Consideration of an NDS or SNDS for NOC/c status may then be granted under one of the following two circumstances:

Upon Completion of Review

21) Where a sponsor has submitted a drug submission for evaluation[7], Health Canada may determine upon completion of a review of the submitted data that the promising evidence of effectiveness provided be viewed as substantial[8]. In such a circumstance however, Health Canada deems it important to monitor the product in a post-market environment through establishment of conditions and the requirement that the sponsor undertake additional confirmatory trials, to be outlined in a Letter of Undertaking. In such an event, sponsors would be contacted to discuss consideration under the NOC/c policy.

Request for Advance Consideration Under the NOC/c policy (Prior to Commencement of Review)

2) Sponsors requesting advance consideration under the NOC/c policy may also be permitted to file the drug submission with the appropriate Directorate within Health Canada.

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7 Where submissions are filed, without a request for advance consideration under the Notice of Compliance with Conditions (NOC/c) policy (Appendix 6a), sponsors may apply for Priority Review status. A product that is accepted for review under the Priority Review Policy, can be issued an NOC/c, at the discretion of the reviewing bureau/centre.

8 Evidence may be viewed as substantial in the context of the disease state treated and in light of current scientific knowledge/advances in the treatment, prevention or diagnosis of the disease.

The sponsor **is required** to deliver a pre-NDS or pre-SNDS presentation to the appropriate Directorate within Health Canada outlining the evidence of effectiveness to be provided in the submission. Sponsors should submit a pre-submission meeting information package to the appropriate Directorate in advance of the meeting. For further information, sponsors are advised to contact the appropriate review Directorate.

Within 10 working days of the finalization of the meeting minutes, the sponsor will be notified by Health Canada of the eligibility of the drug submission for filing and consideration under the NOC/c Policy.

Should Health Canada have no objections, the sponsor may submit the drug submission for screening no later than 60 calendar days following notification of eligibility. A drug submission shall contain all the data and material required to adequately assess the safety, quality and clinical efficacy of the drug. Sponsors must, at this time, clearly state that the product is filed for consideration under the NOC with conditions policy. Drug submissions reviewed under NOC/c policy will be subject to the Management of Drug Submissions Guidance and the applicable fee regulations.

Sponsors filing drug submissions for consideration under the NOC/c policy, without having completed the requirements listed above and without having received notification of eligibility, will be rejected at screening.

Submissions filed for advance consideration under the NOC/c policy on the basis of promising clinical evidence are not eligible for Priority Review status. Upon acceptance at screening, such submissions will be subject to a review target of 200 calendar days[9] (+10 days SIPD + 25 days screening) and monitored in accordance with Performance Measurement standards (Appendix 6b).

Filing an ANDS or SANDS Submission

Consideration of an ANDS or SANDS for NOC/c status will be granted in situations where the CRP also holds the NOC/c status. In instances where the CRP does not hold the NOC/c status, the ANDS can only be considered under the NOC/c policy via an NDS/SNDS for a new indication that fits the NOC/c policy objective.

ANDSs or SANDSs that references a CRP with NOC/c status will be subject to a review target of 180 days (see Appendix 6c for details).

[9] In recognition of the priority status of the submission, in addition to the supplementary time required to determine the validity of endpoints through internal discussion and consultation, a shortened review target of 200 calendar days has been assigned.

Process related queries should be sent to the appropriate Directorate within Health Canada:

Biologic and Genetic Therapies Directorate
For biotherapeutic and radiopharmaceutical submissions:

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
100 Eglantine Driveway
Address Locator 0601C
Tunney's Pasture
Ottawa, Ontario
K1A 0K9
Phone: 613-957-1722
Fax: 613-946-9520
Email: BGTD_ORA@hc-sc.gc.ca

OR

Therapeutic Products Directorate *(choose one)*

For NDSs or SNDSs:

Director, Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS)
c/o Regulatory Project Management Division servicing BMORS
Health Canada
101 Tunney's Pasture Driveway
Address Locator 0202D2
Ottawa, Ontario
K1A 0K9
Fax: 613-941-1365

Director, Bureau of Gastroenterology, Infection and Viral Diseases (BGIVD)
c/o Regulatory Project Management Division servicing BGIVD
Health Canada
101 Tunney's Pasture Driveway
Address Locator 0202B
Ottawa, Ontario
K1A 0K9
Fax: 613-941-1183

Director, Bureau of Cardiology, Allergy and Neurological Sciences (BCANS)
c/o Regulatory Project Management Division servicing BCANS
Health Canada
101 Tunney's Pasture Driveway
Address Locator 0202A1
Ottawa, Ontario
K1A 0K9
Fax: 613-941-1668

For ANDSs or SANDSs referencing CRPs with NOC/c status:

Director, Bureau of Pharmaceutical Sciences (BPS)
c/o Regulatory Project Management Division servicing BPS
Health Canada
101 Tunney's Pasture Driveway
Address Locator 0202A1
Ottawa, Ontario
K1A 0K9
Fax: 613- 957-3989

All submissions should be sent to the following:

Office of Submissions and Intellectual Property
Therapeutic Products Directorate
Health Canada
101 Tunney's Pasture Driveway
1st Floor, Finance Building, Address Locator 0201A1
Ottawa, Ontario
K1A 0K9
Fax: 613-941-0825

2.4 Reconsideration Process and Filing of Subsequent Requests for Notice of Compliance with Conditions (NOC/c) consideration

In the event that an initial request for NOC/c consideration is rejected, sponsors may file a Request for Reconsideration of the decision in accordance with the procedure outlined in the Health Canada's Guidance: *Guidance for Industry Reconsideration of Final Decisions Issued for Human Drug Submissions.* Alternately, sponsors may file a second request, for additional consideration for the same indication, following a period of 60 days from the date of the original request. New information in support of NOC/c eligibility must be evident, i.e. results of additional ongoing clinical trials. Failure to provide new information will result in rejection of the request. Re-analysis of data to address reasons for the rejection of the original request falls

within the scope of the Reconsideration procedure and may not be used as the basis for a subsequent request.

In the event that the second request for NOC/c consideration is rejected, sponsors may file a Request for Reconsideration of the second decision. As per section 5.1 of Health Canada's Guidance: *Guidance for Industry Reconsideration of Final Decisions Issued for Human Drug Submissions*, the rejection of either a first or second Request for Advance Consideration under the *Notice of Compliance with Conditions Policy* is eligible for Reconsideration. However, sponsors may only file a Request for Reconsideration of the first rejection *or* file a second Request for Advance Consideration - they may not file both.

