Health Canada Santé Canada

Draft Guidance Document: Switching a medicinal ingredient from prescription to non-prescription status

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Canada

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

Également disponible en français sous le titre :
Ébauche de la ligne directrice: Modification d'un ingrédient médicinal pour qu'il passe de « sur ordonnance » à « sans ordonnance »

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Document change log

Date	Change	Location (Section, paragraph)	Nature of and/or Reason for Change
April 21, 2022	The document was revised and re-organized.	throughout	The guidance document "Data requirements for switching medicinal ingredients from prescription to non-prescription status" effective May 7, 2014, was revised to • reflect changes to the process for switches from prescription drug to natural health product that will ensure regulatory support; • clarify evidence requirements relative to the Prescription Drug List principles and factors; and • provide guidance to industry on completing a new template that is being requested as part of submissions for switches.

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

Companies can file submissions/applications with Health Canada to request a "switch" of a medicinal ingredient from prescription to non-prescription status for certain conditions of use. Following a successful switch process, the proposed product has non-prescription status. That is, Health Canada authorizes the proposed product as either a Natural Health Product (NHP) or a Non-Prescription Drug (NPD). These kind of switches are referred to as an "Rx to NHP switch" and "Rx to NPD switch", respectively.

2. Purpose

This document includes guidance for companies (applicants) who wish to put forward submissions/applications to request a switch of an ingredient from prescription to non-prescription status. **In this document, the term "applicant(s)" refers to an applicant or a sponsor; and this applicant is the company who is initiating the request for the switch.** A glossary of all key terms is provided in Appendix A.

This document provides applicants with the following information:

- advice on determining whether the proposed non-prescription status product would be an NHP or NPD
- an overview of processes for Rx to NHP and Rx to NPD switches
- details on each step of the process
- direction on evidence to be included in submissions/applications
- guidance on related topics such as
    - applicable requirements in terms of Good Manufacturing Practices (GMP) as well as Site Licences (SLs) and Drug Establishment Licences (DELs) for those carrying out the manufacturing and other activities related to the proposed product; and
    - patent and data protection

3. Scope and application

This guidance document applies to submissions/applications filed with Health Canada requesting the switch of a medicinal ingredient for human use from prescription to non-prescription status (NHP or NPD).

This guidance document does **not** apply to the following:

- switch submissions for biologic or radiopharmaceutical products
- switch submissions for veterinary drugs
- requests for exceptions to the Prescription Drug List (PDL)[1] (e.g. naloxone and the flu vaccine)

For information and guidance regarding veterinary drug switch submissions, contact the Veterinary Drugs Directorate.

4. Background

In this section, Health Canada provides information on the way the federal prescription status is determined and on requests to change the prescription status of a medicinal ingredient. Additionally, the role of the provinces and territories in granting prescription status is discussed.

4.1 Regulatory framework

Prescription drugs, that is, drugs with federal prescription status, are regulated under the *Food and Drug Regulations* (FDR). They are not subject to the *Natural Health Products Regulations* (NHPR) as they are excluded by virtue of Section 2(2) of the NHPR[2].

Products with non-prescription status are regulated under the NHPR if the products meet the definition of an NHP in the NHPR and otherwise, are regulated under the FDR as NPDs.

4.2 Prescription status

Products with federal prescription status have their medicinal ingredient(s) listed in the PDL (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html). The PDL is a web-based administrative list established by the Minister under the authority of the *Food and Drugs Act.* Products with a medicinal ingredient on the PDL are only obtained by the public through a prescription.

Note the above differs for ingredients that are controlled substances under the *Controlled Drugs and Substances Act* (i.e., when they are listed in the schedules to the Act and its regulations). When these drugs are restricted to prescription-only status under the *Controlled Drugs and Substances Act,* the ingredients are not listed on the PDL.

Health Canada determines if a medicinal ingredient under specified conditions of use requires the oversight of a practitioner for its safe and effective use. To make this determination, Health Canada relies on established overarching principles and associated factors.

The overarching principles governing prescription status are stated in section C.01.040.3 of the FDR and are further described, along with the factors, in the guidance document entitled "Determining Prescription Status for Human and Veterinary Drugs" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/guidance-document.html).

When one or more of the PDL principles or associated factors applies to a medicinal ingredient under the specified conditions of use, Health Canada generally considers the medicinal ingredient to require practitioner involvement. When practitioner involvement is necessary, Health Canada gives the medicinal ingredient prescription status and adds it to the federal Prescription Drug List (with the exception described above for controlled substances).

4.3 Removal of medicinal ingredients from the PDL

Companies may request the removal of a medicinal ingredient from the PDL in different contexts and the following are two examples:

- Over time, with extended use of the company's marketed prescription drug, additional information becomes known about the drug product. The company may then file a switch submission to Health Canada to make the case that this additional information supports the safe and effective use of the product without practitioner oversight. Most switches occur in this context.

- The company wishes to propose a new NHP or NPD product for the Canadian market, however, the medicinal ingredient in the proposed product is on the PDL. Additionally, the company does not have an authorized prescription drug related to the proposed product. The company has data supporting the use of the proposed product without practitioner oversight and files a switch submission to request the removal of a medicinal ingredient in order to market the proposed product as an NHP or an NPD.

The majority of switches removing a medicinal ingredient from the PDL occur as a result of applicant-initiated switch submissions to Health Canada. In exceptional circumstances, Health Canada may pursue a switch based on an assessment of available evidence to support the use of a medicinal ingredient in an NHP or an NPD. In such cases, an assessment of the application of the PDL principles and factors remains integral to the decision-making process.

Note that in Canada, a successful switch process, which includes the removal of a medicinal ingredient (or removal of a medicinal ingredient for specific conditions of use) from the PDL, may result in other companies' similar products no longer having prescription status. (More information in section 19.7.)

4.4 Requests for switches

For Rx to NHP switches:

- The applicant files the request in the form of a New Drug Submission (NDS) or a Supplement to a New Drug Submission (SNDS) and, if that submission is successful, the applicant then files a Product Licence Application (PLA). The submissions begin under the FDR in light of section 2(2) of the NHPR.

For Rx to NPD switches:

- The applicant files the request in the form of an NDS or SNDS.

Section 9 of this guidance document outlines when an NDS vs. SNDS is required. Note that, an applicant who wishes to switch their existing, authorized, "Division 1" prescription drug to non-prescription status, must apply under Division 8 (NDS). (The change to 'sale in the non-prescription setting' is considered to be a change in the conditions of use as a drug, thereby meeting the definition of a "New Drug".)

4.5 Provincial and territorial decisions

In addition to federal decisions about a medicinal ingredient's prescription status, provinces and territories can further regulate the conditions and place of sale of products. For example, products with medicinal ingredients that have non-prescription status federally may be required by provincial or territorial law to be sold behind-the-counter in pharmacies or by prescription. Although provinces and territories can further restrict the sale of products, they cannot lessen the imposed federal restrictions. Therefore, products that require a prescription at the federal level will also require a prescription at the provincial and territorial level.

In summary, medicinal ingredients are given prescription status when practitioner involvement is deemed the best method to protect the health and safety of Canadians. If it can be demonstrated that practitioner oversight is not necessary, then the medicinal ingredient, usually under specified conditions of use, can be removed from the PDL allowing for the possibility of its sale in an NHP or NPD.

5. Policy statements

The following policies and regulatory requirements relate to prescription and non-prescription status:

- Health Canada typically considers a medicinal ingredient, under specified conditions of use, to warrant prescription status when practitioner involvement is appropriate. This is determined based on the applicability of one, or more, of the PDL principles or associated factors.

- Health Canada generally considers requests to change the prescription status of a medicinal ingredient on the PDL through the company-initiated switch process described in this document. As products containing medicinal ingredients listed on the PDL are regulated under the FDR, requests for switches pertaining to these ingredients also fall under the FDR. Therefore, it is under the FDR that Health Canada processes requests for Rx to NPD switches and initiates the process for requests for Rx to NHP switches.

- The PDL is an ingredient-based list. In contrast, Health Canada’s assessment of a switch submission to determine whether the PDL should be amended is a product-based decision as it is very difficult to assess all the PDL principles and factors without knowledge of a product’s conditions of use.

- When a Health Canada assessment concludes that an applicant has demonstrated that none of the PDL principles and factors apply to a product and the proposed product has a positive benefit-risk profile as an NHP or NPD, Health Canada initiates the process to amend the PDL.

6. Classification of a product resulting from a successful switch

The applicant needs to determine whether their proposed product would be classified as an NHP or NPD, if the switch were successful. This determination will assist the applicant in identifying which process, the Rx to NHP switch process or the Rx to NPD switch process, applies to their situation.

The applicant should verify whether, following a successful switch, the proposed product would meet the definition of an NHP as set out in the NHPR. If so, a successful switch results in the product being classified as an NHP. Otherwise, it is classified as an NPD under the FDR.

When considering whether the proposed product's ingredients are acceptable in an NHP, the applicant should consult the definition of "natural health product" in the NHPR, Schedule 1 and 2 of the NHPR as well as the Natural Health Products Ingredients Database (NHPID) (http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do).

7. Understanding the overall switch processes

This section provides an overview of the switch processes for Rx to NPD and Rx to NHP switches and is followed by sections 8 to 19 that provide additional guidance on the steps of the process.

7.1 Process 1: A successful Rx to NPD switch

The following is the main process for an Rx to NPD switch that leads to issuance or update of a product authorization:

1) The applicant assembles the pre-submission meeting data package for Health Canada and requests a pre-submission meeting. (See section 8 for further details.)

2) The applicant meets with Health Canada for a pre-submission meeting to present and discuss the data package for the proposed switch. This meeting may lead the applicant to conduct further studies.

3) The applicant assembles the final version of the NDS or SNDS including the necessary data on safety, efficacy and quality; product labelling; and the "PDL Principles and Factors Assessment". (Section 9)

4) The applicant files the NDS or SNDS with Health Canada in the appropriate format and pays the applicable fees. (Sections 10 and 11)

5) Health Canada screens the submission for completeness. If there are no deficiencies, the submission proceeds into review.

