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# Draft Guidance: Accelerated Review of Human Drug Submissions

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Draft date



Canada

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## Foreword

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

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

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

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

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# 1. Introduction

## 1.1 Purpose/Overview

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

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

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

**Effective Date:** TBD, 2019

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

## 1.2 Scope and Application

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

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

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

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

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

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

56

### 57 1.3 Policy objectives

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

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

69

### 70 1.4 Background

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

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

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

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

95  
96 Although cost-effectiveness assessment and financial considerations lie outside of Health  
97 Canada’s regulatory mandate, stakeholders stressed that reimbursement through public  
98 drug programs is vital to making a drug affordable and accessible. Respondents also  
99 expressed the need for Health Canada to maintain a robust evidentiary bar for drug  
100 approvals and to continue to support transparency and alignment in decision-making in  
101 drug submission review, health technology assessment and funding recommendations.

## 102 2. Guidance for Implementation

### 103 2.1 Criteria for Eligibility for Accelerated Review

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

107 To be considered for Accelerated Review status, a request package must first meet eligibility  
108 criteria outlined in Section 1.2. For clarity, this means that the drug product must first be  
109 determined to be intended for the treatment of a serious condition (as described in section  
110 2.1.1) **AND** must meet at least one of the eligibility criteria (as described in sections 2.1.2,  
111 2.1.3, 2.1.4, and 2.1.5).

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

115



116 2.1.1 Definition of Serious, Life-Threatening or Severely Debilitating Disease

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

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

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

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

136

137 2.1.2 Product Eligibility Criterion #1: Effective Treatment, Prevention or  
138 Diagnosis of a Disease for Which No Drug Is Marketed in Canada

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

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

147

148 2.1.3 Product Eligibility Criterion #2: Effective Treatment, Prevention or  
149 Diagnosis of a Disease for Which an Existing Drug Has Been on the Canadian  
150 Market for 12 Months or Less

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

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

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

162

#### 163 2.1.4 Product Eligibility Criterion #3: Significant Increase in Efficacy and/or 164 Significant Decrease in Risk

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

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

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

185

#### 186 2.1.5 Product Eligibility Criterion #4: Evidence That the Drug Addresses a Health 187 Care System Need by Delivering High Clinical Benefit for Public Health or 188 Significantly High Clinical Benefit for Patients

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

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

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

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

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

211

## 212 2.2 Substantial Evidence – Eligibility for Notice of Compliance (NOC)

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

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

223

## 224 2.3 Promising Evidence - Eligibility for Conditional Approval (NOC/c)

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

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

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

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

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

245

## 246 2.4 Accelerated Review Process

### 247 2.4.1 Pre-Submission Meeting

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

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

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

260

### 261 2.4.2 Submission of Clinical Assessment Package and Determination of Product 262 Eligibility for Accelerated Review

263

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

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

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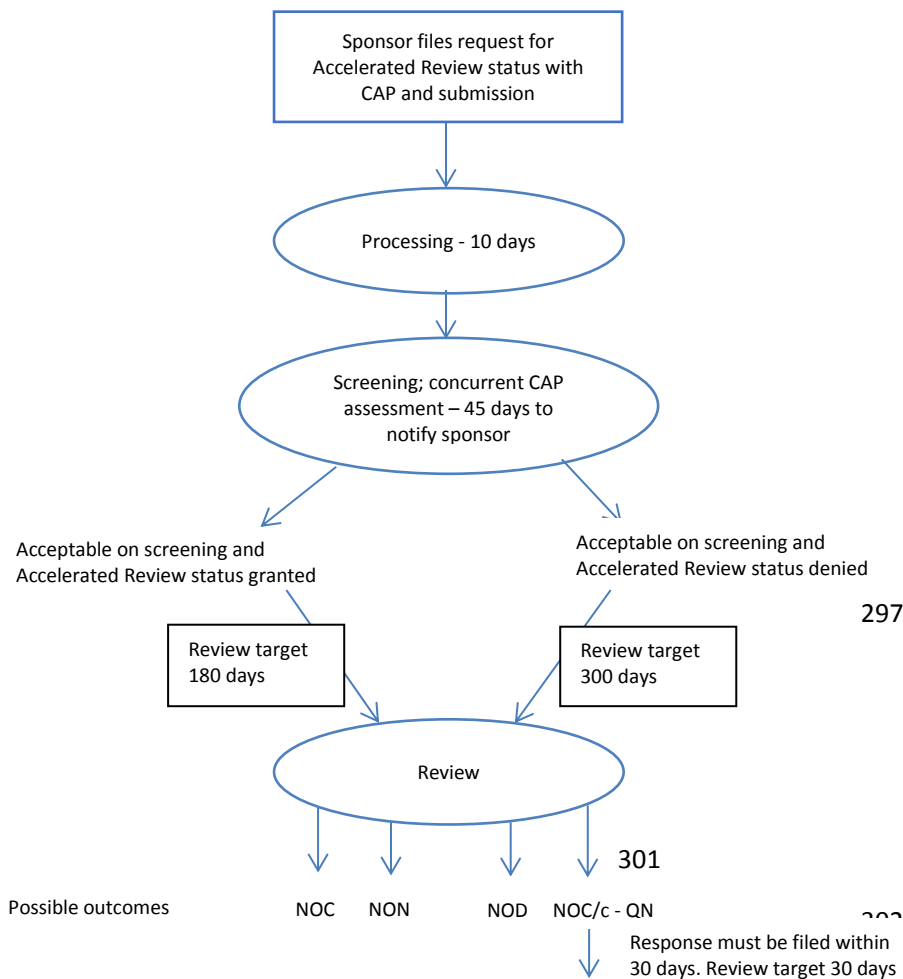
### 273 Option A - Perform Concurrent Screening and CAP Assessment