2.5 Issuance and Response: Notice of Compliance with Conditions - Qualifying Notice (NOC/c - QN)

When the data submitted has been reviewed and are determined to qualify under the NOC/c policy, the appropriate Directorate of Health Canada will contact the sponsor to discuss particulars of the submission, commitments and potential consideration under the NOC/c policy. 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 an NOC, under the NOC/c policy, and outline the additional clinical evidence to be provided in confirmatory trials[10], post-market surveillance responsibilities and any requirements related to advertising, labelling, or distribution. Submission review will cease upon issuance of the Qualifying Notice. The sponsor must submit the following to Health Canada within 30 calendar days of NOC/c - QN receipt:

a) *Any additional information requested by Health Canada*

The Consumer Information Section/Patient Medication Section (Part III of the Product Monograph) and a Product Monograph (PM) consistent with requirements outlined in Sections 5.2.1 and 5.2.2, will be required to support market authorization of the drug. In addition, the sponsor may be requested to provide additional information in a timely fashion.

b) *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;*

[10] Applies to Abbreviated New Drug Submissions or Supplement to a New Drug Submissions where Health Canada has determined that confirmatory trials are appropriate.

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.

It is recognized that when authorization under the NOC/c policy 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.

c) *A letter signed by the Chief Executive Officer, or designated signing authority, indicating if the sponsor agrees to have the submission considered under the NOC/c policy. *Note: In the event that the sponsor does not wish to have the submission considered for an NOC, subject to the NOC/c policy, a Notice of Non-Compliance (NON) will 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 an 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.

d) *A draft Letter of Undertaking signed by the Chief Executive Officer, or designated signing authority, of the sponsor having a form and content satisfactory to Health Canada*.

Prior to authorization of the submission, sponsors must submit a Letter of Undertaking signed by the Chief Executive Officer, or designated signing authority, and having a form and content satisfactory to Health Canada. Specific information on the Letter of Undertaking, is provided in Section 4.0.

Responses to an NOC/c - QN should reference the submission control number and be sent to the appropriate Directorate.

2.6 Agreement of Conditions, and Issuance of the Notice of Compliance with Conditions (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, subject to a 30 day review target. Should the information be considered acceptable, Health Canada will finalize, with the sponsor, the conditions associated with issuance of the NOC and the Letter of Undertaking.

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

2.7 Notation

For NDSs or SNDSs reviewed and receiving an authorization under NOC/c policy, 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 for the purposes recommended from the market under the authority of the Food and Drugs Act and Regulations.*

For ANDSs or SANDSs reviewed and granted authorization under the NOC/c policy 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 for the purposes recommended from the market under the authority of the Food and Drug Regulations.*

3.0 POST-MARKET COMMITMENTS

3.1 Confirmatory Trials

Sponsors must undertake to design and carry out confirmatory trials[11] to verify the clinical benefit of the drug. The sponsor must provide an outline of confirmatory trials including an indication of timeframes for initiation and completion. 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. 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.

3.2 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 brief annual status report should include the commitment summary, the current status of the trial (confirmatory trial pending, ongoing, delayed, terminated, or submitted), details explaining the status and subsequent action taken. An example of the status report template for ongoing confirmatory trials is provided in Appendix 4. 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. If there are any questions regarding the content Health Canada will notify the sponsor within 90 days of the receipt. If there are no questions a notice of acknowledgement will be issued to the sponsor.

Confirmatory Trial Current Status Definitions:

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.

[11] Applies to Abbreviated New Drug Submissions or Supplement to an Abbreviated New Drug Submissions where Health Canada has determined that confirmatory trials are appropriate.

Terminated: The applicant ended the trial before completion, and has not yet submitted a final trial report to Health Canada. Examples of termination include termination of trial arms that are no longer feasible. For specific safety, efficacy or quality concerns related to the drug, Health Canada needs to be notified within 15 days (see section 3.4.4)

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 an SDNS-C and has issued a Notice of Compliance indicating that the sponsor has met the commitment.

3.3 Providing the Results of the Confirmatory Trials

Final results from confirmatory trials must be submitted in the form of an SNDS-C within the agreed-upon timeframe[12]. In the event that there is more than one confirmatory trial underway, final results of the trials may be submitted individually. Submissions will be handled in accordance with the *Management of Drug Submissions Guidance* and will be subject to applicable fee regulations. 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 the SNDS-C must only address the original indication or condition of use for which the NOC was issued. Additional information supporting an expanded indication is not acceptable and must be submitted as a separate NDS or SNDS, 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 Guidance Document.*

Health Canada has introduced enhanced post-market surveillance procedures for all products authorized under the NOC/c policy, including regular monitoring of the conditions associated with an NOC and active surveillance. If such measures fail to confirm the safety and efficacy information presented in the original submission, appropriate regulatory action will be taken to ensure the safety of the patients treated. As such, there is no reduced target associated with the review of a SNDS-C. SNDS-Cs will enter the drug review queue for review and authorization subject to standard submission targets.

[12] Timelines and criteria for submitting progress reports are negotiated with sponsors prior to finalization of the Letter of Undertaking.

A sponsor must also file a supplement or Notifiable Change (NC) with Health Canada if it wishes 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.

*Note: 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 consider invoking section C.01.013 of the *Food and Drug Regulations*.

Submissions should be sent to the appropriate Directorate.

3.4 Monitoring of Safety

Products issued an NOC under the NOC/c policy will be subject to additional post-market surveillance activities.

3.4.1 Adverse Reaction (AR) Reporting

Sponsors must report all serious ARs that occurred in Canada and all serious unexpected ARs that occurred outside of Canada within 15 days to the Marketed Health Products Directorate, in accordance with current regulations (C.01.016) and guidelines. Sponsors may obtain information regarding the ARs received by Health Canada including those received directly from health care professionals and /or consumers by accessing the searchable subset of the Canada Vigilance Database which is available on the Health Canada website at the following location: http://www.healthcanada.gc.ca/medeffect. In addition, requests for AR data in a standard line-listing format may be obtained directly from the Canada Vigilance Program. Requests for additional information not provided in standard formats including original AR case reports may be made through Access to Information.

Health Canada
Director/ Coordinator, Access to Information and Privacy
1010 Somerset Street West
1st Floor, Postal Locator 2301D
Ottawa, Ontario
K1A 0K9

Telephone: 613-954-8744
Fax: 613-941-4541
E-Mail: atip-aiprp@hc-sc.gc.ca

The preferred method of reporting ARs is by fax **or** mail. All AR reports should be sent to:

Canada Vigilance Program
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture
Address Locator 1908C
Ottawa, Ontario
K1A 0K9

For more information on AR reporting, refer to Health Canada's the *Guidance for Industry - Reporting Adverse Reactions to Marketed Health Products*, March 17, 2011.

Adverse events (AE) and AR reports on marketed drugs occurring as part of confirmatory trials subject to clinical trial applications, as outlined in the Letter of Undertaking, should **not** be sent to the Canada Vigilance Program. These reports should be sent by fax to:

613-941-2121 for pharmaceutical drugs to Therapeutic Products Directorate

or

613-957-0364 for biologic and radiopharmaceutical drugs to Biologics and Genetics Therapies Directorate

Serious and unexpected ADRs, subject to expedited reporting, are those considered to be drug specific. Please refer to Section 12.3 of the Guidance for Clinical Trial Sponsors: Clinical Trial Applications for clarification and further details. This document is available on the Health Canada website.