6) Health Canada assesses the submission including the information submitted in the PDL Principles and Factors Assessment. If Health Canada's assessment is positive, the process continues. (Section 12)

7) Health Canada posts a public “Notice of Consultation” on the canada.ca Website outlining its proposal to remove the medicinal ingredient, or remove the medicinal ingredient for certain conditions of use, from the PDL and puts the NDS or SNDS on switch hold. (Section 13)

8) Health Canada reviews the comments provided by the public and other stakeholders during the PDL consultation. (Section 13)

9) After analysis of the comments, if Health Canada decides to proceed, Health Canada posts a “Notice of Intent to Amend” which outlines when the amendment to the PDL will occur. (Section 14)

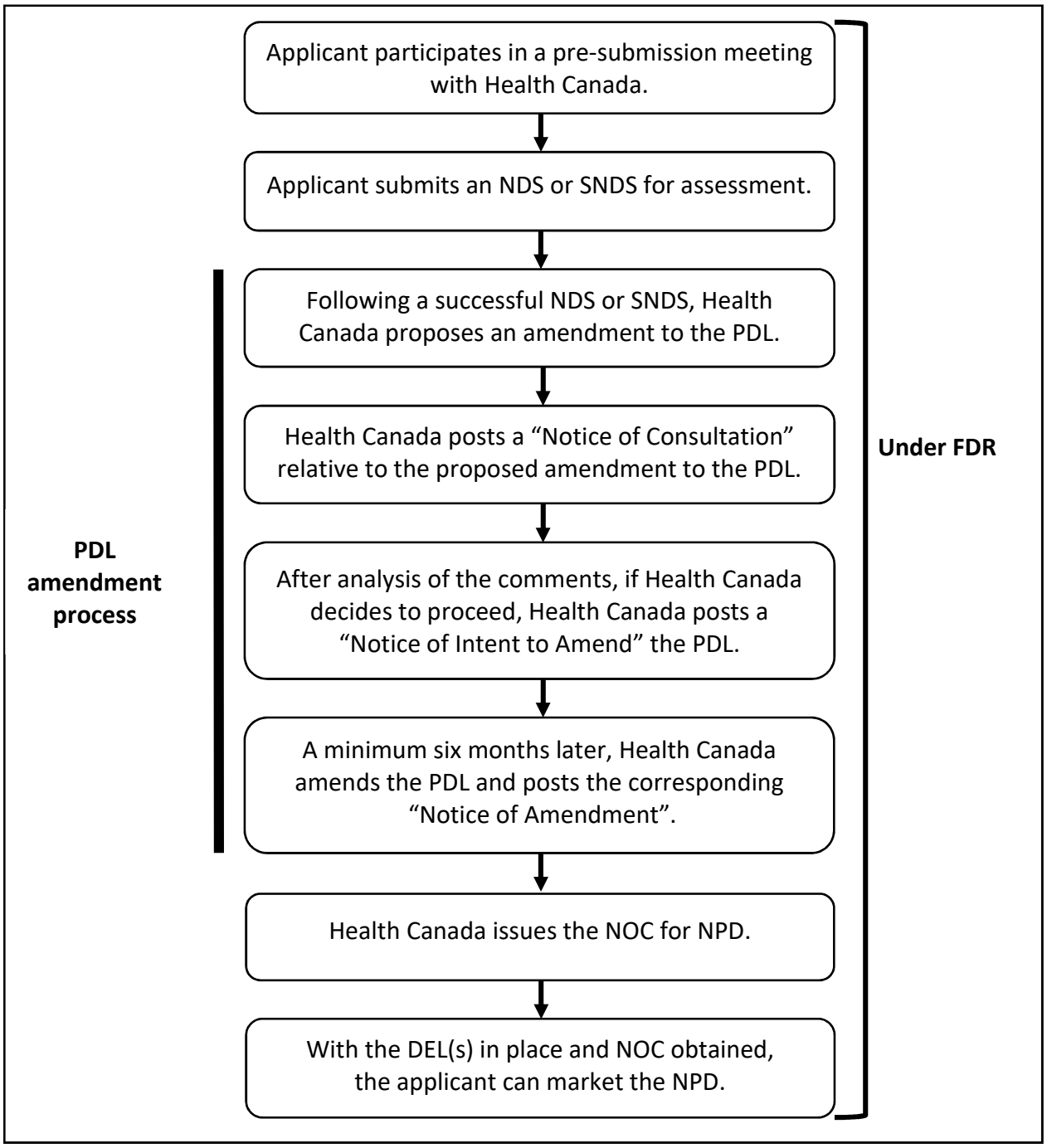
10) Health Canada issues the Drug Identification Number (DIN) for the proposed product if required. (Section 15)

11) Health Canada amends the PDL and posts a “Notice of Amendment” to that effect. (Section 18)

12) Health Canada issues a Notice of Compliance (NOC) for the NPD. (Section 18.1)

13) If in addition to the NOC, the appropriate DEL(s) have been issued to those conducting activities related to the product (e.g. fabricate, import), the product can be sold in Canada in accordance with the FDR. (Section 19.4.1)

191 **Flowchart 1: A successful Rx to NPD switch**



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7.2 Process 2: A successful Rx to NHP switch

The following is the main process for an Rx to NHP switch that leads to the issuance of a product authorization. Note that the first nine steps of this process are the same as those for an Rx to NPD switch.

1) The applicant assembles the pre-submission meeting data package for Health Canada and requests a pre-submission meeting. (See section 8 further details.)

2) The applicant meets with Health Canada for a pre-submission meeting to present and discuss the data package for the proposed switch. This meeting may lead the applicant to conduct further studies.

3) The applicant assembles the final version of the NDS or SNDS including the necessary data on safety, efficacy and quality; product labelling; and the "PDL Principles and Factors Assessment". (Section 9)

4) The applicant files the NDS or SNDS with Health Canada in the appropriate format and pays the applicable fees. (Section 10 and 11)

5) Health Canada screens the submission for completeness. If there are no deficiencies, the submission proceeds into review.

6) Health Canada assesses the submission including the information submitted in the PDL Principles and Factors Assessment. If Health Canada's assessment is positive, the process continues. (Section 12)

7) Health Canada posts a public "Notice of Consultation" on the canada.ca Website outlining its proposal to remove the medicinal ingredient, or remove the medicinal ingredient for certain conditions of use, from the PDL and puts the NDS or SNDS on switch hold. (Section 13)

8) Health Canada reviews the comments provided by the public and other stakeholders during the consultation.(Section 13)

9) After analysis of the comments, if Health Canada decides to proceed, Health Canada posts a "Notice of Intent to Amend" which outlines when the amendment to the PDL will occur. (Section 14)

10) The applicant then files a PLA in accordance with the NHPR reflecting the NDS and SNDS information in anticipation of the PDL amendment. (Section 16)

11) Health Canada verifies the PLA. (Section 17)

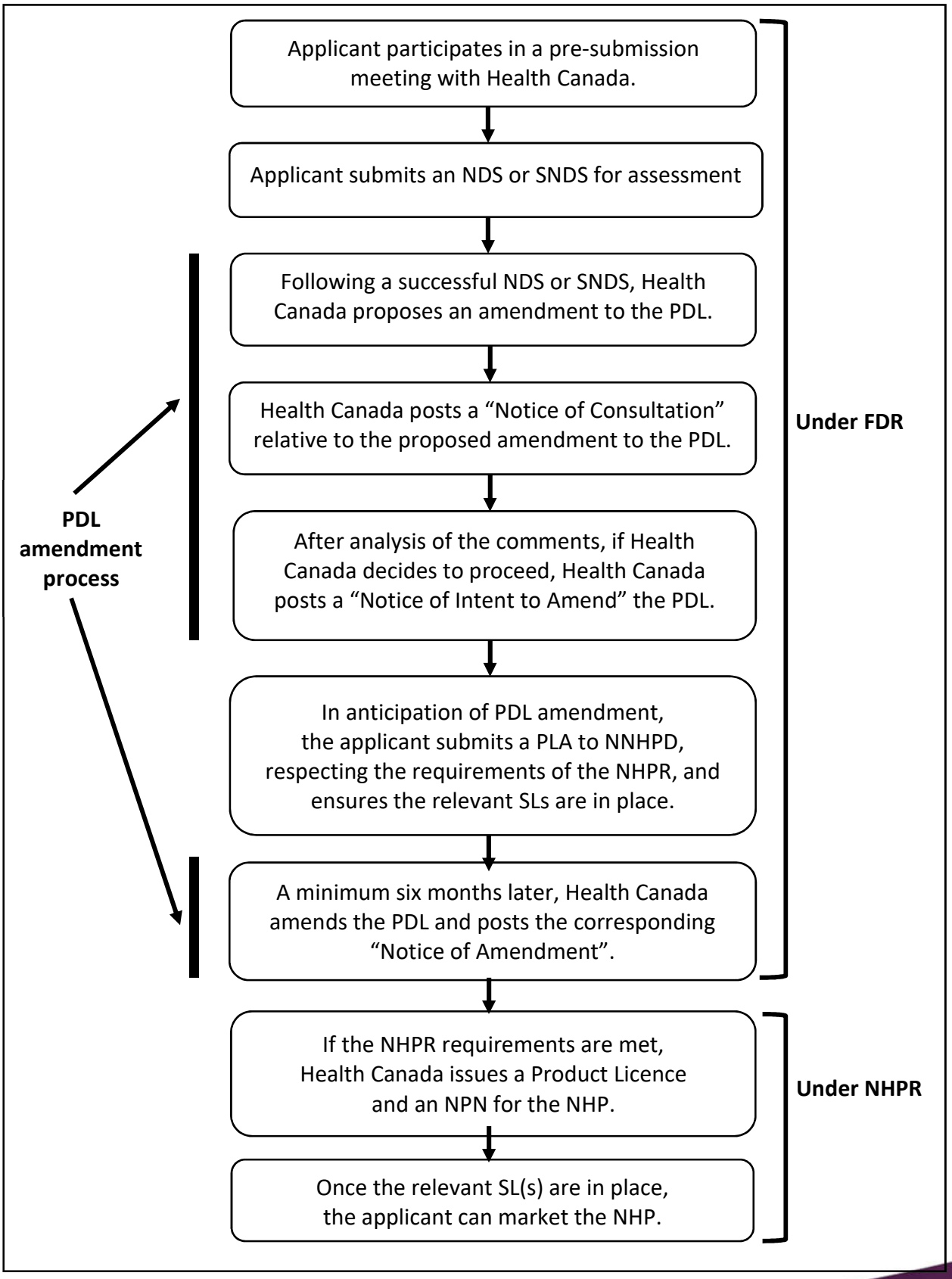
12) Health Canada amends the PDL and posts a "Notice of Amendment". (Section 18)

13) Health Canada issues a Notice of Non-Compliance (NON) for the NDS or SNDS and, if applicable, cancels the DIN(s) because the product is no longer a drug under the FDR. (Section 18.2)

14) If the applicant has satisfied the requirements of the NHPR, Health Canada issues the Product Licence and the Natural Product Number (NPN) for the product. (Section 18.2)

15) If in addition to the Product Licence and NPN, the appropriate SL has been issued to those conducting activities related to the product (i.e. manufacture, import, package and/or label), the product can be sold in Canada in accordance with the NHPR. (Section 19.4.2)

234 **Flowchart 2: Successful Rx to NHP switch**



7.3 Process 3: The assessment of submission leads to a negative decision

Not all switch submissions will be successful. Process 3 outlines the steps that would occur if the applicant has not successfully demonstrated to Health Canada in the NDS or SNDS that

- the product has met the safety, efficacy, and quality requirements; and/or,
- the PDL principles and factors do not apply to the product.

Process 3:

1) If the applicant does not successfully demonstrate the above, Health Canada issues a Notice of Deficiency (NOD) or a NON.

2) The applicant responds to the NOD/NON or withdraws the submission.