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

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

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

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

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

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

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

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

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

333

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

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

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

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

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

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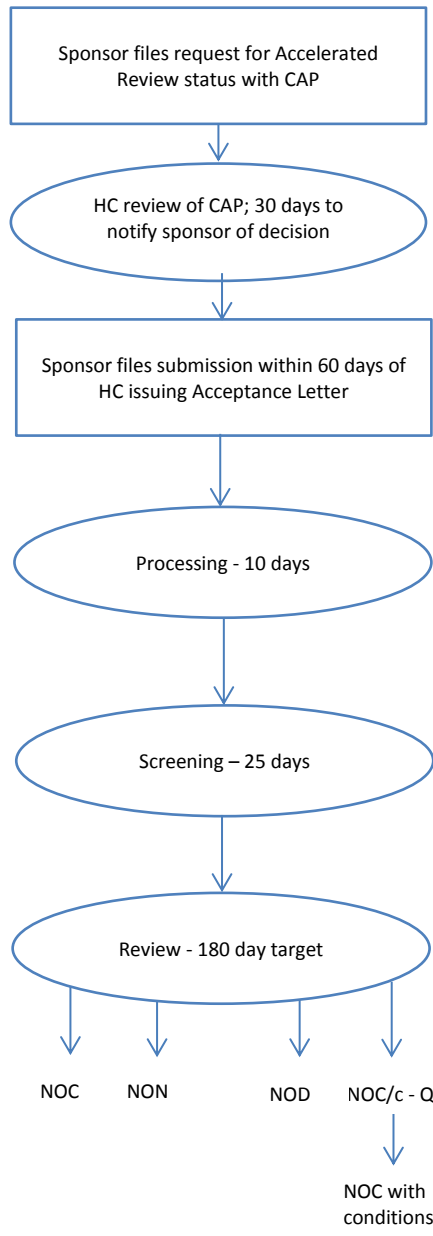
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Possible outcomes

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Sponsor files response to QN within 30 days. Review target 30 days

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

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

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



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

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

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

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

419

### 420 2.4.3 Rejection/Reconsideration

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

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

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

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

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

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

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

443

444 *Option A - Perform Concurrent Screening and CAP Assessment:*

445 The submission review will commence while the Reconsideration of a denial is underway. In  
446 the event that Accelerated Review status is granted as a result of a Request for  
447 Reconsideration, the review target will be adjusted accordingly from the date upon which  
448 screening acceptance was issued.

449

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

451 A submission may be filed with the appropriate review Directorate and undergo screening  
452 while the Reconsideration of a denial is underway. In the event that Accelerated Review  
453 status is granted as a result of a Request for Reconsideration, the review target will be  
454 adjusted accordingly from the date upon which screening acceptance was issued.