3.4.2 Post-Market Surveillance Reporting

For drugs that received their NOC under the NOC/c policy sponsors must include at minimum a provision in the Letter of Undertaking to inform TPD or BGTD in writing of the conclusions from the analysis of their annual summary report. This document should indicate whether or not there is a 'significant change in the risk-benefit profile of the drug relating to its safe use'. In the presence or absence of a significant change in the risk-benefit profile of the drug the sponsor

should also provide a rationale to support their conclusion. The documentation to be submitted to Health Canada can be based on Part 9.0 Overall Safety Summary of the Periodic Safety Update Report (PSUR).

Additional safety information may be required periodically. This requirement may be determined at the time of the pre-market or post-market assessment.

Criteria for 'significant change in risk/benefit profile':

Examples for 'significant change related to the drug's safe use' for drugs that received their NOC under the NOC/c policy include change in frequency and or severity of a known risk or the identification of an unknown risk. The source of data should not be restricted to the approved indication(s), other sources such as ongoing clinical trials in other patient populations should also be submitted.

Post-Market Surveillance Reporting Frequency:

The post-market surveillance document for NDSs and ANDSs will be submitted on an annual basis. If the manufacturer determines a significant change in the risk/benefit profile while preparing the annual summary report it shall notify TPD/BGTD in writing without delay (section C.01.018(4) of the *Food and Drug Regulations (FDR).*

Pursuant to section C.01.018(5) of the *FDR*, TPD/BGTD can request the annual summary report or an interim report and case reports. The preferred format will be the Periodic Safety Update Report (PSUR) format in accordance with the standards defined in the ICH E2C(R1) guideline[13].

In addition, pursuant to section C.01.019 of the *FDR*, TPD/BGTD can request in writing that the manufacturer submits within a specified period an issue-related summary report. The issue - related summary report must contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug and case reports of all or specified adverse drug reactions and serious adverse drug reactions to the drug that are known to the manufacturer. The content of the report will be determined by taking into account the time frame set to submit the document. At minimum the report will include an analysis of the risk of the product based on available data and conclusions regarding the safety of the product as marketed in Canada.

[13] The details for the formatting of the annual summary report are found in Section 5.3 of the "Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products" (March 17, 2011)

Analysis related to NOC/c products should be sent in an electronic common technical document (eCTD) format to:

Office of Submissions and Intellectual Property
Therapeutic Products Directorate
Health Canada
101 Tunney's Pasture Driveway
1st Floor, Finance Building, Address Locator 0201A1
Ottawa, Ontario
K1A 0K9

Process-related queries concerning the submission of the analysis or PSUR-Cs should be directed to the Office of Submissions and Intellectual Property at 613-941-7281, fax: 613-941-0825 or via email to OSIP-BPPI@hc-sc.gc.ca. Specific content-related questions should be directed to the Marketed Pharmaceuticals and Medical Devices Bureau of Marketed Health Products Directorate.

3.4.3 Active Surveillance

Sponsors may be required to undertake active surveillance responsibilities to effectively monitor safety aspects of the drug. Details pertaining to post-market surveillance (including active surveillance responsibilities) will be determined on a case-by-case basis following discussions between Health Canada and the sponsor. In such instances, there is an expectation that the sponsor will be actively involved in the generation of case reports for submission to Health Canada.

Examples of active surveillance include targeted safety monitoring trials (in hospitals and health facilities), prescription event monitoring, registries or sentinel sites.

3.4.4 Notification and Reporting on Specific Issues of Concern

Sponsors are advised that they will be requested by Health Canada to:

a) Notify Health Canada within 15 days when, on the basis of safety, efficacy or quality concerns related to the product, an expert panel or advisory committee has been struck in a foreign jurisdiction to address an issue or when there has been significant regulatory action in another jurisdiction including a direction to issue warnings, a health advisory or the removal of a product from the market; and

b) Prepare and submit a report on the issue that prompted the action in the foreign jurisdiction. The report should be available to Health Canada within 30 days of the notification. This time frame may be subject to negotiation with Health

> Canada when the scope of the issue under investigation warrants additional time to gather the necessary information.

Notifications and reports should be directed to the Marketed Pharmaceuticals, Biologics and Medical Devices Bureau of the Marketed Health Products Directorate.

4.0 DRAFTING THE LETTER OF UNDERTAKING

Prior to authorization under the NOC/c policy, sponsors are required to submit a draft Letter of Undertaking in partial fulfilment of Health Canada's requirements for responding to an NOC/c - QN.

The Letter of Undertaking is drafted by the sponsor and submitted to Health Canada for comment and authorization. The Letter of Undertaking should include the following information:

4.1 Listing of Confirmatory Trials[14]

The following phrase, or an acceptable alternate, must appear before the list of confirmatory trials:

> "As per the Notice of Compliance with Conditions (NOC/c), we hereby agree to accept an 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 as described in section 3.2.

4.2 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

[14] Applies to Abbreviated New Drug Submissions or Supplement to an Abbreviated New Drug Submissions where Health Canada has determined that confirmatory trials are appropriate.

commitments regarding enhanced post-market surveillance, including reporting of adverse reactions (ARs) and active surveillance responsibilities.

> *Note: Details pertaining to post-market surveillance (including active surveillance responsibilities) will be determined on a case-by-case basis following discussions between Health Canada and the sponsor.

4.3 Advertising, Distribution and Labelling Requirements

A paragraph outlining agreed-upon advertising, labelling or distribution requirements imposed on the product must be included. Reference to the provision of revised product monographs as information is made available should also be included.

4.4 Notification and Reporting of Specific Issues of Concern

Sponsors must include within the Letter of Undertaking the provision to comply with Section 3.4.4 - Notification and Reporting on Specific Issues of Concern.

4.5 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[15], 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.

4.6 Market Authorizations

Included with the letter, as an appendix, should be copies of any marketing authorizations for the drug under review from any other drug regulatory authority.

[15] Examples include Pharmacokinetic/Pharmacodynamic (PK/PD) studies, PK boosting, new formulations, drug-drug interaction studies, geriatric, pediatric, special populations or gender studies etc.

5.0 ADVERTISING, LABELLING AND EDUCATIONAL MATERIAL

5.1 Advertising Requirements and Pre-clearance

The display portion of all advertising material[16], for products authorized under the NOC/c policy, 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 monograph. Clear disclosure of any statements in the monograph or labelling that the indication is based on surrogate endpoints and that the clinical benefit has not been confirmed is required.

Sponsors are requested to receive pre-clearance by the Pharmaceutical Advertising Advisory Board (PAAB) for all promotional material related to products authorized under the NOC/c policy. Questions related to pre-clearance of such materials may be directed to PAAB:

Pharmaceutical Advertising Advisory Board
200-375 Kingston Road
Pickering, Ontario
L1V 1A3
Telephone: 905-509-2275
Fax: 905-509-2486

For further information, refer to PAAB's *Guideline on Advertising Disclosure for Drugs with "Notice of Compliance with Conditions (NOC/c)*", available on the PAAB website (www.paab.ca.).

[16] 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.