3) If the applicant responds, Health Canada assesses the response.

   a) If the response does not satisfactorily address the issues, Health Canada issues a NOD-Withdrawal (NOD-W) or NON-Withdrawal (NON-W). There is no change to the PDL.

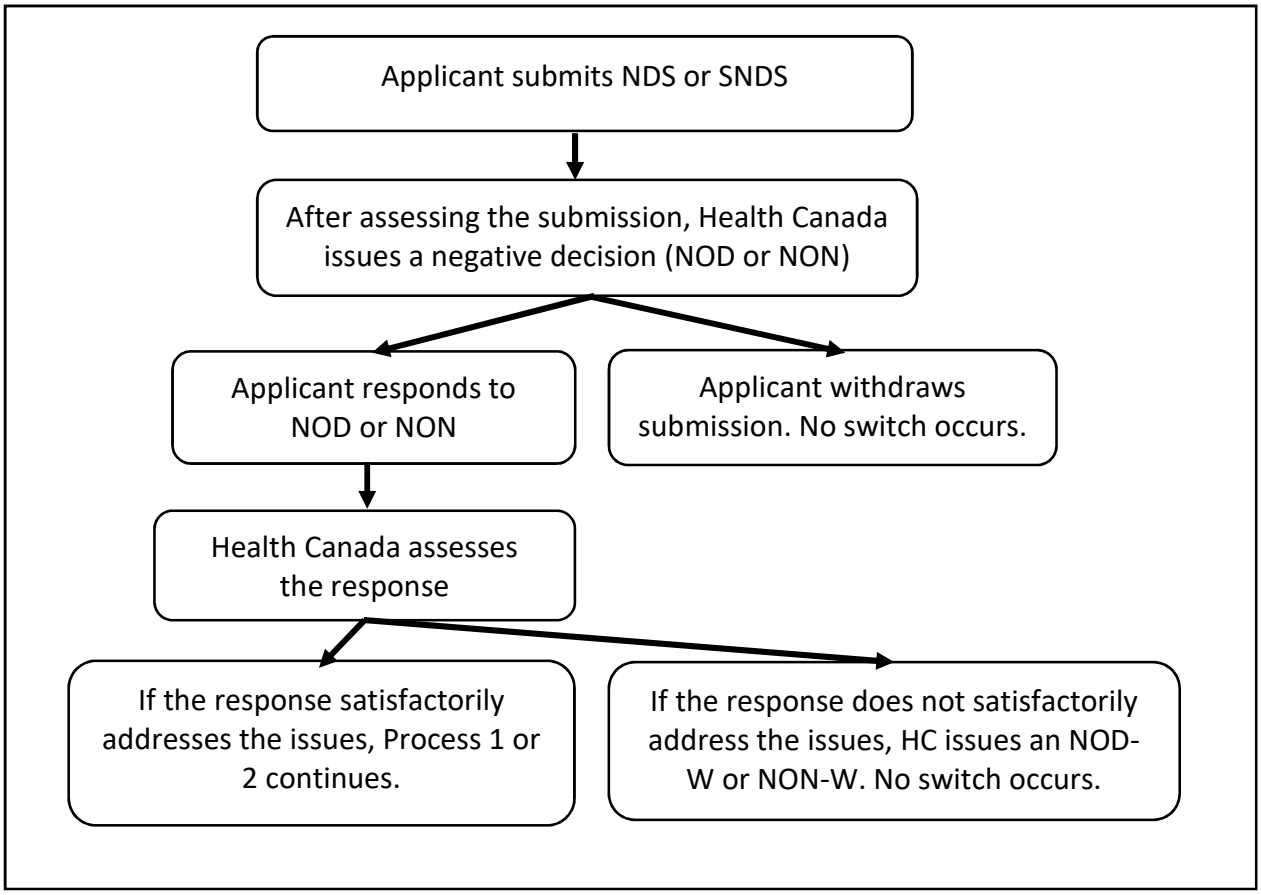
   b) If the response satisfactorily addresses the issues, the switch process (as described in Process 1 for successful Rx to NPD switches or Process 2 for successful Rx to NHP switches) would continue.

For more information on NODs, NONs, NOD-Ws and NON-Ws, please consult the guidance document “Management of Drug Submissions and Applications” (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html).

Some other examples of where a switch may fail include the following:

- an incomplete NDS or SNDS package
- significant stakeholder objections being raised during the PDL consultation which cannot be appropriately addressed otherwise (e.g. additional data demonstrating new safety concerns / need for practitioner oversight)
- for Rx to NHP switches, an incomplete PLA and/or a failure to meet the requirements of the NHPR in the second part of the switch process

Flowchart 3: Assessment of submission leading to a negative decision



8. Requesting a pre-submission meeting

Prior to filing an NDS or an SNDS, the applicant is strongly encouraged to request a pre-submission meeting with Health Canada to discuss questions the applicant has related to the adequacy of their evidence in support of the proposed switch. For example, before undertaking clinical trials or consumer use studies, the applicant should meet with Health Canada. Note that it is possible for a company to have more than one pre-submission meeting.

For information on pre-submission meetings for an NDS or SNDS, the applicant should consult section 7 of the guidance document "Management of Drug Submissions and Applications" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html).

Table 1: Pre-submission meeting participants

Type of Switch:	In the pre-submission meeting, the applicant will meet with:
Rx to NHP switches	• staff from the relevant assessment division in the Therapeutic Products Directorate (TPD) who will be the Health Canada lead for the meeting. (For more information on divisions in TPD, refer to section 20.1.) • staff that conduct the assessment of NHPs from NNHPD • staff from the Marketed Health Products Directorate • staff from other areas based on the nature of the product and the proposed switch
Rx to NPD switches	• staff that conduct the assessments of NPDs from NNHPD who will be the Health Canada lead for the meeting • staff from the Marketed Health Products Directorate • staff from other areas based on the nature of the product and the proposed switch

9. Assembling NDS or SNDS – all switches

Submission Type

The applicant assembles an NDS or an SNDS requesting the switch. The type of submission required depends on the specific situation.

Situations requiring an NDS

- If the proposed switch relates to a currently authorized "Division 1" prescription drug, the applicant files an NDS relative to the proposed non-prescription status product, as this switch represents a change in the conditions of use (namely, the sale in a non-prescription setting without practitioner oversight) as per C.08.002 of the FDR.

- If there is no existing currently authorized prescription drug, the applicant files an NDS as per C.08.002 of FDR.

- If the proposed switch would result in:

    - the applicant's currently-authorized "Division 8" prescription drug becoming an NHP or NPD with changes to the conditions of use relative to those authorized for prescription drug; and

- the prescription drug remaining on the market for some of its other conditions of use;

then the applicant files an NDS, as per C.08.002 of FDR, relative to the proposed non-prescription status product as it will be an additional product introduced to the market. In this way, future changes to the non-prescription status product can be tracked against the new authorization separate from the prescription drug authorization. (Note that if the switch is successful, the applicant will also file an SNDS relative to their currently authorized prescription drug to reflect the removal of some of its conditions of use.)

Situations requiring an SNDS

- If the proposed switch would result in:
  - the applicant's currently-authorized "Division 8" prescription drug becoming an NHP or NPD, with or without changes to the conditions of use, and
  - the prescription drug **no** longer existing on the market,

then the applicant files an SNDS, as per C.08.003 of the FDR.

Submission content

In the NDS or SNDS, the applicant includes the following content:

- the necessary information on safety, efficacy and quality of the proposed product
- the applicant's PDL Principles and Factors Assessment
- the proposed labelling

9.1 Evidence of safety, efficacy and quality

For both Rx to NHP and Rx to NPD switches, the applicant files an NDS or SNDS in which the applicant provides evidence to demonstrate the safety, efficacy and quality of the proposed product. The amount of evidence will depend on the type of switch the applicant is proposing, as outlined below.

9.1.1 The applicant is proposing a switch of an authorized prescription drug without changes

Generally, in this type of switch, the safety, efficacy and quality of the product have already been demonstrated in the submission(s) for the authorized prescription drug. Therefore, the applicant generally submits less evidence than for other types of switches. (The only condition of use that is changing is the context in which the product is sold.)

At a minimum, the applicant provides the following:

- the most recent Health Canada authorized Product Monograph or Prescribing Information for the prescription drug along with an annotated version of the proposed changes
- any available post-market information
- any more recent clinical trial data, if available, investigating the safety of the drug under similar conditions of use along with the appropriate clinical and non-clinical overviews/summaries
- consumer use studies

9.1.2 The applicant is proposing the switch of an authorized prescription drug that includes changes to its conditions of use

The conditions of use of an authorized prescription drug are specified in the Product Monograph or Prescribing Information. If the applicant is proposing changes to the conditions of use as part of the switch then additional evidence will be required. Examples of how the proposed NHP or NPD could differ from the authorized prescription drug include changes to the indication, maximum single and/or daily dose, strength of the dosage unit, route of administration, dosage form, manufacturing, formulation and target population.

The nature of the changes to the product and the conditions of use will determine what evidence is required. If applicable, the applicant can build on the data previously submitted to Health Canada for the authorized prescription drug.

The applicant is encouraged to seek guidance from the NNHPD for Rx to NPD switches and from the relevant TPD review bureau for Rx to NHP switches regarding the need for, and scope of, the data that would be required.

9.1.3 The applicant is proposing a switch and does not own a related authorized prescription drug

In these instances, the applicant provides a full data package to demonstrate the safety, efficacy and quality of the proposed product.

9.1.4 Outdated data

Applicants should be aware that if they are relying in their submission on safety, efficacy or quality studies that were generated by investigations that do not meet present day standards for safety, efficacy or quality assessments, then additional data may be required. Applicants are encouraged to discuss this type of issue with Health Canada in a pre-submission meeting.

9.1.5 Further information

For more information on the evidence of safety, efficacy and quality that is required, the applicant should consult the following:

- the applicable guidance documents that are available on the Website "Guidance Documents – Applications and submissions – Drug products" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents.html)
- Health Canada (e.g., in a pre-submission meeting)
- the sections 9.1.1 to 9.1.4 of this document

9.2 PDL Principles and Factors Assessment

The applicant follows the guidance provided in Appendix B, C and D when completing their PDL Principles and Factors Assessment. This is one of the key elements for a successful switch. The template for the assessment document is found in Appendix E. The applicant includes the completed assessment in the NDS or SNDS.

9.3 Labelling for inclusion in the NDS or SNDS

For both Rx to NHP switches and Rx to NPD switches, the applicant follows all the requirements regarding labelling of NPDs when preparing the labels for inclusion in the NDS or SNDS.

The applicant can consult the Government of Canada Website for relevant guidance documents on labelling (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents.html#l).

As discussed in Appendix C, the applicant conducts their consumer use studies using a label that closely reflects the final label that consumers will see on the market. This will help achieve the objective of having the data from the consumer use studies accurately reflect how well consumers will be able to understand and apply the 'final' labelling information.

For Rx to NPD switches, the labelling must include a Canadian Drug Facts Table (CDFT). For information on CDFT formats and flexibilities, the applicant can consult the guidance document "Labelling Requirements for Non-prescription Drugs" (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/labelling-requirements-non-prescription-drugs.html).

