Health Canada Santé Canada

Guidance Document: Switching from prescription to non-prescription status

Date adopted	2014-05-07
Revised date	2024-08-14
Effective date	2024-10-13

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 :
Lignes directrices : Changement de statut de vente de « sur ordonnance » à « sans ordonnance »

To obtain additional information, please contact:

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

Publication date: August 2024

Cat.: H164-379/2024E-PDF
ISBN: 978-0-660-72823-0
Pub.: 240377

Document change log

Date	Change	Location	Nature of and/or reason for change
August 14, 2024	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 product to natural health product; • clarify evidence requirements related to the Prescription Drug List principles and factors; and • provide guidance to companies on completing a new template that is being requested as part of submissions for switches. The new title for the guidance document is *Switching from Prescription to Non-Prescription Status*.

Foreword

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

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

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

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

Table of Contents

1. Introduction 9
2. Scope and application 9
3. Background 10
    3.1 Regulatory framework 10
    3.2 Prescription status 10
    3.3 Removal of medicinal ingredients from the PDL 11
    3.4 Requests for switches 12
    3.5 Provincial and territorial decisions 12
4. Policy statements 13
5. Determining which switch process applies 14
6. Understanding the switch processes 14
    6.1 Process 1: A successful Rx to NPD switch 15
    6.2 Process 2: A successful Rx to NHP switch 17
    6.3 Process 3: The assessment of submission leads to a negative decision 20
7. Requesting a pre-submission meeting (all switches) 21
8. Assembling the NDS or SNDS (all switches) 22
    8.1 Evidence of safety, efficacy and quality 24
        8.1.1 The applicant proposes a switch of an authorized prescription drug product without changes 24
        8.1.2 The applicant proposes the switch of an authorized prescription drug product that includes additional changes to its conditions of use 24
        8.1.3 The applicant proposes a switch and does not own a related authorized prescription drug product 25
        8.1.4 Outdated data 25
        8.1.5 Further information 25
    8.2 Principles and factors assessment for inclusion in the NDS or SNDS 25
    8.3 Labelling for inclusion in the NDS or SNDS 25
9. Formatting and filing an NDS or SNDS (all switches) 26
10. Paying fees (all switches) 26
11. Health Canada screens the submission for deficiencies 27

12. Health Canada assesses the NDS or SNDS 27
12.1 Assessment 27
12.2 Internal decision-making process for PDL amendments 27
13. Health Canada consults the public 28
14. Health Canada announces its intention to amend the PDL 28
14.1 Proceed 28
14.2 Modify 29
14.3 Stop 29
15. Filing the PLA (Rx to NHP switches only) 30
16. Health Canada verifies the PLA (Rx to NHP switches only) 30
17. Health Canada amends the PDL 31
18. Health Canada issues the market authorization 31
18.1 Rx to NPD switches 31
18.1.1 Situations requiring a new DIN 31
18.1.2 Market authorization (Rx to NPD switch) 31
18.2 Rx to NHP switches 32
18.2.1. Resolution of the NDS or SNDS 32
18.2.2 Market authorization (Rx to NHP switch) 32
19. Additional information 33
19.1 Timelines for the switch process 33
19.2 Reconsiderations 34
19.3 Switches involving products with multiple medicinal ingredients on the PDL 34
19.4 Switches involving medical devices 34
19.5 GMP, DEL and SL requirements 35
19.5.1 Rx to NPD switches 35
19.5.2 Rx to NHP switches 36
19.6 Intellectual property 37
19.7 The impact of a switch on other prescription drug products 37
19.8 Other companies interested in marketing products given the PDL amendment 37

20. The PDL principles and factors assessment 38
Principle 1: Supervision by a practitioner is necessary 38
Factor 1.1: The drug is used in the treatment of a serious disease not easily diagnosed by the public 38
Factor 1.2: The use of the drug may mask other diseases 40
Factor 1.3: Practitioner supervision is necessary for treatment and/or monitoring. 40
Factor 1.4: The use of the drug requires complex or individualized instructions. 42
Factors 1.5: Practitioner expertise is necessary to administer the drug or oversee the drug's administration 42
Factor 1.6: The drug has a narrow margin of safety 43
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 44
Factor 1.8: The drug has dependence and/or addiction potential 45
Principle 2: The level of uncertainty respecting the drug, its use or its effects justifies supervision by a practitioner 46
Factor 2.1: There is limited market experience with the use of the drug 47
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 47
Factor 3.1: There is potential for harm to public health 47
Factor 3.2: There is potential for abuse or diversion leading to harmful non-medical use. 47
21. Consumer use studies 49
21.1 Label comprehension studies 50
21.2 Self-selection studies 51
21.3 Actual use studies 52
21.4 Human factors studies 52
22. Market experience 53
22.1 Information to be provided 53
22.2 Additional contextual information to be provided 54