5.2 Labelling

Products authorized under the NOC/c policy will be subject to enhanced labelling requirements. At the discretion of Health Canada, sponsors may also be required to commit to individual labelling restrictions on a case-by-case basis. The Consumer Information Section/Patient Medication Section and Product Monograph must be supplied with each product authorized under the NOC/c policy. In addition, health care practitioners must be instructed in the Product Monograph to notify the patient of the nature of the authorization granted.

Package labelling requirements will be assessed on a case-by-case basis, as per use (e.g. hospital setting, physician administered), indication (multiple or singular) and other potential considerations.

5.2.1 Product Monograph

The Product Monograph (PM) must contain the standard information as outlined in Guidance for Industry: Product Monograph document. Sections for which particular NOC/c requirements may be applied including the following:

- General NOC/c Information Section (see Appendix 2);
- Part I: Indications and Clinical Uses; Action and Clinical Pharmacology; Warnings and Precautions; Adverse Reactions; Dosage and Administration;
- Part II: Clinical Trials;
- Part III: Consumer Information Section/Patient Medication Section.

Boxed text:

Boxed text is required for all products authorized under the NOC/c policy. The text must appear in the following areas of the PM:

> *"<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. For further information for <Brand name> please refer to Health Canada's Notice of Compliance with conditions - drug products website:*
> *http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php*
>
> [For market authorizations without conditions]
> *"Brand name> indicated for*:
> *- <>*
> *has been issued marketing authorization without conditions. "*

- Immediately following product-specific information on the PM cover (Appendix 1);
- At the beginning of each major section of the PM. Part I: Health Professional Information, Part II: Scientific Information; and Part III: Consumer Information Section/Patient Medication Section; and
- Included in the General NOC/c Information Section provided by Health Canada (Appendix 2).

For circumstances where the drug product has received both conditional and non-conditional market authorizations, the box text should be modified to specify the nature of market authorization for each indication.

Boxed text present on the cover page, and at the beginning of Parts I and II, should resemble the following:

General Information Section:

Appendix 2 provides text for inclusion in the PM immediately following the cover page. It contains general information relating to issuance of the NOC under the NOC/c policy.

Symbolic Identifier:

Each section of the PM for which NOC/c status requires particular attention[17] must be identified by an "NOC/c" symbol in the left margin next to the numeric subsection for which it applies.

Indications and Clinical Uses:

Wording for this section must reflect that the indication, for which an NOC/c applies, is based on promising information that the product may be useful in the treatment of <x>.

Adverse Reactions:

NOC/c products may be subjected to enhanced Adverse Reaction reporting requirements which must be highlighted in the PM.

Clinical Trials:

Sponsors will complete the tabular summary of available clinical trials with information upon which market authorization was granted. Details of confirmatory trials should not be provided in this section.

Further information related to Product Monographs is available on the Health Canada website.

5.2.2 Consumer Information Section/Patient Medication Section

The sponsor is required to submit to Health Canada, the Part III: Consumer Information Section/Patient Medication Section of the Product Monograph in a format that is outlined in *Product Monograph: Guidance for Industry*. The Consumer Information Section/Patient Medication Section must be written in lay terminology with a consumer defined as the general public. In addition to the lay-language translation of information contained in Parts I and II of the Product Monograph, the Consumer Information Section/Patient Medication Section will contain a prominent disclosure of the nature of authorization granted and the need to pursue undertakings in order to confirm the clinical benefit of the drug. The Consumer Information Section/Patient Medication Section replaces the previous Product Specific Fact Sheet and will be posted to the Health Canada website upon issuance of the NOC.

[17] Refers to all segments of the Product Monograph for which the nature of the authorization has implications (for example, conditions of use, restrictions, warnings etc).

An example of the prominent disclosure for the general public is shown below:

> **What is a Notice of Compliance with Conditions (NOC/c)?**
> An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.
>
> Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

5.3 Notice of Market Authorization with Conditions

All products issued an NOC, qualifying under the NOC/c policy, require a Notice of Market Authorization with Conditions to support market authorization of the drug. This notice highlights the conditional market authorization of the health product and will be communicated through Health Canada's Health Product InfoWatch.

The Notice of Conditional Market Authorization (see Appendix 3) will include the brand name and proper name of the drug, its dosage form, strength and indication, as well as a prominent disclosure of the nature of authorization granted and the need to communicate this to patients. Relevant links to the Product Monograph and sponsor contact are also included. The Health Product InfoWatch will be posted on Health Canada's Web site, and disseminated to key health care groups.

The Notice of Market Authorization with Conditions will be completed by Health Canada. Health Canada will send a courtesy copy of the information on the Notice of Market Authorization with Conditions to the sponsor, as it will appear in the Health Product InfoWatch, 2 business days (48 hours) prior to publication. The sponsor will have the opportunity to verify the accuracy of the information on the Notice of Market Authorization with Conditions during this 48 hour period.

Please note that since the Health Product Infowatch is a monthly publication, the Notice of Market Authorization with Conditions will be published in the month immediately following issuance of the NOC.

6.0 SUBSEQUENT SUBMISSIONS

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

i) supplemental (Level 1) changes that rely on the safety and efficacy data of the original submission, for which authorization was granted under the NOC/c policy, will be processed as SNDSs and if authorized, will receive NOC/c status. Examples include, but are not limited to, a submission 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 NOC/c status 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 an 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 in the original submission.

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

In the event that all conditions associated with authorization of the original drug submission have been fulfilled and are removed by Health Canada, the authorization status (i.e., NOC/c status) of all subsequent submissions which rely on efficacy and safety information provided in the original application, will be revisited and amended accordingly where justified. Similarly, upon revocation or suspension of the original NOC, appropriate action will be taken for all subsequent submissions.

Sponsors wishing additional clarification on filing and processing of subsequent submissions, are advised to contact the Office of Submissions and Intellectual Property of the Therapeutic Products Directorate.

7.0 OVERSEEING COMMITMENTS

7.1 Terminating Conditions or Restrictions

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

> As outlined in their Letter of Undertaking, sponsors will submit the results from confirmatory trials to Health Canada in the form of a SNDS-c. 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 ANDS's NOC will be removed by Health Canada once the clinical benefit has been confirmed by the CRP and the conditions are also removed for the CRP. ANDS sponsor will submit a SANDS-c (labelling only) to remove the conditions within 90 days. ANDS sponsors are responsible to monitor the NOC database and most recent Product Monographs for any updates posted for the Canadian Reference Product.

7.2 Negotiating a New Letter of Undertaking

If, based on the outcome of that 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 as described in Section 4.0. The sponsor must submit a letter to the Director of the appropriate review Bureau/Centre requesting a change in the agreed-upon confirmatory trials and/or an extension to the timelines along with a rationale for the request.

7.3 Failure to Satisfy Conditions

All authorized products, including those qualifying under the NOC/c policy, are subject to the provisions within the *Food and Drugs Act and Regulations*.

In the event that the outcome of subsequent reviews determine that undertakings have not been satisfied, the responsible Directorate will contact the sponsor to discuss next steps.