For Rx to NHP switches, the applicant has two options:

- The applicant can use labelling **with** a product facts table or drug facts table in their consumer use studies and for inclusion in the NDS or SNDS, if this Facts Table will be included on the final NHP label.

- The applicant can use labelling **without** a product facts table or drug facts table in their consumer use studies and for the NDS or SNDS, if the applicant is not intending on having a Facts Table on the final NHP label.

10. Formatting and filing an NDS or SNDS – all switches

In terms of the format of the submission, the applicant follows the instructions in section 8 of "Management of Drug Submissions and Applications" as well as the guidance documents referenced therein. Furthermore, the applicant includes the PDL Principles and Factors Assessment in Module 1.0.7, the consumer use studies in Module 5 and the summary of the consumer use studies in Module 2.

If there is an authorized prescription drug that is being switched and it was authorized as the result of a paper-based submission, Health Canada encourages the applicant to re-submit the evidence pertaining to authorization of the prescription drug in electronic format to expedite the review.

Information on submission filing procedures are outlined in the guidance document "Management of Drug Submissions and Applications" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html).

11. Paying fees – all switches

All applicants pay the cost recovery fees for the assessment of the information submitted in support of their NDS or SNDS. Note that it is **the content** of the NDS and SNDS that determines the size of the fee and associated performance standard, not whether it is an NDS or SNDS. For example, in 2021, the fee was $224, 242 for a switch that required clinical or non-clinical data as well as chemistry and manufacturing data and did not include a new active substance. The relevant fees for product assessment are found in Schedule 1 of the "Fees in Respect of Drugs and Medical Devices Order" (https://laws-lois.justice.gc.ca/eng/regulations/SOR-2019-124/FullText.htm), SOR/2019-124.

For more information on fees, refer to the guidance document "Fees for the Review of Human Drugs and Disinfectant Submissions and Applications" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fees/fees-review-drug-submissions-applications.html). Note that at the top of this Website, the applicant will find links (the boxes) to other sections of the document which provide information on the fee categories and fee mitigation measures.

12. Health Canada assesses the NDS or SNDS

Health Canada assesses the NDS or SNDS, including the applicant's PDL Principles and Factors Assessment, to determine if the applicant has successfully demonstrated that:

- the product meets the safety, efficacy and quality requirements of the FDR for product authorization; and
- the PDL principles and factors do not apply to the product.

Specifically, the assessment officers for NPDs in NNHPD assesses the NDSs or SNDSs for Rx to NPD switches and the assessment officers in relevant bureaux in TPD assesses the NDS or SNDS for Rx to NHP switches.

The performance standards for the assessment of the NDS or SNDS under the FDR are outlined in Appendix 3 of the guidance document "Management of Drug Submissions and Applications" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html).

13. Health Canada consults the public

If the assessment described in section 12 comes to a positive conclusion, Health Canada starts the PDL amendment process.

More information on the PDL and the PDL amendment process can be found in the guidance document entitled "Questions and Answers - Prescription Drug List" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/questions-answers.html).

For switches, Health Canada consults the public and other stakeholders on amendments to the PDL by posting a "Notice of Consultation" to the canada.ca Website. In the Notice of Consultation, Health Canada outlines the proposed amendment to remove the medicinal ingredient or remove the ingredient for certain conditions of use from the PDL. In the second scenario, for example, a medicinal ingredient can be removed from the PDL for only some indications or at lower doses.

At the same time, Health Canada places the NDS or SNDS on switch hold (that is, a temporary pause on the progress of the submission) pending the outcome of the consultation and PDL amendment process.

After the public consultation, Health Canada analyzes the comments received. Depending on the nature of the comments and the issues raised, the analysis could result in Health Canada deciding to:

- proceed,
- modify, or
- no longer pursue the proposed amendment.

If the results of the analysis supports proceeding, the next step will be to publish a Notice of Intent to Amend.

If the proposal needs modification, Health Canada continues the PDL amendment process with a modified version of the proposed amendment or conducts a new consultation depending on the nature of the modification. In the past, modifications have ranged from minor changes in the wording of the qualifier to significant re-working of the proposal. Health Canada communicates these plans to the applicant prior to publishing the Notice of Intent to Amend or the new Notice of Consultation.

If the analysis results in Health Canada deciding not to pursue the amendment, Health Canada communicates with the applicant and issues a notice to the public indicating that Health Canada will not amend the PDL.

14. Health Canada announces its intent to amend the PDL

When the analysis of the consultation comments results in Health Canada moving to the next stage of the PDL process, Health Canada posts a “Notice of Intent to Amend”. This Notice specifies the date when the amendment of the PDL will occur, typically after a minimum six-month transition period. The transition period is in accordance with the international Technical Barriers to Trade (TBT) Agreement and allows market authorization holders of other affected products time to comply with the upcoming new regulatory requirements (e.g., revise labelling).

15. Health Canada issues a DIN – Rx to NPD switches only

After Health Canada posts the Notice of Intent to Amend the PDL, Health Canada issues the applicant a Drug Notification Form (DNF) with the assigned DIN, if applicable. A new DIN is required along with the NOC, if any of the following apply:

- A DIN has not been previously assigned to the product.

- The applicant is requesting that the switch occur for certain conditions of use of the prescription drug, such that after the switch there will be both the prescription drug and the NPD on the market. The new DIN would be relative to the new NPD.

- A DIN was previously assigned, but the switch changes one or more of the drug characteristics listed in paragraphs C.01.014.1(2)(a) to (f) of the FDR and after the switch there will only be the NPD on the market.

Relative to the last situation, note that the applicant submits a "Notification of discontinuation of sale" to Health Canada for the previously assigned DIN. The notification must be sent within 30 days of the cessation of sale. Health Canada then cancels the previously assigned DIN.

16. Filing a Product Licence Application – Rx to NHP switches only

After Health Canada posts the Notice of Intent to Amend, the applicant files a second time. This time the applicant submits a web-based Natural Health Product Licence Application (web PLA) to obtain a Product Licence and the NPN. This filing can be either during or after the transition period as Health Canada is willing to contemplate the PLA prior to the PDL amendment, however decisions will only occur under NHPR after the PDL is amended.

The applicant files a web PLA as outlined in the "Natural Health Products Management of Applications Policy" (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-health-products/legislation-guidelines/guidance-documents/management-product-licence-applications-attestations.html). There are no fees for the assessment of the PLA.

The applicant completes the web PLA Form by accurately reflecting the information in the labelling that was finalized during the NDS or SNDS assessment. Note that the Product Monograph constitutes part of the labelling. Additionally, the applicant indicates in the cover letter of the web PLA Form that "Evidence in support of the NHP Product Licence is contained in the switch submission control # [insert control number assigned to the NDS or SNDS]." The applicant does not need to resubmit evidence that was submitted as part of the NDS or SNDS, nor the PDL Principles and Factors Assessment.

17. Health Canada verifies the PLA

NNHPD in Health Canada verifies the web PLA. If the applicant does all of the following:

- applies within 60 days of the publication of the Notice of Intent to Amend;
- appropriately reflects the final labelling from the NDS or SNDS in the web PLA form; and
- complies with all the requirements of the NHPR,

NNHPD can then issue the Product Licence and the NPN when the PDL is amended. An applicant who submits the web PLA any later than this may not receive their NPN until some time after the PDL amendment occurs.

18. Health Canada amends the PDL and issues the product authorization

Once the transition period is over, Health Canada amends the PDL and posts the "Notice of Amendment" on the canada.ca Website to announce that the amendment to the PDL has occurred.

18.1 Rx to NPD switches

At this time, Health Canada issues the applicant an NOC for the NPD.

18.2 Rx to NHP switches

At this time, Health Canada issues the applicant a NON with respect to the NDS or SNDS on switch hold and, if applicable, cancels the DIN(s) because the product is no longer a drug regulated under the FDR (refer to paragraph C.01.014.6 (1) (c) of the FDR). It is now a product subject to the NHPR.

The applicant then has the option to withdraw the submission or respond to the NON acknowledging the product is no longer a drug under the FDR. In the latter case, upon receiving a response to the NON, Health Canada issues the NON-W re-iterating the product is no longer a drug under the FDR.

Additionally, if all the conditions set out in section 17 of this guidance document are met, Health Canada issues a Product Licence and NPN for the proposed NHP.

19. Additional information

19.1 Reconsiderations

If the applicant wishes to request a reconsideration of a negative decision issued by Health Canada for an Rx to NHP or Rx to NPD switch, the applicant should refer to the guidance document "Reconsideration of Decisions Issued for Human Drug Submissions and Natural Health Products" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/reconsideration-final-decisions/reconsideration-final-decisions-issued-human-drug-submissions.html).

Note that the Director General (DG) of the directorate who issued the negative decision will be the DG responsible for making the decision on the reconsideration.

19.2 Switches involving products with multiple medicinal ingredients on the PDL

If the applicant's proposed NHP or NPD contains more than one medicinal ingredient listed on the PDL, the applicant needs to:

- complete only one PDL Principles and Factors template and
- include information about each of the ingredients on the PDL in each section of the template.

19.3 Switches involving medical devices

For a drug-device combination product, the applicant is encouraged to contact Health Canada to discuss switch requirements and applicable authorizations.

When a switch involves a medical device that is not part of a combination product, such as an independent drug-delivery device or monitoring device, the applicant must ensure the medical device is authorized where required by the *Medical Devices Regulations* (MDR).

Additionally, the device should be consumer-friendly and useable without practitioner intervention. That is, the consumer should be able to follow the instructions for use that are provided with the device; monitor the device function; and where applicable, understand the device output. Any human factors or usability assessments using the medical device components and formally conducted with Healthcare Professionals or specialized health technicians should be repeated with representative consumer test groups to confirm the medical device design remains optimal for the new user population. Applicants may contact Medical Devices Directorate (email: meddevices-instrumentsmed@hc-sc.gc.ca) for additional guidance on what to submit relative to the medical device in the switch submission.

19.4 GMP, DEL and SL requirements

In addition to obtaining a product authorization for an NPD or NHP pursuant to a switch, there are GMP, DEL and SL requirements that must be met for products to be sold in Canada.

19.4.1 Rx to NPD switches

Prescription and non-prescription drugs are both subject to DEL requirements as per Part C, Division 1A of the FDR and GMP as per Part C, Division 2 of the FDR.

Activities, such as fabrication and importation, can be conducted by the switch applicant or by other parties. If the applicant or other parties conducting the activities already comply with the relevant DEL and GMP requirements, no change to the DEL is required. If they do not already comply, they need to ensure compliance with the DEL and GMP requirements prior to selling the NPD in Canada.

In terms of filing the NDS or SNDS, the applicant is reminded to comply with the notice "Submission Filing Requirements - Good Manufacturing Practices (GMP)/Drug Establishment Licences (DEL)" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/notice-submission-filing-requirements-good-manufacturing-practices-establishment-licences.html).

Note that wholesaling of an NPD does not require a DEL, but must still meet GMP requirements, as per Part C, Division 2 of the FDR.