Appendix 1: Contact information 57
Appendix 2: Glossary 58
a) Acronyms 58
b) Definitions 59
c) Dependence, addiction, misuse and abuse terminology 61
Appendix 3: Template for the PDL Principles and Factors Assessment 62

1. Introduction

The purpose of this document is to provide guidance for companies that wish to:

- request a "switch" of a medicinal ingredient for specific conditions of use from prescription (Rx) to non-prescription status; and
- file submissions/applications for a market authorization for their proposed product.

Following a successful switch process, the proposed product will have non-prescription status. That is, Health Canada authorizes the proposed product as either a Non-prescription Drug (NPD) or a Natural Health Product (NHP). These kinds of switches are referred to as an "Rx to NPD switch" and "Rx to NHP switch", respectively.

In this document, the term "applicant" refers to the company that is the applicant or sponsor that is initiating the request for the switch.

Contact information is found in Appendix 1 and definitions of other key terms are in Appendix 2.

This document provides applicants with the following information:

- Advice on determining whether the proposed non-prescription status product would be an NPD or NHP;
- An overview of the federal processes for Rx to NPD and Rx to NHP switches;
- Details on each step of the process;
- Direction on evidence to be included in submissions and applications; and
- Guidance on related topics such as applicable requirements in terms of Good Manufacturing Practices (GMP), Site Licences (SLs) and Drug Establishment Licences (DELs) for those carrying out the manufacturing and other activities relative to the proposed product.

2. Scope and application

This guidance document applies to applicants requesting:

- a market authorization for their proposed product; and
- the switch of a medicinal ingredient for human use from prescription to non-prescription status such that the proposed product could be sold as an NPD or an NHP.

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

- switch submissions for biologic or radiopharmaceutical products;
- switch submissions for veterinary drugs; and
- requests for exceptions to the Prescription Drug List (PDL) (e.g., naloxone when indicated for emergency use for opioid overdose and the flu vaccine).

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

For information on exceptions, consult the guidance document Determining Prescription Status for Human and Veterinary Drugs. Note that the process for assessing switches is not the same as the process for assessing the need for exceptions to prescription status.

3. 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.

3.1 Regulatory framework

Prescription drug products, that is, products 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 subsection 2(2) of the NHPR.

Subsection 2(2) states: "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."

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

3.2 Prescription status

Products with federal prescription status have at least one medicinal ingredient listed in the PDL and are only obtained by the public through a prescription. The PDL is a web-based administrative list established by the Minister under the authority of the *Food and Drugs Act*.

The situation is somewhat different for ingredients that are controlled substances under the *Controlled Drugs and Substances Act* (CDSA) (i.e., ingredients listed in the schedules to the *Act* and its regulations). When these ingredients are restricted to prescription-only status under the CDSA, they are not listed on the PDL. However, drugs containing controlled substances still must meet the requirements of the FDR to be sold lawfully for therapeutic purposes.

Health Canada determines if a product or a medicinal ingredient under specific conditions of use requires the oversight of a practitioner for its safe and appropriate use. To make this determination, Health Canada relies on established principles and associated factors. The principles governing prescription status are broad and include the concepts detailed in the factors.

The overarching principles are stated in section C.01.040.3 of the FDR. They are further described, along with the factors, in the guidance document Determining Prescription Status for Human and Veterinary Drugs.

When one or more of the PDL principles and associated factors applies to a product (i.e., to a medicinal ingredient under specific 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 PDL, with the exception noted for controlled substances.

3.3 Removal of medicinal ingredients from the PDL

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

- Over time, with extended use of a company's marketed prescription drug product, additional information (such as post-market safety data) becomes known, reducing uncertainties about the product. The company may then wish to make the case to Health Canada that this additional information supports the safe and effective use of its product without practitioner oversight. To do so, the company files a submission for a market authorization for its proposed NPD or NHP and requests the switch. Most switches occur in this context.