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

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

467

#### 468 2.4.4 Submission and Review

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

##### 472 *Option A - Perform Concurrent Screening and CAP Assessment:*

473 The submission will be screened as per usual practice. Sponsors will be requested to remove  
474 any information not pertaining to the indication(s) for which Accelerated Review was  
475 granted within 15 days of the submission being accepted in to review.

##### 476 *Option B – Use Current Priority Review Steps and Timelines for All Submissions:*

477 The submission will be screened as per usual practice. A Screening Deficiency Notice (SDN)  
478 may be issued to request the removal of any information not pertaining to the indication(s)  
479 for which Accelerated Review was granted.

480

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

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

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

496

#### 497 2.4.5 Discontinuation

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

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

506

## 507 2.5 Conditional Authorization (Notice of Compliance with Conditions)

### 508 2.5.1 Notice of Compliance with Conditions - Qualifying Notice (NOC/c - QN)

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

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

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

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

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

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

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

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

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

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

564

## 565 2.5.2 Agreement of Conditions and Issuance of the NOC/c

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

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

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

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

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

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

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

591

### 592 2.5.3 Health Product InfoWatch Communication

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

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

601

## 602 2.6 Post-Market Commitments Under Conditional Authorization

### 603 2.6.1 Confirmatory Trials

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

611

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

615

### 616 2.6.2 Providing Annual Progress Reports of Confirmatory Trials and Other 617 Ongoing Trials

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



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

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

626

### 627 2.6.3 Advertising and Labelling Material

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

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

640  
641 The display portion of all advertising material, as well as all labelling material, for products  
642 authorized with conditions must contain boxed text with prominent disclosure of the nature  
643 of the market authorization granted and the need to conduct trials to confirm its clinical  
644 benefit.

645 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."*

646

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

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

658

#### 659 2.6.4 Subsequent Submissions

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

- 664 i. Supplemental changes that rely on the safety and efficacy data of the original  
665 submission, for which conditional authorization was granted will be processed as  
666 SNDSs and if authorized, will receive a NOC/c. Examples include, but are not limited  
667 to, submissions for a new strength or formulation;
- 668 ii. Administrative changes in product and/or manufacturer name which therefore rely  
669 on the safety and efficacy data of the original submission, will receive a NOC/c if  
670 authorized; and
- 671 iii. Subsequent submissions for a new indication must demonstrate efficacy, safety and  
672 clinical pharmacology independent of the original submission. As such, upon  
673 outcome of a review of the data provided, such submissions may qualify for a NOC,  
674 with or without conditions. Submissions should be filed as Supplement to a New  
675 Drug Submissions (SNDSs) cross-referencing the chemistry and manufacturing, pre-  
676 clinical and clinical pharmacology (if appropriate) data from the original submission.

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

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

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

685

#### 686 2.6.5 Providing the Results of the Confirmatory Trials

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



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

696  
697 Information contained within a SNDS-c must only address the original indication or  
698 condition of use for which the NOC/c was issued. Additional information, as well as  
699 revisions or expansions to the indication(s), are not acceptable and must be submitted  
700 within a separate SNDS, or a separate NDS with cross-reference to the chemistry and  
701 manufacturing information contained within the original application.

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

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

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

713

## 714 2.6.6 Overseeing Commitments

715 Terminating Conditions or Restrictions

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

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

723 ANDS / SANDS where confirmatory trials were not requested:

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

730 Negotiating a New Letter of Undertaking

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

#### 739 Failure to Satisfy Conditions

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

- 746 i. Failure of a sponsor to undertake or complete a confirmatory trial may provide  
747 Health Canada with reason to suspect the product is unsafe or ineffective at that  
748 time. Failure to provide results of a confirmatory trial by a specified date may also be  
749 interpreted as suggesting the possibility of insufficient evidence, at the time, for  
750 establishing the effectiveness of the drug for the purposes recommended. In either  
751 case, consideration will then be given to the Director to invoke section C.01.013 of  
752 the *Food and Drug Regulations*;
- 753 ii. Failure of confirmatory trials to demonstrate clinical benefit and/or if such trials  
754 raise safety concerns about the drug, may result in the regulator exercising section  
755 C.08.006(2)

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

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

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

768

769 2.7 Determining Conditional Eligibility for an Abbreviated New Drug Submission  
770 (ANDS) or Supplement to an Abbreviated New Drug Submission (SANDS) Where  
771 the Innovator Has Conditional Authorization

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

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

- 780 a. contain all the information and material to comply with the requirements of sections  
781 C.08.002.1 and C.08.005.1, pursuant to section C.08.004 of the *Food and Drug*  
782 *Regulations*; and
- 783 b. pursuant to section C.08.002.1(3)(d) of the *Food and Drug Regulations*, the sponsor for  
784 the ANDS or SANDS will be requested to provide undertakings similar, but not  
785 necessarily identical, to those required for the sponsor of the CRP.