For further information, the applicant and other parties can consult the following:

- the DEL Website (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences.html):
    - For guidance on DEL requirements, refer to "Guidance Document on Drug Establishment Licences" (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/guidance-drug-establishment-licences-drug-establishment-licensing-fees-0002.html) (GUI-0002).
    - For information regarding the fees associated with a DEL application, refer to "Fees for the Review of Human and Veterinary Drug Establishment Licence Applications" (https://www.canada.ca/en/health-canada/services/drugs-health-products/funding-fees/review-drug-establishment-licence.html).

- the GMP Website (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents.html):
    - For guidance on GMP requirements for drug products, refer to the "Good manufacturing practices guide for drug products" (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001.html) (GUI-0001).

19.4.2 Rx to NHP switches

Normally at the beginning of an NDS or SNDS review, Health Canada conducts a screening of the submission relative to the DEL, GMP compliance rating or DEL applications as outlined in the notice "Submission Filing Requirements - Good Manufacturing Practices (GMP)/Drug Establishment Licences (DEL)" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/notice-submission-filing-requirements-good-manufacturing-practices-establishment-licences.html). However, for Rx to NHP switches, Health Canada defers this screening until later in the submission assessment process.

In order to market the NHP in Canada, the switch applicant or other parties who are carrying out activities such as manufacturing or importing are required to follow GMP, as per Part 3 of the NHPR. Also, the switch applicant or other parties must obtain an SL, as per section 2 of the NHPR.

There are three possible scenarios relative to the SL for the applicant or other parties carrying out the activities:

- If they already have the relevant SL, no further action is required.
- If they already have a DEL but no SL, they apply for an SL via a streamlined pathway, which is described in section 2.1.1 of the guidance document "Site Licensing Guidance Document, December 1, 2015 - Version 3.0" (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/site-licensing-guidance-document.html).
- If they do not have an SL or DEL, they apply for an SL as described in "Site Licensing Guidance Document" (link in preceding bullet).

The applicant or other parties must obtain an SL prior to the marketing of the NHP. Performance standards for SL issuance are listed under Section 3.1.1 "Application completion timelines" (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/site-licensing-guidance-document.html#a3.1.1) within Table 1: "Summary of Service Standards for the Management of Site Applications".

The applicant and other parties can find additional guidance documents on the SL and NHP GMP requirements on the Website "Guidance Documents – Legislation and guidelines- Natural health products" (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents.html).

If the Rx to NHP switch involves an authorized prescription drug that will become an NHP with the prescription drug no longer being marketed, the FDR DEL requirements continue to apply for the prescription drug until it is no longer sold or until the date the PDL is amended, whichever occurs first. Once one of those two criteria is met, the DEL holder can submit a request for DEL cancellation. It should be noted that the timeline for the applicable GMP requirements, for example records and samples retention, continues beyond the holding of the DEL. All relevant evidence is required to be kept for one year beyond the expiration date of the product.

19.5 Data protection

Subsection C.08.004.1(3) of the FDR provides an eight-year period of market exclusivity for innovative drugs. Pursuant to subsection C.08.004.1(4), the exclusivity period may be extended by six months.

"Innovative drug" is defined as a drug that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate or polymorph. Drugs that contain medicinal ingredients that have been previously approved in Canada, including drugs that have previously received an NOC, an NPN, and/or a DIN, are not eligible for data protection.

Only drugs governed by Division 8 of the FDR are eligible to benefit from data protection. Further, the switch of a prescription drug to a Division 8 NPD will not result in the granting of a new or additional term of data protection.

For more information on data protection, manufacturers are encouraged to consult Health Canada's guidance document entitled "Data Protection under C.08.004.1 of the *Food and Drug Regulations"* (https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/data_donnees_protection-eng.pdf) or to contact the Office of Patented Medicines and Liaison at opml-bmbl@hc-sc.gc.ca.

19.6 *Patented Medicines (Notice of Compliance) Regulations*

The *Patented Medicines (Notice of Compliance) Regulations* ("*PM(NOC) Regulations*") provide a link between the regulatory approval of a generic or biosimilar drug to the patent status of the Canadian Reference Product or Canadian Reference Biologic Drug that is marketed under an NOC.

Only drugs governed by Division 8 of the FDR are eligible to benefit from protections afforded under the *PM(NOC) Regulations*. Further, the switch of a prescription drug to a Division 8 NPD will not result in a new opportunity to submit a patent list for inclusion on Health Canada's Patent Register under subsection 4(2) of the *PM(NOC) Regulations*.

For more information on the *PM(NOC) Regulations*, manufacturers are encouraged to consult Health Canada's guidance document entitled "*Patented Medicines (Notice of Compliance) Regulations*" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/patented-medicines/notice-compliance-regulations.html) or to contact the Office of Patented Medicines and Liaison at opml-bmbl@hc-sc.gc.ca.

19.7 The impact of a switch on other prescription drugs

In Canada, a successful switch results in an amendment to the PDL and this can have an impact on other **prescription** drugs. Companies, who are not initiating the switch, need to assess if proposed amendment to the PDL would mean that their products will no longer be prescription. If the amendment will impact their prescription drugs, Health Canada will inform the companies of their options (e.g. the companies could file an application to obtain their product authorization as a non-prescription status product [NHP or NPD] or cease sale). Note that these submissions or applications are not considered "switch submissions".

19.8 Other companies interested in marketing products given the PDL amendment

Other companies may become aware based on the PDL notices that the PDL is changing. These companies may have an interest in marketing a new product in the non-prescription setting (i.e. NPD or NHP) now that the medicinal ingredient is permitted or permitted for some conditions of use. To obtain market authorizations, these companies would file either an NDS (for NPDs) or Class III application (for NHPs) after the PDL amendment occurs. As long as the proposed new products align with the PDL amendment, these submissions/applications follow the regular requirements and they are not “switch submissions”.

20. Contact information

If applicants have any questions regarding switches, they should contact Health Canada.

20.1 Rx to NPD switches

Please contact NNHPD by email: hc.nnhpd-dpsnso.sc@hc-sc.gc.ca

20.2 Rx to NHP switches

Relative to the NDS or SNDS portion of the switch process, please contact the relevant review bureau in TPD. The description and contact information for the various bureaus can be found in Appendix 2 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry/document.html#a87) of the guidance document “Management of Drug Submissions and Applications”.

Relative to the PLA part of the switch process, which occurs after a successful NDS or SNDS, please contact NNHPD by email: hc.nnhpd-dpsnso.sc@hc-sc.gc.ca

Appendix A: Glossary

Acronyms

DEL – Drug Establishment Licence

DIN – Drug Identification Number

DNF – Drug Notification Form

EMA – European Medicines Agency

FDR – *Food and Drug Regulations*

GMP – Good Manufacturing Practices

MDR – *Medical Device Regulations*

NDS – New Drug Submission

NHP – Natural Health Product

NHPR – *Natural Health Products Regulations*

NHPID – Natural Health Products Ingredients Database

NNHPD – Natural and Non-prescription Health Products Directorate

NOC – Notice of Compliance

NOD – Notice of Deficiency

NOD-W – NOD-Withdrawal

NON – Notice of Non-compliance

NON-W – NON-Withdrawal

NPD – Non-prescription Drug

NPN – Natural Product Number

PBRER – Periodic Benefit-Risk Evaluation Report

PDL – Prescription Drug List

PLA – Product Licence Application

PSUR – Periodic Safety Update Report

Rx – Prescription

SL – Site Licence

SNDS – Supplement to a New Drug Submission

TPD – Therapeutic Products Directorate

US FDA – Food and Drug Administration of the United States of America

Terms

Note that all the definitions that follow are for the purposes of this guidance document and the use of these terms may differ in other Health Canada documents.

Abuse – refers to the use of a product for purposes other than for which it was prescribed; for example, using it for its reinforcing properties.

Addiction – refers to the problematic use of a drug resulting in harm. These harms can range from mild (being late for work), to severe (losing a job or home) and are accompanied by impaired control over drug use; compulsive drug-seeking behaviour; continued use despite harms; and cravings.

Applicant – refers to the applicant or sponsor who is initiating the request for an Rx to NPD or Rx to NHP switch.

Canadian Drug Facts Table – refers to a table on the outer label of NPDs that is required to display specific information, per section C.01.004.02 (1) of the FDR. The purpose of the Canadian Drug Facts Table is to display the information in a standardized, easy-to-read format in order to enhance the safe and effective use of NPDs.

Combination Product – refers to a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is integrated in a singular product.

Conditions –refers to diseases, conditions, disorders, abnormal physical states or their symptoms (for the purposes of simplifying the text of this guidance document).

Conditions of Use – include elements such as

- the use, indication or purpose of a health product;
- the dosage form;
- the route of administration;
- the dose (including sub-population, amount, dosage unit, frequency and directions for use);
- the duration of use, if any; and
- the risk information including precautions, warnings, contraindications, or known adverse reactions associated with the use of the product or its medicinal ingredients.

Dependence – refers to a difficulty discontinuing drug use due to unpleasant physical and/or psychological withdrawal effects.

Drug – refers to natural health products, pharmaceuticals and biologics.

Market Experience – is knowledge gained about an authorized product once it is being sold.

Medicinal Ingredient(s) – refers to the substance(s) in the product that contributes to the product's therapeutic effect (synonym: active ingredient(s)).

Near Miss – is an event that could have resulted in unwanted consequences, but did not, either by chance or through timely intervention.

Non-prescription status – refers to the default status of products that are not prescription drugs (i.e. products with prescription status). For example, NHPs and NPDs both have non-prescription status.

Psychoactive Effects – are effects of a substance or mixture of substances on the central nervous system that results in temporary changes in cognition, perception, mood and consciousness, which can in turn lead to temporary changes in behaviour. Examples of these include, but are not limited to, dizziness, calmness, stimulation, anxiety, irritability, cognitive impairment, hallucinations, drowsiness and euphoria.

Practitioner – refers to people who are entitled to treat patients with prescription drugs according to provincial/territorial laws and are practicing their profession in that province/territory. Two common examples are doctors and dentists.

Problematic Use – is intentionally taking a medication or drug substance to get high or to alter one's mood. The most common types of prescription drugs that can lead to problematic use include opioids, benzodiazepines and stimulants. Problematic substance use over time is linked to drug dependence, drug tolerance and substance use disorder (addiction).

Serious Adverse Reaction – is a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

Switch Submission – for Rx to NPD switches, this refers to the NDS or SNDS in which a switch is requested; for Rx to NHP switches, this refers to the NDS and PLA, or the SNDS and PLA, in which the switch is requested.

Switch – refers to a change of status from prescription status to non-prescription status.

Tolerance – refers to the need to take progressively higher doses of a drug substance in order to achieve the same desired effect.

Appendix B: Completing the PDL Principles and Factors Assessment

All applicants should complete a "PDL Principles and Factors Assessment" (see template in Appendix E). The applicant should provide summaries of evidence and rationales demonstrating that none of the PDL principles and factors applies to the medicinal ingredient under the proposed conditions of use. In other words, the applicant demonstrates that the product does not require practitioner oversight and is therefore appropriate for self-care.