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

The majority of switches removing a medicinal ingredient (or a medicinal ingredient for specific conditions of use) 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 that supports the use of a medicinal ingredient in an NPD or an NHP. In both cases, an assessment of the applicability of the PDL principles and factors remains integral to the decision-making process.

Note: In Canada, a successful switch process, which includes the removal of a medicinal ingredient (or a medicinal ingredient for certain conditions of use) from the PDL, may result in other companies' similar products no longer having prescription status. For more information, refer to section 19.7.

3.4 Requests for switches

For Rx to NPD switches:

- The applicant files the request as part of a New Drug Submission (NDS) or a Supplement to a New Drug Submission (SNDS).

For Rx to NHP switches:

- The applicant files the request as part of an NDS or an SNDS and, if that submission is successful, the applicant then provides a Product Licence Application (PLA). The submissions begin under the FDR in light of subsection 2(2) of the NHPR.

Section 8 of this guidance document outlines when an NDS versus SNDS is required. Note that an applicant who wishes to switch their existing prescription drug product that was authorized under Division 1 of Part C of the FDR to non-prescription status must apply in accordance with Division 8 of Part C of the FDR (i.e., NDS). (The change to "sale in the non-prescription setting" is considered to be a change in the conditions of use of a drug. In most instances, this condition of use will not have established safety and effectiveness. Therefore, the proposed product would meet the definition of a "New Drug".)

3.5 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. They do so through the regulation of health care professionals and health care establishments.

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 federally imposed 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 of protecting and promoting 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 NPD or NHP.

4. Policy statements

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

- Health Canada verifies the applicability of the PDL principles and factors to the product as part of the assessment of all applications and submissions under the FDR and NHPR, where the medicinal ingredient(s) under the specified conditions of use have not previously been authorized.

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

- If none of the PDL principles and factors apply to a product, it would typically have non-prescription status either as an NPD or an NHP.

- 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 to determine whether the PDL should be amended is a product-based decision. This is explained by the fact that it is very difficult to assess all the PDL principles and factors without knowing 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 and the proposed product has a positive benefit-risk profile as a non-prescription status product, Health Canada initiates the process to amend the PDL.

5. Determining which switch process applies

The applicant needs to assess whether their proposed product ought to be classified as an NPD or NHP, if the switch was successful. This determination will help the applicant identify which process in this guidance document applies to their situation:

- the Rx to NPD switch process or
- the Rx to NHP switch process.

The applicant should verify whether, following a successful switch, the proposed product would meet the definition of an NHP as set out in subsection 1(1) of 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, tools such as the Natural Health Products Ingredients Database (NHPID) can also be consulted for information on current ingredient classifications and restrictions.

Applicants can discuss their proposed product's classification with Health Canada prior to filing (e.g., in a pre-submission meeting) to hear what Health Canada's preliminary thoughts on a likely classification (NPD or NHP).

Regardless of whether this issue is dealt with in a pre-submission meeting, Health Canada will make the final decision on the classification once the submission is in review and Health Canada has access to the full information. If, at this time, Health Canada disagrees with the classification proposed by the applicant, Health Canada will discuss this with the applicant as well as how the switch process will then change.

The remaining sections of this document are based on the assumption that there are no issues regarding classification of the product after the PDL amendment.

6. Understanding the switch processes

This section provides an overview of the federal switch processes for Rx to NPD and Rx to NHP switches. Section 6.1 and 6.2 provide a stepwise description of the overall processes for successful switches. Flowcharts 1 and 2 visually depict this information. In section 6.3, Health Canada discusses unsuccessful switches.

Following the overview of these processes, sections 7 to 19 provide detailed guidance on the steps of the processes.

6.1 Process 1: A successful Rx to NPD switch

The following is the main process for an Rx to NPD switch that leads to Health Canada issuing or updating a market authorization:

1) Optional (but recommended): The applicant assembles the pre-submission meeting data package for Health Canada and requests a pre-submission meeting. (Refer to section 7 for further details.)

2) Optional (but recommended): 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 and may identify whether there are any classification issues that could arise during review.