For products authorized under the NOC/c policy, 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 policy 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); and

iii) Failure to comply with any authorized or post-market labelling requirements will be subject to compliance measures including invoking a stop-sale where required (C.08.008).

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 the indication authorized under the NOC/c policy or when the sponsor recalls the drug from the market, an 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 of the original NOC.

8.0 APPENDICES

APPENDIX 1: Product Monograph - Sample Cover Page

PRODUCT MONOGRAPH

<Scheduling Symbol> <**BRAND NAME**>

<Proper name>

<Dosage Form(s) and Strength>

<Pharmaceutical standard (if applicable)>

<Therapeutic Classification>

<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.

For further information for <Brand name> please refer to Health Canada's Notice of Compliance with conditions - drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php"

"Brand name> indicated for:
- <>
has been issued marketing authorization without conditions. "

<SponsorName>
<Sponsor Address>

Submission Control Number <control #.> [optional]

Date of Preparation:
<MON, DD, YYYY>
or
Date of Revision:
<MON, DD, YYYY>

APPENDIX 2: Product Monograph General Information Insert

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol "NOC/c". These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

APPENDIX 3: Notice of Market Authorization with Conditions

NOTICE OF MARKET AUTHORIZATION WITH CONDITIONS

A Notice of Compliance with Conditions (NOC/c) is a form of market authorization with conditions granted to a product on the basis of ***promising*** *evidence of clinical effectiveness following review of the submission by Health Canada. Communicating a NOC/c is intended to raise awareness on the details of the drug and the nature of authorization granted.*

Healthcare professionals are encouraged to report to Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) any adverse reactions suspected of being associated with marketed health products, including drugs authorized under the NOC/c policy.

AUTHORIZATION WITH CONDITIONS OF <*DRUG NAME*>

Health Canada has issued a Notice of Compliance with Conditions under the Notice of Compliance with Conditions (NOC/c) policy for <Brand name (Proper name)>, <dosage forms and strength>, for <indication(s)>. Patients should be advised about the conditional market authorization for this indication.

For the complete prescribing information and information available for the patients/caregivers, please consult the <Brand Name> Canadian Product Monograph (CPM). The CPM can be accessed through: <website URL> or by request by contacting <Company Name> at <toll free number>. Contact the company for a copy of any references, attachments or enclosures.

*All Notices of Compliance with conditions (NOC/c) are included in the listing on the Health Canada website (*http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php).

APPENDIX 4: Progress of Ongoing Confirmatory Trials Report - Sample Report

Annual Status Report: Submitted on DATE

Manufacturer/Sponsor:

Product: BRAND NAME (active ingredients), oral, dosage form and strength

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

Letter of Undertaking Date: Year/month/day

Description of Confirmatory Trial:

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

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

Explanation of the Status:
Brief description and action taken

APPENDIX 5: Frequently Asked Questions

PROCEDURE/TIME FRAMES

1. The NOC/c policy is inconsistent with the Management of Drug Submissions Guidance.
The *Management of Drug Submission Guidance* (MDSG) is updated regularly to reflect ongoing changes in drug policy. Subsequent updates to the MDSG shall reflect all effective changes with respect to the *Notice of Compliance with Conditions policy*.

2. Explain why a longer review target (200 days) is needed to review a submission for an NOC/c compared to a Priority Review submission (180 days).
The data to support authorization under the NOC/c policy is often:
a) limited due to a small number of patients eligible for clinical trial participation;
b) based on surrogate marker data predictive of clinical benefit; or
c) larger trials in which final outcomes of morbidity and mortality are lacking.

NOC/c submissions are comparable in size to "standard" submissions and the regulatory decisions rely on a more difficult clinical assessment of the available evidence and a determination of the benefit/risk profile of the product. When compared to a Priority Review submission, additional time is required to consult internally with review staff or outside experts to determine the validity of clinical endpoints as well as determine and discuss the nature of confirmatory trials with the sponsor.

3. Why are NOC/c submissions ineligible for Priority Review status? In order to satisfy the intent of the policy, in providing accelerated access to life-saving therapies, submissions seeking advance NOC/c consideration are assigned a shortened review target to account for the Priority nature of the submission plus additional time requirements outlined in question # 2. NOC/c-eligible submissions, based on evidence including unvalidated surrogate markers or those lacking final outcomes data, are unlikely to meet the evidence requirements of the Priority Review Policy. Review targets for the NOC/c policy however, reflect the Priority status of the submission and following a comprehensive review of the information contained within the submission, the data may support NOC/c authorization.

*Note: A product, accepted for Priority Review status, may still receive authorization with conditions, under the NOC/c policy, at the discretion of the reviewing Bureau/Centre.

4. Why would anyone request NOC/c consideration if Priority Review is quicker? See response to question #3. The nature of the promising evidence provided in the NOC/c submission is unlikely to meet criteria for Priority Review status. The acceptance of promising evidence under the NOC/c policy however, will allow for the filing of an eligible drug submission earlier than normally possible and should the outcome of the review be positive,

provide patients suffering with serious or life-threatening diseases with earlier access to promising new drugs.

5. Please clarify the impact of the NOC/c review queue on the review queues of other submissions. Please clarify if the start of the review of a standard submission with a 300 day target will be delayed by a NOC/c submissions having an earlier review completion target date. Submissions deemed eligible for advance consideration under the NOC/c policy or those granted Priority status, enter Health Canada's review workload on the basis of shortened review targets.

The acceptance of an NOC/c submission into the drug submission workload will not necessarily impact or delay the review of "standard" submissions with a 300 day review target. Submission workload consists of all submission types, differentiated across biological, pharmaceutical and medical device product lines. Specific therapeutic expertise within BGTD and TPD is directed towards the review of corresponding submission types where required. As such, the review of an NOC/c or Priority submission will commence before the review of other pending submissions **of the same therapeutic area**, which have a target completion date after that of the NOC/c or Priority submissions.

6. If the undertakings have not been satisfied for reasons other than a safety concern, the sponsor should be able to file another submission for a different indication without having to address the undertakings in the original submission. Submissions supporting a new indication may be filed with complete safety, efficacy and quality information as per the *Management of Drug Submissions Guidance*. No information may be cross-referenced to unauthorized chemistry and manufacturing or clinical data.

7. What is the purpose of posting the NOC/c-QN? Posting of the NOC/c-QN will allow for enhanced transparency of process, outlining in general terms (i.e. non-proprietary), the nature of the confirmatory trials required of the sponsor, including timeframes, as well as any restrictions outlined in the Letter of Undertaking. It is imperative that information concerning the conditions on authorization be readily available to patient groups, health care providers or interested stakeholder groups.

8. Would it be possible to request Priority Review status or NOC/c consideration for a subsequent submission for an indication independent from the original submission? Yes. Subsequent submissions supporting an indication independent of the original NDS are filed as either NDSs or SNDSs and may qualify under either the NOC/c or Priority Review Policies should the eligibility criteria be met. For further information, refer to the respective policies on Priority Review and NOC/c.