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

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

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

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

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

818

## 819 2.8 Post-Market Safety Monitoring for All Products

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

825  
826  
827  
828  
829  
830

## Appendices

### Appendix 1 – Template - Clinical Assessment Package

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

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

<p><i>Refer to Sections 2.2 and 2.3 this guidance document for further information</i></p>
<p><b>Product Eligibility: Treatment of a Serious, Life-threatening, or Severely Debilitating Disease or Condition</b></p> <p><i>Provide a brief description of the disease or condition and the clinical context within which the product will be used to support the request. Indicate briefly how the product will add to the clinical management of the disease or condition.</i></p>
<p><b>Product Eligibility Criterion #1: Effective treatment, prevention or diagnosis of a disease for which no drug is marketed in Canada</b></p> <p><i>Describe how the drug satisfies an unmet medical need for treatment, prevention or diagnosis of the disease state as outlined in Section 2.1.2. It must be clearly indicated that no other drug which provides the same therapeutic profile is available on the Canadian market and, where applicable, that there are no available non-drug therapies.</i></p>
<p><b>Product Eligibility Criterion #2: Effective treatment, prevention or diagnosis of a disease for which an existing drug has been on the Canadian market for 12 months or less</b></p> <p><i>Discuss the marketing status of any existing drugs on the Canadian market with the same indication. Any drug product seeking the accelerated review must exhibit the same or better safety and efficacy profile as others on the market.</i></p>
<p><b>Product Eligibility Criterion #3: Significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada</b></p> <p><i>Provide a rationale for the overall improvement in benefit/risk profile over therapies currently available on the Canadian market.</i></p>
<p><b>Product Eligibility Criterion #4: Evidence that the drug addresses a health care system need by delivering high clinical benefit for public health or significantly high clinical benefit for patients</b></p> <p><i>Provide information relevant to the Canadian context, with appropriate references or data, including patient and clinician input. Clinical and statistical significance should be demonstrated to substantiate significant high clinical benefit for patients.</i></p>
<p><b>Clinical Evidence:</b></p> <p><i>Include the following:</i></p> <ol style="list-style-type: none"> <li><i>1. Concise information about the studies to be submitted including design, patient population, number of patients withdrawn due to safety concerns or lack of efficacy, etc. This information may be presented in point form or in a tabular format;</i></li> <li><i>2. Properly tabulated results demonstrating statistically significant and clinically relevant data in support of the claim, including brief discussion and comments on the results</i></li> <li><i>3. The status of ongoing studies. Should they be interim results (e.g. oncology products based on surrogate markers), provide anticipated completion dates.</i></li> </ol>

*The status of evidence (substantial vs promising) supporting the proposed indication to be included in the submission should be clearly discussed. Does the sponsor believe a Notice of Compliance with Conditions may be appropriate?*

**References:**

*Up to twelve key references supporting the data/indication as cross-referenced in the Clinical Assessment Package should be provided. Any remaining references must be available on request within one business day.*

**Additional Information (for information purposes only):**

*Do you intend to, and are you capable of, marketing the above product within 30-60 calendar days of authorization?*

*Will this submission also be made through the aligned review process with CADTH/INESSS?*

831

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

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

**Sponsor:**

**Contact Information:**

**Date:**

**Listing of Confirmatory Trials**

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

*"As per the Notice of Compliance with Conditions (NOC/c), we hereby agree to accept a NOC for <product name>, indicated for use in/as <...>. We also agree, as the condition for authorization of <product name> to submit to Health Canada, a Supplement to a New Drug Submission - Confirmatory (SNDS-C) which will include:"*

*Sponsors must provide an outline of confirmatory trials intended to verify the drug's clinical benefit including an indication of timeframes. Details pertaining to the above will be agreed upon in discussions between Health Canada and the sponsors. The sponsor must undertake to carry out any such trials in accordance with established scientific standards. The trials must be well designed and initiated in a timely fashion. Sponsors must also agree to submit an annual progress report.*