3) The applicant assembles the final version of the NDS or SNDS including the necessary data on safety, efficacy/effectiveness and quality; product labelling; and the PDL Principles and Factors Assessment. (Section 8)

4) The applicant files the NDS or SNDS with Health Canada in the appropriate format and pays the applicable fees. (Sections 9 and 10)

5) Health Canada screens the submission for completeness. If no screening deficiencies are identified, the submission proceeds into review. (Section 11)

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 outlining its proposal to remove the medicinal ingredient or the medicinal ingredient for certain conditions of use from the PDL. Health Canada also puts the NDS or SNDS on "switch hold". (Section 13)

8) After a 75-day PDL consultation period, Health Canada reviews the comments received from the public and other stakeholders.

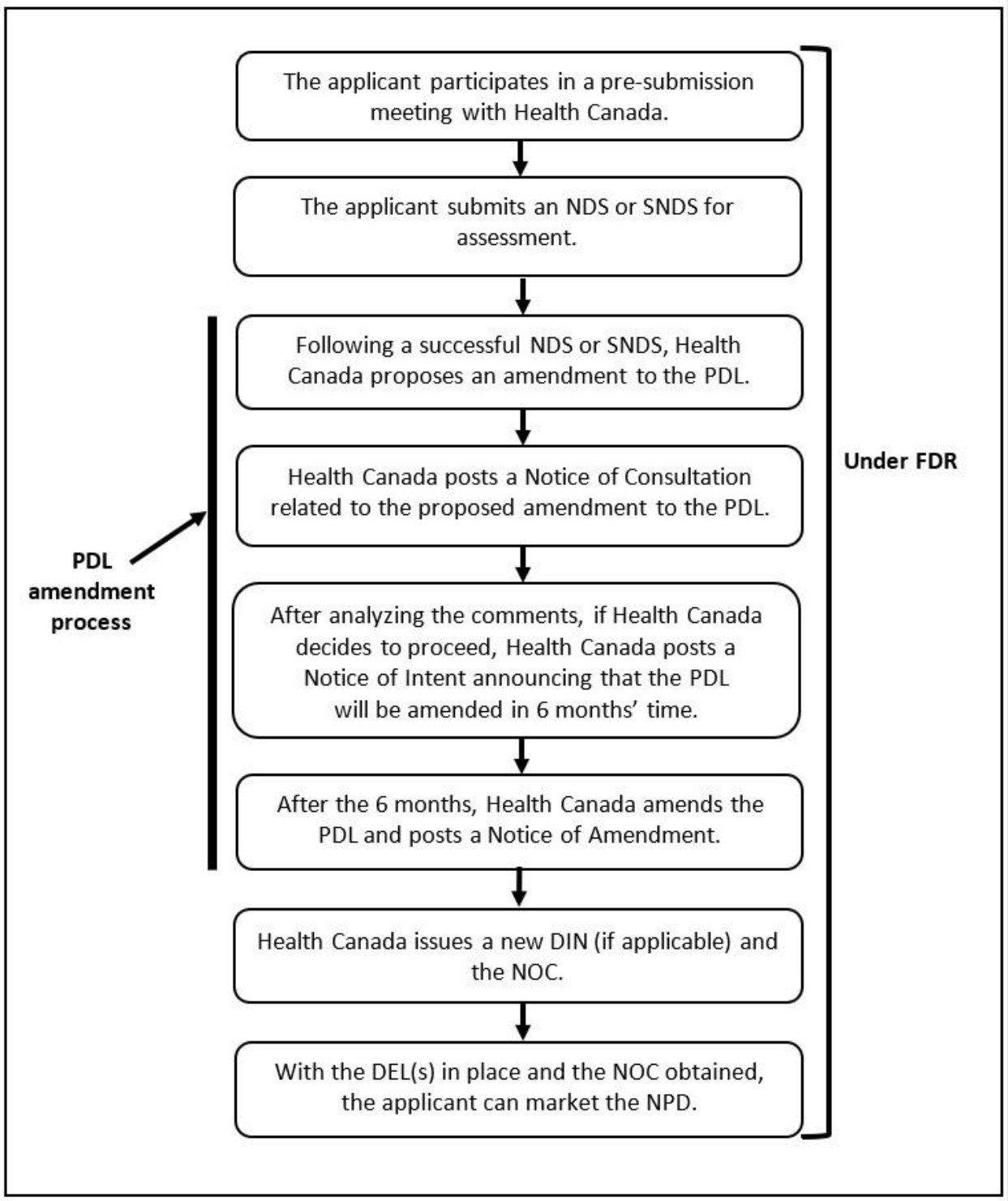
9) After analyzing the comments, if Health Canada decides to proceed, Health Canada posts a Notice of Intent announcing that the amendment to the PDL will occur in six months' time. (Section 14)