9. If during the course of a regular pre-NDS or SNDS meeting for a given drug, Health Canada was to consider that evidence of effectiveness presented is promising but not complete, could Health Canada advise upfront that the submission may be filed with advance

consideration under the NOC/c policy? It may be possible for Health Canada review staff to provide advice to sponsors as to the potential eligibility of the submission for NOC/c consideration. However, often information presented may not be sufficient or review staff may require additional time to review the information in order to provide a response concerning NOC/c eligibility. In the event that the information provided is sufficient, the decision will be rendered within 10 working days of the finalization of the meeting minutes. No further meetings to satisfy NOC/c policy requirements would be necessary. For further information regarding pre-submission meetings, sponsors are advised to contact the Submission Management Unit of the respective review Directorate/Bureau.

10. During the pre-meeting, could the details and/or issues regarding the confirmatory clinical trials that will be required be already discussed during the meeting? Details and requirements related to confirmatory trials, associated with NOC/c authorization, may only become apparent in the later stages of review. As such, although some advice may be offered, it is in "principle" only and will be subject to the outcome of submission review. Generally it is not possible to provide such details during a pre-submission meeting, in advance of a full submission review.

11. In some instances, a sponsor would like to seek input from Health Canada at an earlier point in the drug development process to discuss the possibility of a NOC/c. In addition to regular pre-NDS or pre-SNDS meetings, sponsors are welcome to provide brief presentations to Health Canada review staff in advance of filing clinical trial applications. Although some discussion surrounding potential eligibility under the NOC/c policy may be carried out (depending on the stage of development), it would be unlikely for details related to confirmatory trials and conditions associated with any potential authorization to be addressed at this time (see response to question #10).

12. Can the sponsor consider the review to be complete at the point of issuance of the NOC/c-QN? The review of the submission package may be considered complete at the time of NOC/c-QN issuance. An additional review of requested material will take place upon receipt of the response to the Qualifying Notice. The decision to authorize the product, under the NOC/c policy, will be dependent on Health Canada's satisfaction with all submission elements, including those received in response to the NOC/c-QN.

13. Are the PSUR-Cs a Canadian specific document? No. PSUR-Cs are PSURs that relate to products authorized under the NOC/c Policy. The "-C" allows the Marketed Health Products Directorate to track PSURs as a submission type and relate them to a NOC/c product.

CLINICAL EVIDENCE/COMMITMENTS

14. Should validated surrogate markers be used in a clinical development program, the NDS or SNDS should be considered for full NOC and not a NOC/c. Unclear as to whether clinical trials generated with surrogate marker data only would then be considered eligible for full authorization. The decision to authorize or reject a product for market authorization is complex and based on numerous factors governed by regulatory requirements. NOC authorization without conditions may be granted on surrogate marker data should the supporting evidence of effectiveness, provided by such validated markers, be considered substantial and should all additional requirements be fulfilled. The basis for NOC/c decision is not the surrogate marker status but rather the body of evidence supporting the efficacy of the product in the drug submission.

15. It appears that it will only be acceptable to address clinical benefit in the same indication for which the NOC/c was issued. We request that Health Canada reconsider this condition in particular for oncology drugs. From the United States experience it has been possible to demonstrate clinical benefit in other populations in different stages of the disease. Generally, an NOC/c is considered for an indication in a disease when the treatment addresses the disease itself or a specific stage of the disease. It is only the confirmatory trials that might capture the nuances of a disease relating to its different stages or different severities. The example for oncology is the most common situation where confirmatory trials in a different stage of the disease or with different severity are considered. These trials will then add to the option of therapeutic regimens for the disease and will take into account these stages and degrees of severity.

We believe that the Guidance Document and the process as described are flexible enough to allow for these variations within a disease entity, based on discussions held with the reviewing organizations.

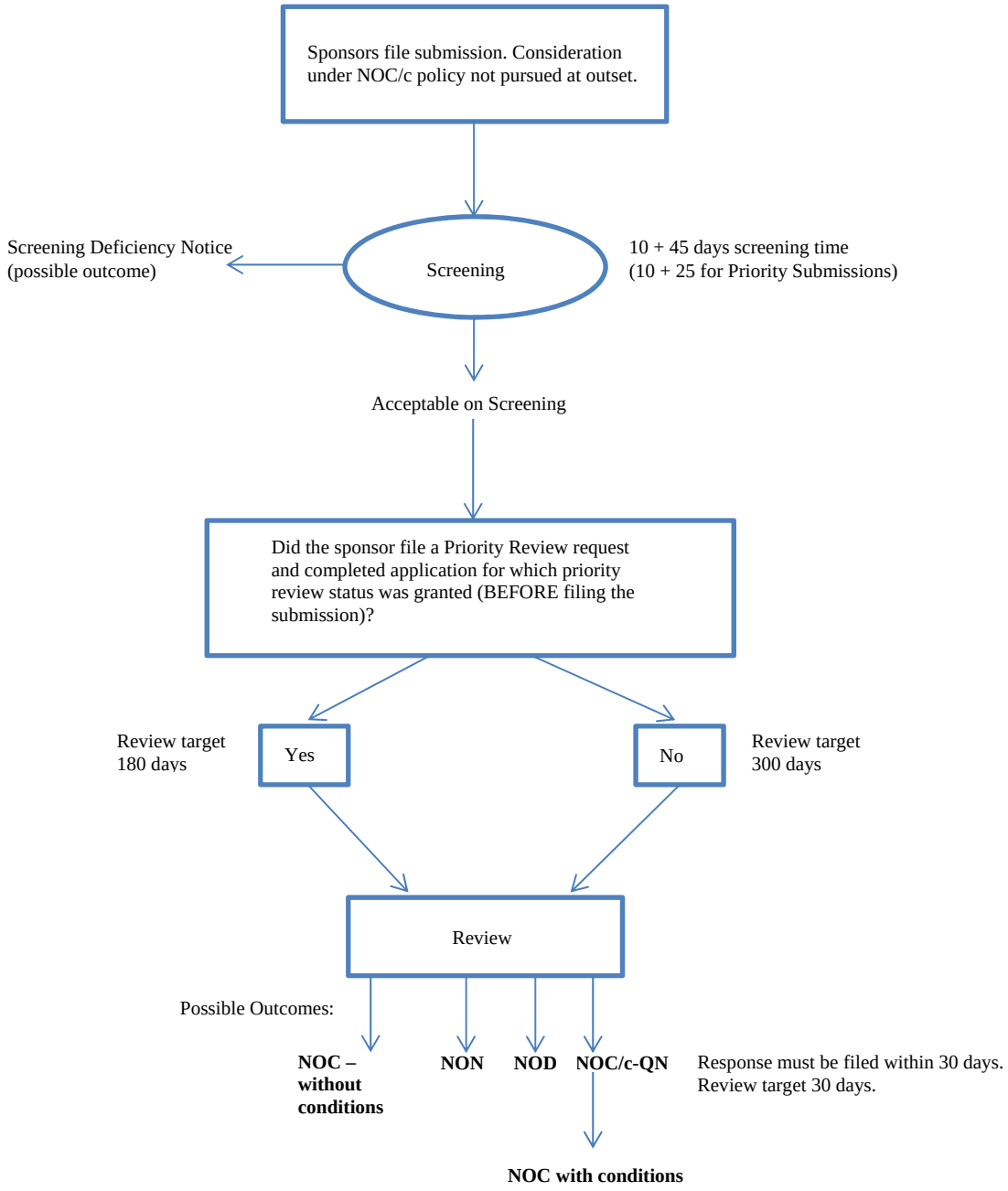
16. The amount of data to review in an NOC/c NDS should be smaller since the data package is not complete. The amount of data in a submission is not related to NOC or NOC/c status. It is impossible to draw direct comparisons of the review times of different submissions, since each presents a different challenge. The data included in an NOC/c submission, is generally equivalent to that of a "standard" NDS. Evidence may be supported by numerous trials with surrogate endpoints or data for which evidence as a whole proves promising. Submissions of this nature often require more than the normal length of time for review as data are often complex and may require additional research and/or discussion with additional evaluators and outside experts to verify the legitimacy of clinical endpoints.