Below, under the headings for each of the PDL principles and factors, Health Canada outlines points for the applicant to consider when developing the evidence and rationale for each of the principles and factors.

In addition, for a complete understanding of the PDL principles and factors, Health Canada advises the applicant to read the guidance document "Determining Prescription Status for Human and Veterinary Drugs" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/guidance-document.html).

Note that the term "condition" in the text that follows refers to diseases, conditions, disorders, abnormal physical states or their symptoms.

> Principle 1: Supervision by a practitioner is necessary (i) for the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in respect of which the drug is recommended for use, or (ii) to monitor a disease, disorder or abnormal physical state, or its symptoms, in respect of which the drug is recommended for use, or to monitor the use of the drug.

In this part of the template, the applicant should include additional information associated with this principle that the applicant has not explicitly detailed under Factors 1.1 to 1.8 below. In the case where there is no additional information to that detailed under Factors 1.1 to 1.8, the applicant should indicate that all the information relative to this principle is included in Factors 1.1 to 1.8 below.

> Factor 1.1: The drug is used in the treatment of a serious disease not easily diagnosed by the public.

This factor relates to concerns associated with misdiagnosis. Products intended for the non-prescription setting should be for conditions that are amenable to self-diagnosis.

For this factor, the applicant should include the following:

- a description of how the condition is diagnosed
- an assessment of the ease with which the consumer would be able to self-diagnose
- an assessment of the risks associated with a misdiagnosis
- possible risk mitigation measures that would decrease the seriousness of the potential health consequences if the condition is misdiagnosed

Description of diagnosis

The applicant should outline how the condition in question is typically diagnosed and in so doing, reference a reputable medical text or clinical practice guidelines.

Ease of consumer self-diagnosis

In terms of the assessment of the ease with which the consumer would be able to self-diagnose, the applicant needs to demonstrate that the consumer can accurately determine the nature of the condition on the basis of well-recognized symptomatology as well as the severity and duration of symptoms.

If the symptoms in question are common to a number of conditions, the applicant needs to demonstrate that the consumer can differentiate between these conditions. The applicant may need to provide consumer use studies to help demonstrate that the consumer has the ability to self-diagnose the condition correctly. For more information on consumer use studies, refer to Appendix C.

The applicant should indicate whether laboratory tests or other procedures involving a practitioner are required for diagnosis. If this is required for diagnosis, generally, the product would maintain its prescription status.

If effective use of the product requires additional measures, such as a monitoring device, the applicant needs to demonstrate that these measures or devices do not require practitioner involvement. For more information on medical devices, refer to section 19.3.

Risks associated with misdiagnosis

The applicant's assessment of the risks associated with a misdiagnosis of symptoms should address the following:

- the impact of a delay in using the appropriate treatment
- the impact of the use of sub-optimal treatment
- the long-term effects of an inappropriately selected treatment (i.e., the risk of long-term exposure to the product with no health benefit to the consumer)

If the applicant's assessment identifies risks, the applicant needs to demonstrate that the measures put in place, such as labelling, mitigate these risks.

In rare cases, Health Canada may authorize a product for self-care use where an initial diagnosis is required by a practitioner to ensure that the consumer is completely familiar with the symptomatology (e.g., vaginal antifungals). In these cases, the applicant should demonstrate that the consumer is able to conduct subsequent diagnoses. The applicant also needs to address the risks of a consumer choosing not to see a practitioner for the initial diagnosis and the resulting consequences of product use.

Factor 1.2: The use of the drug may mask other diseases.

This factor relates to the potential risk that use of a product could hide a serious condition. Specifically, a consumer may treat his or her own symptoms with a product and obtain relief of those symptoms. However, in obtaining relief, the consumer may be less likely to consult a practitioner, potentially resulting in a more serious condition not being addressed in a timely manner. Products for self-care should not mask other serious conditions.

To address this factor, the applicant should include the following:

- information on the product's mechanism of action as this will help identify potential conditions which might be masked
- an assessment of whether the pharmacological effects of the product have the potential to mask underlying condition(s) requiring medical attention

If a potential risk of masking other conditions exists, the applicant should also include an assessment of the consequences resulting from each of the following situations:

- a significant worsening of the underlying condition
- a delay in diagnosis and proper treatment of the serious condition
- any other situation that could prevent a more successful therapy for the underlying condition

The applicant should provide an assessment of whether the product labelling, or other measures, could mitigate the identified consequences of masking other conditions.

Note that if the risk of masking other conditions pertains to a serious condition, generally, the prescription status is maintained.

Factor 1.3: Practitioner supervision is necessary for treatment and/or monitoring.

This factor relates to whether the indication is suitable for the non-prescription context and the consumer's ability to self-treat and self-monitor. Generally, conditions suitable for self-care are self-limiting, that is, they will resolve on their own. Many conditions are not suitable for self-care. Thus, in summary, the use of the product, as well as the condition itself, cannot require practitioner supervision if the product is to obtain a non-prescription status as an NHP or NPD.

The applicant should include an assessment of how the use of the product is amenable to self-treatment and self-monitoring. In this assessment, the applicant needs to demonstrate that the consumer can correctly do all of the following without practitioner assistance:

- identify that he or she belongs to the intended target population for the product on the basis of the age range and the risk statements (precautions, warnings, contraindications) included in the product labelling;
- make an appropriate product selection;
- understand what potential side effects may emerge and how to manage them;
- determine whether or not the treatment is being effective;
- identify what foods or medication to avoid while taking the product;
- perform any additional measures (e.g., use of an ancillary medical device);
- understand and follow the dosage regimen proposed for the product; and
- identify situations where treatment should be discontinued and/or medical advice sought.

Consumer use studies may be necessary to substantiate an applicant's position that the involvement of a practitioner is unnecessary. For more information on consumer use studies, refer to Appendix C. Note that if effective use of the product requires additional measures, such as a monitoring device, the applicant needs to demonstrate that these measures do not require practitioner supervision. For more on medical devices, refer to 19.3.

The applicant should provide a rationale for why the condition and product do not require practitioner expertise for treatment and monitoring activities. The rationale should address the reasons why practitioner expertise is **not** needed for any of the following:

- the selection of the correct product for the individual;
- the management of adverse reactions;
- decisions on dose adjustments and discontinuation;

- the development of risk mitigation strategies for the individual;
- any testing required prior, during or following the use of the product; and
- adjustments of the treatment and monitoring relative to comorbidities.

Factor 1.4: The use of the drug requires complex or individualized instructions.

Products for use in self-care should not require practitioner involvement to tailor the use of the product to an individual's unique circumstances or to explain product information. Consumers should be able to easily understand the product information and use the product. Therefore, the applicant should demonstrate that the product's use does **not** involve any of the following:

- dose titration
- complex dosage regimens
- doses tailored to the individual's specific circumstances
- complex instructions

Some examples of the above situations that would lead to the prescription status being maintained include the following:

- where the dose needs to be determined based on co-morbidities and/or test results
- where the product elicits tolerance requiring increasing doses to maintain efficacy
- where the product requires adjustments of the dose for the individual by a practitioner
- where the product elicits clinically significant withdrawal or discontinuation symptoms that require tapering or symptom monitoring upon product removal
- where there are complex risk statements

With respect to the degree of complexity of directions for use, risk statements, etc., results from consumer use studies can assist the applicant in demonstrating the consumer's ability to understand the instructions without practitioner assistance. For more information on consumer use studies, refer to Appendix C.

Factors 1.5: Practitioner expertise is necessary to administer the drug or oversee the drug's administration.

Products with non-prescription status should be easy for consumers to self-administer. To demonstrate this, the applicant should provide the following:

- a description of why practitioner expertise is not needed to administer or oversee the administration of the product
- an assessment of the consequences of the product being administered improperly
- a discussion of any risk mitigation measures the applicant has put in place

Note that Health Canada considers most injectable products unsuitable for self-care use.

Factor 1.6: The drug has a narrow margin of safety.

The margin of safety is the difference between the optimal effective dose and the dose at which undesirable or unmanageable side effects begin to appear. For products that have a narrow therapeutic index, the individual must receive precisely the right dose to prevent serious consequences. In contrast, products for use in self-care ideally have a wide margin of safety to ensure minimal risk to health if the consumer uses the product incorrectly.

Safety profile

The applicant's evidence and rationale for this factor should include a summary of the product's safety profile. The summary should reflect the following:

- the content of the most recent Health Canada approved Product Monograph or Prescribing Information for the prescription drug, if that exists;
- the safety data from all *in vitro*, pre-clinical and clinical studies;
- the market experience data (refer to Appendix D);
- the published literature;
- the safety assessments from other major regulatory jurisdictions as well as any available safety information from the World Health Organization or other national or international health organizations; and
- for products that contain known psychoactive substances, information on the dose at which unintended and intended psychotropic drug effects occur.
    - These psychotropic drug effects can include, but are not limited to, alterations in perception, cognition, levels of arousal and mood.

The applicant needs to demonstrate that there is an adequate margin between the product's therapeutic dose(s) and the doses at which clinically significant adverse reactions occur. Adverse reactions can be clinically significant because of their seriousness, severity or frequency. They can also be clinically significant if there are no suitable preventative measures.

Assessment of the consequences of inaccurate dosing and risk mitigation measures

The applicant should show that the impact of minor dose deviations would not result in significant harm. To this end, the applicant needs to:

- address the likelihood and the severity of the risks associated with inaccurate dosing; and
- summarize any related market experience data that is available.

Note that in terms of inaccurate dosing, the applicant should address overdosing as it pertains to the product's margin of safety and under-dosing as it pertains to a lack of efficacy. The applicant also needs to demonstrate how the directions for use could help mitigate these risks.

Additionally, the applicant should identify whether the product has a narrow margin of safety in particular sub-populations, such as pregnant and nursing women, children and the elderly. The applicant should also identify any risk mitigation measures that the applicant has made with respect to these sub-populations and the effectiveness of those measures.

In some cases, an NHP and prescription drug, or an NPD and prescription drug, will co-exist on the market after a successful switch. If this is the anticipated outcome of the switch, the applicant should address how the risks of consumer taking both products at the same time are being mitigated.

Factor 1.7: At normal therapeutic dosage levels, the drug has potential or is known to cause serious adverse reactions or serious interactions with food or other drugs.

This factor relates to the potential harm arising from serious adverse reactions or interactions with commonly used medications (prescription drugs, NPDs and NHPs) or foods. To be suitable for self-care use, the product should not be associated with potential or known serious adverse reactions or serious drug-drug or drug-food interactions in the target population.

The applicant should include an assessment of the serious adverse reactions and potential serious interactions of the product with food or other drugs, at the proposed dose and regimen, with reference to the following:

- the safety results for all relevant clinical trials;
- drug-drug and drug-food interaction studies;
- available market experience data (refer to Appendix D); and
- any other available safety data.

Other available safety data includes information from *in vitro* studies; Absorption, Distribution, Metabolism and Excretion (ADME) studies; mechanism of action studies; toxicological studies and other relevant pharmacokinetic and pharmacodynamics studies.