10) After the six-month transition period, Health Canada amends the PDL and posts a Notice of Amendment. (Section 17)

11) Health Canada issues a Drug Identification Number (DIN), if applicable, and a Notice of Compliance (NOC) for the NPD. (Section 18.1)

12) If in addition to the NOC, the appropriate DEL(s) have been issued to those conducting licensable activities related to the product (e.g., fabricate), the product can be sold in Canada in accordance with the FDR. (Section 19.5.1)

Flowchart 1: A successful Rx to NPD switch



6.2 Process 2: A successful Rx to NHP switch

A successful Rx to NHP switch moves the proposed product from the FDR to the NHPR. An Rx to NHP switch must begin under the FDR in light of subsection 2(2) of the NHPR. The proposed product can only move to the NHPR if the NDS or SNDS results in removal from the PDL of the medicinal ingredient or medicinal ingredient for the relevant conditions of use.

However, to facilitate market access, Health Canada is willing to contemplate whether the PLA would meet the NHPR requirements prior to the PDL amendment, provided the applicant follows the process set out in this guidance document. Note: Decisions under the NHPR can only be made after the PDL is amended and the proposed product becomes subject to these regulations.

The following is the main process for an Rx to NHP switch that leads to a market authorization being issued. (Note that the first eight steps of this process are the same as those for an Rx to NPD switch.)

1) Optional (but recommended): The applicant assembles the pre-submission meeting data package for Health Canada and requests a pre-submission meeting. (Refer to section 7 further details.)

2) Optional (but recommended): 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 and may identify whether there are any classification issues that could arise during review.

3) The applicant assembles the final version of the NDS or SNDS including the necessary data on safety, efficacy/effectiveness and quality; product labelling; and the PDL Principles and Factors Assessment. (Section 8)

4) The applicant files the NDS or SNDS with Health Canada in the appropriate format and pays the applicable fees. (Section 9 and 10)

5) Health Canada screens the submission for completeness. If no screening deficiencies are identified, the submission proceeds into review. (Section 11)

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 outlining its proposal to remove the medicinal ingredient or the medicinal ingredient for certain conditions of use from the PDL. Health Canada also puts the NDS or SNDS on "switch hold". (Section 13)

8) After a 75-day PDL consultation period, Health Canada reviews the comments received from the public and other stakeholders.

9) After the analyzing the comments, if Health Canada decides to proceed, Health Canada posts a Notice of Intent announcing that the amendment to the PDL will occur in six months' time. Then Health Canada issues the applicant a Notification of Potential Reclassification. (Section 14)

10) The applicant submits a PLA in accordance with the NHPR reflecting the information from NDS or SNDS in anticipation of the PDL amendment. (Section 15)

11) Health Canada verifies the PLA. (Section 16)