17. Can the data be trending towards statistical significance and be sufficient for NOC/c or does it have to reach a certain level of significance? The data must be statistically significant and clinically relevant to be considered under the NOC/c policy.

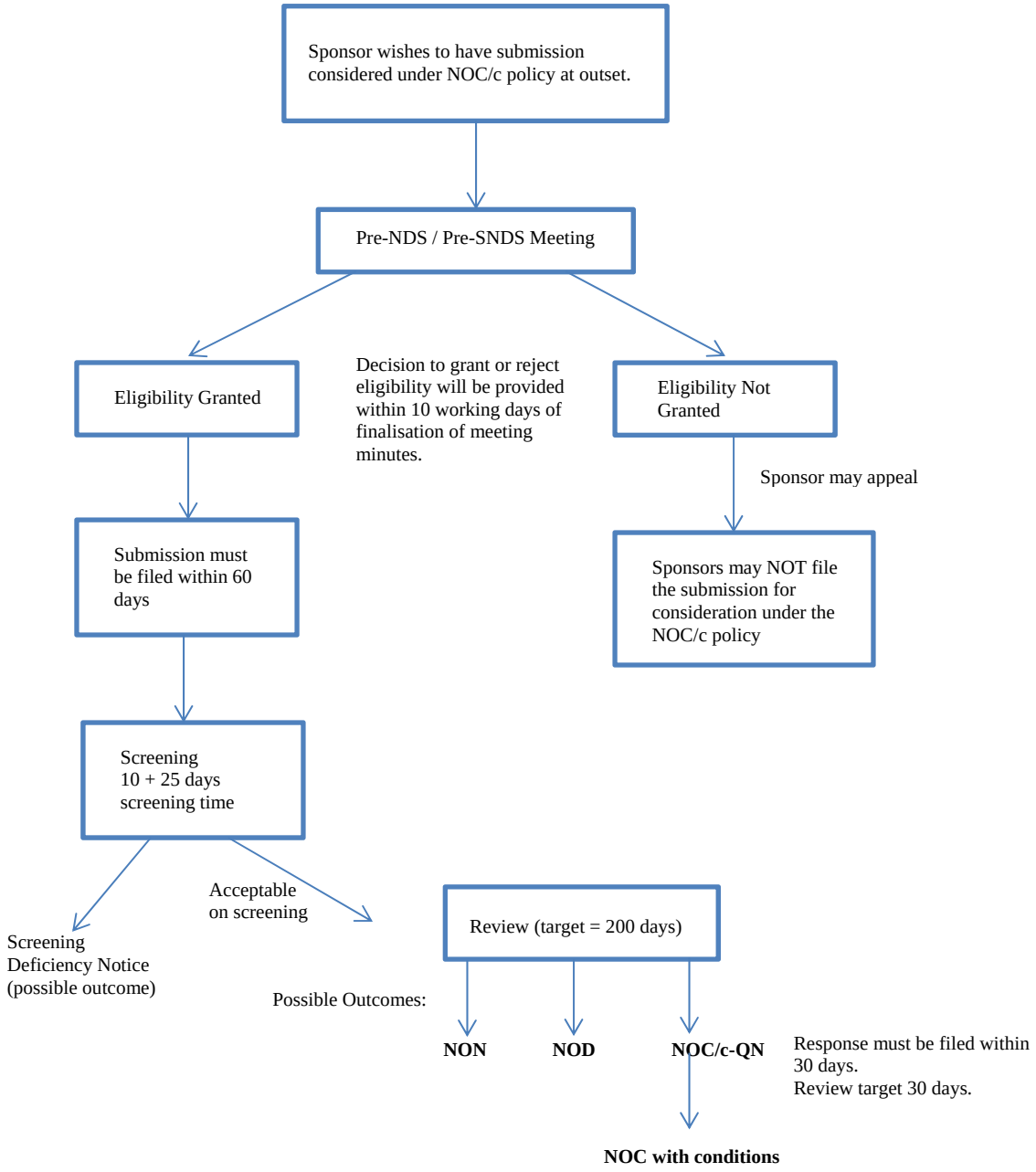
18. Considering a situation where a new indication has been granted an NOC/c for a drug that has been previously been authorized under regular NOC conditions, please confirm that the failure of the confirmatory trials to demonstrate clinical benefit would prompt the withdrawal/recall of the indication authorized under the NOC/c policy ONLY and not the withdrawal of the drug itself from the market. Correct.

19. Will specific restrictions be removed one at a time as data are submitted and reviewed? No. Only once all commitments have been satisfied to the acceptance of Health Canada will the conditions be removed from the NOC.