If applicable, the applicant is expected to describe any risk mitigation measures, including labelling, that may address the risk of serious adverse reactions or potential serious interactions. The applicant can use data from consumer use studies to help demonstrate that these measures are effective in altering consumer behaviour so that serious adverse reactions and potential serious interactions are avoided. For more information on consumer use studies, refer to Appendix C.

The applicant also needs to identify any special considerations for vulnerable sub-populations, such as pregnant and nursing women, children and the elderly.

Factor 1.8: The drug has dependence and/or addiction potential.

Products for use in self-care should not have the potential to cause dependence and/or addiction[3].

Some products have the potential to induce psychoactive effects. These effects can be the primary/desired effect of the product (e.g., sedatives) or unintended/undesired secondary effects. These effects include symptoms such as dizziness, anxiety, cognitive impairment or irritability; but also symptoms that can be experienced as reinforcing, such as euphoria, changes in consciousness, perception and/or mood. Psychoactive ingredients that cause these types of reinforcing effects are of particular concern as they may carry a heightened risk for dependence and/or addiction (refer also to Factor 3.2).

Some products have the potential to induce symptoms related to discontinuing or reducing the dose, including withdrawal and rebound effects. These types of adverse reactions can result in a consumer having significant difficulty with stopping use of the product. For example, patients who no longer require the use of a product may continue to use it because an attempt to discontinue it had resulted in worsening symptoms. Practitioner oversight in this situation may be necessary to determine if the symptoms are solely rebound in nature or if the underlying condition still exists. In addition, some products may require dose tapering or secondary medications to manage the withdrawal symptoms and thus require practitioner oversight (refer to Factor 1.4). Importantly, discontinuation symptoms are not confined solely to psychoactive ingredients.

The applicant should demonstrate that the use of the product does not cause the following:

- clinically significant psychoactivity requiring practitioner oversight
- symptoms upon discontinuation or rapid dose reduction that require practitioner oversight

The applicant may demonstrate this by providing data from clinical trials that include adverse event profiles and outcomes from specific validated scales or questionnaires, as well as post-market data or literature.

Note that Health Canada expects the product to have clinically significant effects when its indication is based on a psychoactive effect (e.g., sedatives); nonetheless, the applicant still needs to provide evidence to characterize these effects and demonstrate that these effects are manageable in a non-prescription context without practitioner involvement.

In some cases, secondary psychoactive effects may be sufficient to necessitate maintaining prescription status. However, in other cases the effects may be effectively mitigated (for example, through labelling) such that practitioner involvement is not required. For instance, slight drowsiness may be addressed through label warnings for a product used to treat the symptoms of allergies and may not necessitate practitioner intervention. The applicant should include information on any mitigation measures the applicant has instituted relative to secondary psychoactive effects and the effectiveness of these measures.

Principle 2: The level of uncertainty respecting the drug, its use or its effects justifies supervision by a practitioner.

This principle relates to the possibility that some uncertainties may remain about the product, such as:

- a lack of market experience (e.g., new product, new use, small target population and/or a lack of adequate post-market data);
- a lack of full characterization of its pharmacological effects; and/or
- unknown consequences of its long-term use.

Note that where uncertainties exist, the product would generally maintain its prescription status.

In contrast, products for self-care use should have a long history of use under the proposed conditions of use and be well characterized. Ideally, a product is well characterized if in addition to its safety and efficacy, the pharmacodynamics, the pharmacokinetics and the toxicological profile of the product are known and well documented.

The applicant needs to provide any information relevant to this principle not mentioned under Factor 2.1 (described below). The applicant should demonstrate that the proposed NHP or NPD has limited uncertainties that do not warrant practitioner oversight. The applicant needs to summarize where uncertainties and gaps in the information exist, including analysis on the following:

- uncertainties and gaps in the data regarding the toxicology and safety of the product
- uncertainties and gaps in the body of evidence supporting the product's safety and efficacy relative to its proposed use in the non-prescription context and under the proposed conditions of use

The applicant needs to substantiate that there is only a minimal level of uncertainty and minimal gaps in the evidence. Furthermore, the applicant should explain the reason(s) any remaining uncertainties and/or gaps would not result in a need for practitioner oversight.

Factor 2.1: There is limited market experience with the use of the drug.

Products for which there is limited market experience typically maintain their prescription status. Market experience may be limited with respect to years of sales or in terms of volume of sales (population exposure).

The applicant should address all the elements outlined in Appendix D of this guidance document when demonstrating that there is adequate market experience supporting the safety of the product.

Principle 3: Use of the drug can cause harm to human or animal health or a risk to public health and the harm or the risk can be mitigated by a practitioner's supervision.

To be granted non-prescription status, products should not pose a danger to the health and safety of individuals, animals or the public at large. If the applicant has identified ways to mitigate potential dangers, the applicant should demonstrate that the mitigation measures are effective.

If the applicant has additional information relevant to this principle that is not covered in the sections on Factors 3.1 and 3.2 (detailed below), the applicant should include it in this part of the template. If the applicant does not have additional information, the applicant should indicate in this section of the template that all the information relative to this principle is included under Factors 3.1 and 3.2.

Factor 3.1: There is potential for harm to public health.

To be suitable for self-care use, the widespread or improper use of a product should not have the potential to cause public health issues.

Examples of public health issues are the development of drug resistance in strains of microorganisms (bacteria, viruses, or fungi) and parasites emerging as opportunistic pathogens.

A product whose use in the non-prescription setting could contribute to the development of drug resistance will generally maintain its prescription status.

For this factor, the applicant should include an assessment of whether there is potential for harm to public health and if applicable, any risk mitigation measures.

Factor 3.2: There is potential for abuse or diversion leading to harmful non-medical use.

A product for use in the non-prescription setting should not have the potential to lead to abuse[4,5] and/or diversion. Products that have the potential to lead to abuse typically have reinforcing or rewarding properties (refer to Factor 1.8). These properties can be associated with alterations in perception, cognition, mood and/or levels of arousal and, therefore, could lead to harmful patterns of use. The potential for diversion of these products also exists, both between individuals, as well as from veterinary use to human use. Generally in these cases the medicinal ingredient will be regulated as a controlled substance under the *Controlled Drugs and Substances Act* and its regulations.

In order for the product to be switched to non-prescription status, the applicant should demonstrate that it has a low likelihood for abuse[6]. This may necessitate that the applicant provides some or all of the following:

- an examination of whether the structure of the medicinal ingredient in question is similar to other known substances associated with abuse
- receptor binding studies to determine the affinity of the medicinal ingredient and its metabolites to cellular targets known to be common to drugs associated with abuse
- functional assays to determine the nature of neurotransmitter activity
- non-clinical and clinical studies designed to assess whether the ingredient or its metabolites contain reinforcing or rewarding properties and whether there is an increased likelihood that the product will be used for these reinforcing properties
- an assessment of whether the product elicits withdrawal symptoms upon discontinuation
- dose-response studies to characterize the psychoactivity as well as the total content of the medicinal ingredient available in each dose/container/package
- a review of available information[7] to determine if abuse or diversion has been reported with the ingredient
- a summary of market experience listing adverse events associated with abuse

The applicant should be clear on what effects are observed under normal conditions of use (the conditions for which the switch is being sought) versus those seen under other conditions of use, such as at higher doses. The applicant should also address whether the product could be tampered with in order to accentuate the reinforcing psychoactive properties.

For a product to be granted non-prescription status, the applicant needs to demonstrate that these types of concerns do not exist or can be successfully mitigated without practitioner involvement. In all situations, the applicant should address whether there are any special concerns for particular sub-populations, such as those with a history of problematic drug use.

Appendix C: Consumer use studies

Consumer use studies help provide evidence that consumers can use the proposed product safely and effectively without practitioner oversight.

There are four main types of consumer use studies:

1. label comprehension studies
2. self-selection studies
3. actual use studies
4. human factors studies

Health Canada expects the applicant to provide all or some combination of the above-noted consumer use studies in switch submissions. The applicant is encouraged to discuss the need for consumer use studies with Health Canada before filing their submissions.

Ideally, consumer use studies should be conducted using study subjects who are representative of Canadian demographics.

In terms of language, in some cases, consumer use studies can be conducted solely in English or French if the text of the other language on the product label is an accurate translation of the tested label. In other cases, such as for all label comprehension studies, Health Canada may request that studies be conducted in both official languages. Health Canada will give consideration to consumer use studies conducted in French- or English- speaking foreign countries on a case-by-case basis, if equivalent studies are not available for the Canadian population.

The applicant may choose to follow methodologies for consumer use studies suggested by other regulatory agencies[8] and can discuss their choice of methodologies at a pre-submission meeting.

C.1 Label comprehension studies

Central to justifying a switch is the demonstration that the labelling effectively supports the consumer using the proposed product without practitioner involvement. Label components can include the outer and inner product labels; and package inserts. A label comprehension study assesses the consumer's understanding of the major communication elements that relate to the safe and effective use of the product.

This may include assessing the consumer's understanding of the following:

- what the product is indicated for;
- the dose and interval;

- when to stop using the product; and
- any potential contraindications, warnings and interactions with other medication.

The labels used in the label comprehension studies should be as close as possible to the final proposed label to be included in the switch submission. Label comprehension studies should include a heterogeneous group of subjects, representative of the target population, that vary in age, sex, underlying medical conditions, concomitant medications and level of literacy. Studies should include individuals who have a low level of literacy as assessed by a validated instrument such as the Rapid Estimate of Adult Literacy in Medicine (REALM) test, the Test of Functional Health Literacy in Adults (TOFHLA) or the Short Test of Functional Health Literacy in Adults in French (Fren-STOFHLA). Proper study design and an appropriately constructed questionnaire are critical for an accurate interpretation of the study results. Note that online questionnaires are not acceptable evidence, due to the increased risk of bias.

The applicant needs to include a comprehensive statistical analysis plan in the study protocol being provided to Health Canada. The applicant should also provide an analysis of both quantitative and qualitative data to support and interpret study findings. Additionally, the applicant should organize the results by age cohorts and literacy levels. Generally, a success rate of 80% is expected for the major communication elements relating to safety and efficacy. These label elements include, but are not limited to, the following:

- indication;
- treatment duration;
- route of administration;
- dose and dosing interval;
- non-medicinal ingredient(s);
- medicinal ingredient(s) and strength(s);
- circumstances requiring the consumer to stop treatment and seek medical advice; and
- risk information including precautions, warnings, contraindications and interactions with other medication or food.

C.2 Self-selection studies

Label comprehension studies do not necessarily predict correct self-selection or the actual way the consumer will use the proposed product. Therefore, self-selection studies are conducted to test whether consumers can apply the label information to their personal medical situations and make correct decisions to use or not use the product.

In self-selection studies, researchers answer the following key questions:

- Can consumers identify the purpose of the product?
- Based on their health conditions, can they demonstrate good judgment about whether the product is right for them?