*Requirements for confirmatory trials may also apply to an ANDS or SANDS where the CRP is authorized with conditions.*



**Post-market Surveillance Commitments**

*A paragraph must be provided wherein the sponsor shall include the provision to submit to Health Canada in writing a summary of significant change(s) or no change to the risk/benefit profile of the drug on an annual basis, until such time as the conditions have been fulfilled and removed from the NOC by Health Canada. In addition, the paragraph should include commitments regarding any enhanced post-market surveillance, as determined on a case-by-case basis following discussions between Health Canada and the sponsor.*

**Advertising, Distribution and Labelling Requirements**

*A paragraph outlining agreed-upon advertising, labelling or distribution requirements imposed on the product must be included. All sponsors must clearly reflect and highlight the conditions under which the drug product is authorized in the Product Monograph, the Consumer Information Section/Patient Medication Information Section and/or the labelling for that product.*

**Other Ongoing Clinical Trials**

*A complete listing of ongoing additional clinical trials related to the product should be provided in brief as an appendix to the Letter of Undertaking. All ongoing trials, apart from agreed-upon confirmatory trials, are to be filed to the appropriate review bureau/centre and classified in accordance with the Food and Drug Regulations and the Post Notice of Compliance (NOC) Changes Guidance documents.*

*Ongoing clinical trials are not necessarily linked to the conditions of the NOC/c submission. In all cases, safety aspects of ongoing trials cannot be excluded from the assessment of the submission.*

**Regulatory Status of the Drug Worldwide:**

*Indicate whether product is authorized in other jurisdictions, including date of authorizations and whether any conditional authorizations have been granted. Include details of authorized indications.*

*Indicate whether product is currently under review in other jurisdictions.*

836

## 837 Appendix 3- Template - Progress of Ongoing Confirmatory 838 Trials Report

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



<p><b>Letter of Undertaking Date:</b></p>
<p><b>Description of Confirmatory Trial:</b></p> <p><b>Trial Schedule:</b>  <i>Provide the following dates: Protocol approval date; Trial enrollment start date and conclusion date; Last patient evaluation date; Health Canada submission date.</i></p> <p><b>Current Status:</b>  <i>Indicate the current status of the confirmatory trial(s) using to the terminology listed below; explain status changes and subsequent action taken, as applicable.</i></p> <ul style="list-style-type: none"> <li>• <i>Pending (the confirmatory trial has not been initiated by the sponsor)</i></li> <li>• <i>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)</i></li> <li>• <i>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)</i></li> <li>• <i>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.</i></li> <li>• <i>Submitted (the sponsor has submitted a final trial report to Health Canada, and the submission is currently in review)</i></li> <li>• <i>Fulfilled (Health Canada has conducted the review of the final trial report filed as a SNDS-C and has issued a Notice of Compliance indicating the sponsor has met the commitment)</i></li> </ul>

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840 **Appendix 4 - References**

841

842 1. Government of Canada, Food and Drugs Act, R.S.C., 1985, c. F-27, Act current to 2018-  
843 12-12 and last amended on 2018-05-23

844 2. Government of Canada, Food and Drug Regulations

845 3. Health Canada, Access to Drugs in Exceptional Circumstances

846 4. Health Canada, Pathogens of Interest List

847 5. Health Canada, Guidance for Industry: Management of Drug Submissions

848 6. Health Canada, Guidance for Industry Reconsideration of Final Decisions Issued for  
849 Human Drug Submissions

850 7. Health Canada, Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Guidance  
851 Document, 2018

852 8. Health Canada, Guidance Document Product Monograph, 2016

- 853 9. Health Canada, Product Monograph Template: Notice of Compliance with Conditions,  
854 2016
- 855 10. Health Canada, Guidance Document - Submission of Risk Management Plans and  
856 Follow-up Commitments, 2015
- 857 11. Health Canada, List of Canadian Advertising Preclearance Agencies
- 858 12. Health Canada, Notice to industry: Aligned reviews between Health Canada and health  
859 technology assessment organizations
- 860 13. Health Canada, Guidance Document: Preparation of Drug Regulatory Activities in eCTD  
861 Format
- 862 14. Government of Canada, Notice: Vanessa's Law
- 863 15. Reporting Adverse Reactions to Marketed Health Products - Guidance Document for  
864 Industry, 2018

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