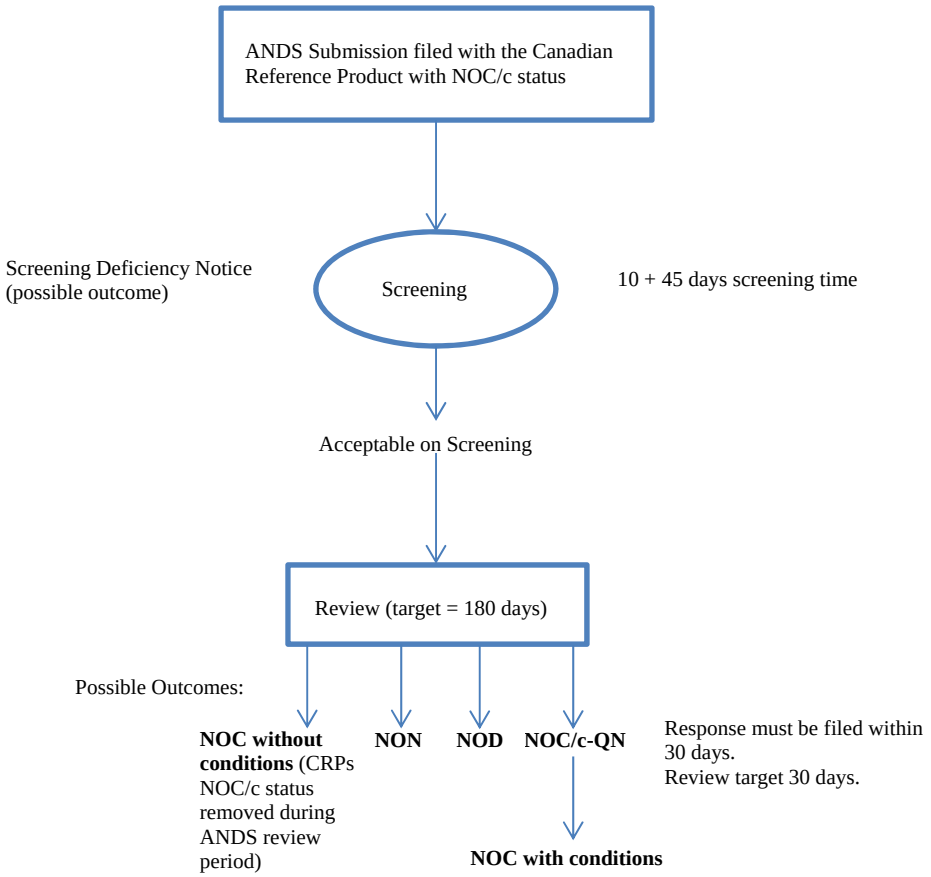
APPENDIX 6a: Notice of Compliance with Conditions (NOC/c) Consideration Upon Completion of an New Drug Submission (NDS) or Supplement to a New Drug Submission (SNDS) Review



APPENDIX 6b: Advance Notice of Compliance with Conditions (NOC/c) Consideration Requested for a New Drug Submission (NDS) or Supplement to a New Drug Submission (SNDS)



APPENDIX 6c: Abbreviated New Drug Submission (ANDS) or Supplement to an Abbreviated New Drug Submission (SANDS) Review Referencing a Canadian Reference Product with Notice of Compliance with Conditions Status



APPENDIX 7: Notices - Revisions to Notice Compliance with Conditions and Guidance Documents dated April 2, 2008 and March 17, 2009

April 2, 2008

Our file number: 08-108989-515

Revision of the Notice of Compliance with Conditions (NOC/c) Policy and Guidance

Health Canada is undertaking the revision of the Notice of Compliance with Conditions (NOC/c) Policy and Guidance. This is to allow for the filing of Abbreviated New Drug Submissions (ANDSs) with respect to a Canadian Reference Product (CRP) that has been issued a Notice of Compliance (NOC) under the NOC/c Policy. Specifically, it is to address an ANDS filing when the CRP sponsor has yet to fulfill the conditions outlined in the Qualifying Notice and Letter of Undertaking.

Health Canada will accept for screening this type of ANDS. Sponsors of ANDSs should be aware that the NOC for the CRP was issued based upon the acceptance by the CRP sponsor of specific conditions summarized in the Qualifying Notice and detailed in the Letter of Undertaking. These conditions typically include post-approval commitments to gather additional information necessary to confirm the effectiveness of the new drug; to more closely monitor its safety; and to provide enhanced communication with health care professionals and patients. Similar, but not necessarily identical, conditions may be necessary prior to the approval of any subsequent-market entry drug and would be requested as per Part C, Section C.08.002.1 (3) (d) of the *Food and Drug Regulations* which states that that the Minister may request "any additional information or material respecting the safety and effectiveness of the new drug".

Submission sponsors are encouraged to contact the Senior Regulatory Project Manager of the Bureau of Pharmaceutical Sciences preferably prior to the filing of an ANDS, to discuss the context under which a clinical evaluation regarding post-marketing conditions will take place. Until revisions to the Policy and Guidance are finalized, post-marketing conditions requested of the ANDS sponsor will be determined on a case-by-case basis.

Draft revisions to the NOC/c Policy and Guidance will be made available for appropriate consultation when completed. Further information on the current Policy and Guidance is available on the Health Canada website at:

Policy: Notice of Compliance with Conditions

Guidance Document: Notice of Compliance with Conditions

Feedback regarding this notice will be taken into consideration for revision of the policy and guidance and should be directed within 30 calendar days to:

Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
Health Canada
1600 Scott Street
Holland Cross, Tower B
2nd Floor, Address Locator 3102C5
Ottawa, Ontario
K1A 0K9

Fax: 613-941-1812
E-mail: Policy_Bureau_Enquiries@hc-sc.gc.ca

March 17, 2009

Our file number: 09-106932-832

On April 2, 2008, Health Canada posted a Notice to inform stakeholders that it was revising the *Notice of Compliance with Conditions (NOC/c) Policy* and *Guidance* to allow for the filing of Abbreviated New Drug Submissions (ANDSs) with respect to a Canadian Reference Product (CRP) that has been issued a Notice of Compliance (NOC) under the NOC/c Policy, and for which the CRP sponsor has yet to fulfill its conditions outlined in the Letter of Undertaking.

Health Canada is notifying stakeholders that it will be inviting manufacturers filing ANDS submissions to provide undertakings - similar, but not necessarily identical, to those provided by the manufacturer who sponsored the CRP - prior to the approval of an ANDS that references a CRP that was issued an NOC pursuant to the NOC/c Policy.

For subsequent-market entry products the minimum undertakings will include: a commitment to closely monitor and provide post-market safety information with respect to the subsequent entry product; and a commitment that the subsequent entry product's labelling and related materials contain adequate information to permit health care professionals and patients to understand the NOC/c nature of the approval. As for the CRP, these conditions will be reflected in a request for a Letter of Undertaking (similar to the CRP's Qualifying Notice) and detailed in the Letter of Undertaking for the subsequent-market entry product.

Confirmatory trials will not be automatically sought from manufacturers who file ANDS submissions that reference a CRP that was issued an NOC pursuant to the NOC/c policy. The need for post-marketing conditions, including confirmatory trials and/ or heightened post-market surveillance, will be determined on a case-by-case basis.

This Notice for ANDSs is effective immediately.

Health Canada is continuing its review of the Policy and Guidance documents. Draft revisions to the NOC/c Policy and Guidance documents will be made available for appropriate consultation when completed.

The target performance standard for this type of submission review has not been set. Until the performance standard is determined this type of submission will not be included in performance to standard calculations.

Submission sponsors are encouraged to contact the Senior Regulatory Project Manager of the Bureau of Pharmaceutical Sciences prior to the filing of this type of an ANDS involving a CRP with NOC/c indications.

Further information on the current Policy and Guidance documents is available on the Health Canada website: Policy: Notice of Compliance with Conditions, and Guidance Document: Notice of Compliance with Conditions.

Feedback regarding this Notice will be taken into consideration for revisions to the policy and guidance documents and should be directed within 30 calendar days to:

Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
Health Canada
1600 Scott Street
Holland Cross, Tower B
2nd Floor, Address Locator 3102C5
Ottawa, Ontario
K1A 0K9

Facsimile: 613-941-1812
E-mail: Policy_Bureau_Enquiries@hc-sc.gc.ca