Self-selection studies therefore assess the ability of consumers to determine whether a product is appropriate for them based on their personal health history and the recommended use(s) of the product, dosing, precautions, warnings and contraindications specified on the proposed product label.

Self-selection studies involve the use of well-planned recruitment and sampling strategies; a well-developed and pre-tested questionnaire; and specifically trained interviewers to ask the questions. Exclusion criteria should be minimal and limited to the inability to speak, read or understand either official language. Additionally, open-ended questions should be asked to assess the reasons subjects make incorrect self-selection decisions. Responses to these questions will guide labelling modifications that may be required to improve self-selection.

As is the case with any study, the applicant should include a comprehensive statistical analysis plan in the protocol for the self-selection study that is being submitting to Health Canada. Additionally, the applicant should provide an analysis of both quantitative and qualitative data to support and interpret study findings.

C.3 Actual use studies

Actual use studies incorporate elements from self-selection and label comprehension studies. These studies are intended to simulate the way consumers will use the proposed products in a "real life" setting.

Observation of study participants in the actual use studies can assist in anticipating what the implications would be of removing a practitioner's involvement in the diagnosis of the condition, the selection of the product and the monitoring of its use. The design and interpretation of the results of actual use studies are complex. These studies provide information about the following:

- consumer compliance and adherence with the product labelling
- safety issues that arise during actual product use

The applicant should consult the Office of Clinical Trials in the TPD to determine if a Clinical Trial Application is required for their actual use studies.

C.4 Human factors studies

When the switch requested pertains to a prescription drug with a medical device or prescription drug-device combination product, human factors studies may be necessary in order to provide evidence of the safety and efficacy of the medical device with the proposed product for the intended use(s) by consumers and in the intended use environments.

Human factors studies:

- assess the ability of the user to understand the packaging and labeling information;
- assess the ability of the user to safely and effectively use the product with the device;
- validate the performance of the device;
- provide information on device design; and
- assess the adequacy of the device-user interface in order to eliminate or mitigate potential user related hazards.

Appendix D: Market experience data

In the context of this guidance document, market experience is knowledge gained about an authorized product once it is being sold. Market experience provides additional information on the safety and effectiveness of a product in a much larger and diverse population than that of a clinical trial.

D.1 Information to be provided

The applicant needs to provide post-market experience information from Canada and other jurisdictions as part of submission for a switch, if available. This information should ideally be related to the proposed NHP or NPD under the same conditions of use, and when that is not available, the information should be presented relative to products with the same medicinal ingredient and similar conditions of use.

Health Canada expects the applicant to provide the following information from Canada and other jurisdictions, if available:

- a summary of adverse reaction data including, if applicable, information from the applicant's own safety databases (e.g., a summary of Canadian Adverse Reaction Reports);
- a summary of the safety signals discussed in Periodic Safety Update Reports (PSURs) and Periodic Benefit-Risk Evaluation Reports (PBRERs);
- a summary of the findings from the applicant's comprehensive review of scientific literature containing safety information;
    - The applicant should include the comprehensive review, the reference articles and the search methodology in the submission package.
- a summary of safety information from any available clinical trials involving the product;
- information on accidental overdose and/or intentional or unintentional misuse;
- a summary of all serious and non-serious medication incidents including near misses, reports of concern (potential errors) and complaints; and
- a summary of any foreign regulatory actions taken with respect to the product's safety, including a summary of available risk communications and/or recalls.

The applicant should analyze the data above to determine whether safety signals differ when the status of the product is prescription vs non-prescription, if applicable.

With respect to adverse reaction information, Health Canada reminds the applicant to do the following:

- The applicant should consult the World Health Organization's Vigibase for information on adverse reactions as well as reporting signals from other international databases and include their findings in their analysis.

- When highlighting adverse reactions reported in clinical trials that have occurred since product authorization, the applicant should also address the comparability of the product tested in the clinical trials to that of the proposed NHP or NPD.

- The applicant should take into account the regulatory requirements and procedures by which adverse reactions are collected in the foreign country to contextualize the data. For example, the applicant should outline whether in the foreign country adverse reaction reporting is voluntary or mandatory and under which circumstances (e.g., only mandatory in hospital settings).

D.2 Additional contextual information for key regulatory jurisdictions to be provided

Health Canada expects the applicant to contextualize the market experience information obtained from other key regulatory jurisdictions (e.g., European Union - European Medicines Agency (EMA), United States – Food and Drug Administration (US FDA)). This contextual information will be helpful in Health Canada's evaluation of the market data provided. To this end, the following details about the product and its regulation in these jurisdictions are necessary:

- foreign product information
- regulatory status
- level of health professional involvement and consumer access
- foreign labelling and other risk mitigation measures
- level of product exposure

The subsections below include further guidance on the difference types of contextual information.

Foreign product information

The applicant should describe the degree of similarity between the foreign product(s) and the proposed NHP or NPD to be marketed in Canada. This includes addressing recommended single and maximum daily dose; duration of use; route of administration; dosage form; and indications in the foreign jurisdiction(s).

Regulatory status

Health Canada expects the applicant to provide information on the regulatory status of the product in key regulatory jurisdictions. That is, the applicant should indicate whether these jurisdictions have classified their product as a prescription drug, non-prescription product, behind-the-counter product, a food supplement, etc.

Level of health professional involvement and consumer access

If there are key regulatory jurisdictions in which the product is not a prescription drug (i.e., has non-prescription status), the applicant should outline the restrictions from all levels of government that pertain to the product's oversight and access. Specifically, the applicant should indicate the level of health professional involvement in the selection and sale of the product. For example, in some key jurisdictions, the product may be non-prescription but can only be obtained through consultation with a pharmacist or naturopath. The applicant should also indicate how accessible the product is for purchase. For example, in some key regulatory jurisdictions, the product may be freely available for purchase in all retail locations, while in others, its sale may be restricted only to pharmacies or hospital pharmacies.

Labelling and other risk mitigation measures

The applicant should highlight the differences between their proposed labelling and the approved foreign product labelling if the product is non-prescription in any of the key regulatory jurisdictions.

The applicant should also present information about any specific risk mitigation measures in place for the product's use in any other countries and any significant safety-related changes highlighted in PBRER reports.

Level of product exposure

The applicant should indicate, when applicable, the length of time the product has been marketed and estimate the product exposure in the key regulatory jurisdictions.

Appendix E: Template for the PDL Principles and Factors Assessment

To apply for a switch, complete the PDL Principles and Factors Assessment using the headers of all the principles and the factors as shown below in the template. Include the assessment in Module 1.0.7 of the SNDS or NDS.

When completing the template, ensure the following:

- Each section contains the summary of evidence and the rationale to show that the indicated principle or factor does not apply to the proposed NHP or NPD.
- Each section includes a reference to the location of the full data in your submission package, where applicable.
- No section is left blank or only contains "N/A"; otherwise, Health Canada may issue a Screening Rejection Letter or Screening Deficiency Notice.

Table 2: Template

PDL Principles and Factors Assessment
Principle 1: Supervision by a practitioner is necessary (i) for the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in respect of which the drug is recommended for use, or (ii) to monitor a disease, disorder or abnormal physical state, or its symptoms, in respect of which the drug is recommended for use, or to monitor the use of the drug.
[The applicant puts the rationale and evidence related to Principle 1 here.]
Factor 1.1 The drug is used in the treatment of a serious disease not easily diagnosed by the public.
[Insert text here.]
Factor 1.2 The use of the drug may mask other diseases.
[Insert text here.]
Factor 1.3: Practitioner supervision is necessary for treatment and/or monitoring.
[Insert text here.]

Factor 1.4: The use of the drug requires complex or individualized instructions.
[Insert text here.]
Factors 1.5: Practitioner expertise is necessary to administer the drug or oversee the drug's administration.
[Insert text here.]
Factor 1.6: The drug has a narrow margin of safety.
[Insert text here.]
Factor 1.7: At normal therapeutic dosage levels, the drug has potential or is known to cause serious adverse reactions or serious interactions with food or other drugs.
[Insert text here.]
Factor 1.8: The drug has dependence and/or addiction potential.
[Insert text here.]
Principle 2: The level of uncertainty respecting the drug, its use or its effects justifies supervision by a practitioner.
[Insert text here.]
Factor 2.1: There is limited market experience with the use of the drug.
[Insert text here.]
Principle 3: Use of the drug can cause harm to human or animal health or a risk to public health and the harm or the risk can be mitigated by a practitioner's supervision.
[Insert text here.]

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Factor 3.1: There is potential for harm to public health.
[Insert text here.]
Factor 3.2: There is potential for abuse or diversion leading to harmful non-medical use.
[Insert text here.]

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1366 # Appendix F: Endnotes

[1] For more information on exceptions, refer to the guidance document "Determining Prescription Status for Human and Veterinary Drugs". Note that the process for the assessment of switches is not the same as the process for assessing the need for exceptions to prescription status.

[2] NHPR section 2(2): " For the purposes of these Regulations, a substance or combination of substances or a traditional medicine is not considered to be a natural health product if its sale, under the *Food and Drug Regulations*, is required to be pursuant to a prescription when it is sold other than in accordance with section C.01.043 of those Regulations."

[3] Refer to Appendix A for definitions of "dependence" and "addiction" as used herein. Health Canada notes that the American Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has moved away from using the term addiction and has replaced the previous diagnostic categories of "substance dependence" and "substance abuse" with "substance use disorders", suggesting that use of these terms is evolving. Health Canada has opted to retain the terms "dependence" and "addiction" herein because post-marketing adverse reactions collected by International Conference on Harmonisation (ICH) members are categorized based on Medical Dictionary for Regulatory Activities (MedDRA) terminology, which continues to use these terms. As adverse reactions data is central to switches, Health Canada wants to ensure that industry is clear on the search terms to use when collecting data for submissions.

[4] Terminology in this field is evolving. The term "abuse" has been retained for the reasons outlined in endnote 3. Refer to Appendix A for definitions of "abuse" as used herein.

[5] The Government of Canada is proposing the use of new terminology relative to substance use to minimize stigma and discrimination. Terms such as substance use disorder, problematic substance use and dependence are favoured over substance abuse or substance misuse. More information on the Government of Canada's guide to terminology can be found in the document "Stigma: Why Words Matter" (https://www.canada.ca/en/health-canada/services/publications/healthy-living/stigma-why-words-matter-fact-sheet.html).

[6] For guidance on the assessment of abuse potential of substances, refer to "Notice: Guidance on the Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity" (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/clinical-assessment-abuse-liability-drugs-central-nervous-system.html) which outlines Health Canada's expectations.

[7] The review should include an extensive survey of various sources of information (published peer-reviewed literature; grey literature such as reports from international health organizations and media reports; etc.). In addition, Health Canada expects the applicant to provide a list of all known street names of the product or its active ingredient(s) and include these terms in the applicant's search. The applicant's search strategy should be included in the response.

[8] For example, the US FDA has developed the following documents:

- "Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products" (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf) (2010)

- "Guidance for Industry: Self-Selection Studies for Nonprescription Drug Products" (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm272122.pdf) (2013)

- "Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development" (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm484345.pdf) (2016)