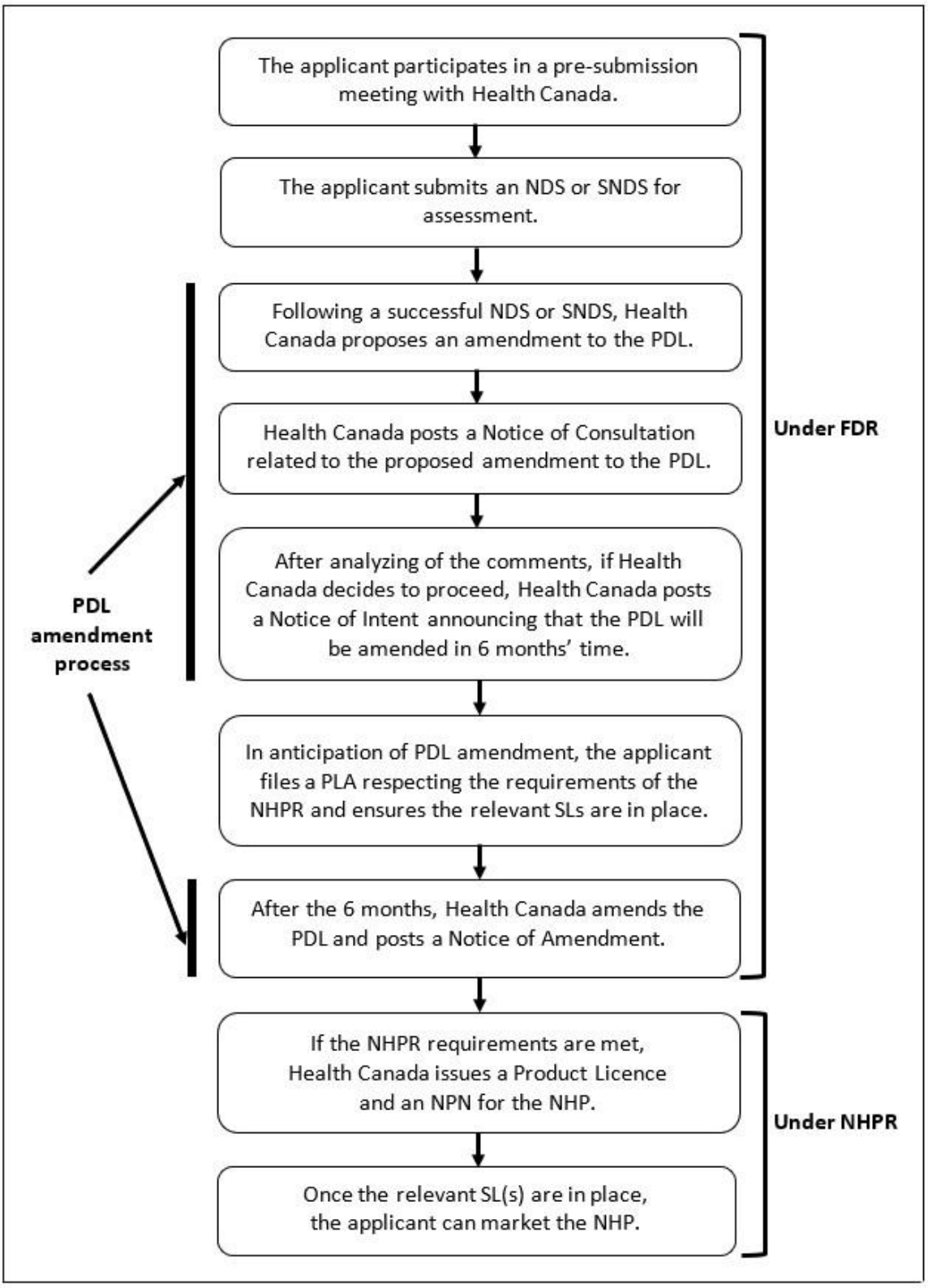
12) After the six-month transition period, Health Canada amends the PDL and posts a Notice of Amendment. (Section 17)

13) Health Canada issues the applicant a Notification of Reclassification which outlines that there is no legal authority to continue with the assessment of the NDS or SNDS because the product is no longer a drug under the FDR. (Section 18.2.1)

14) If the applicant has satisfied the requirements of the NHPR, Health Canada also issues the Product Licence and the Natural Product Number (NPN) for the product. (Section 18.2.2)

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 19.5.2)

Flowchart 2: A successful Rx to NHP switch



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

Not all switch submissions will be successful. Process 3 outlines what would occur during the NDS or SNDS assessment if the applicant is unsuccessful. This is also illustrated in Flowchart 3.

Process 3:

1) Health Canada issues a Notice of Deficiency (NOD) or a Notice of Non-Compliance (NON) if the applicant has not demonstrated in the NDS or SNDS that the proposed product meets the requirements of the FDR. This includes those related to the product's:

    - safety, efficacy and quality; and
    - labelling.

    The applicant must successfully demonstrate that the PDL principles and factors do not apply to the proposed product with its proposed labelling. If the applicant cannot successfully demonstrate this, the proposed product could only be authorized as a prescription drug. However, because the applicant included non-prescription labelling in the submission, it would not meet the labelling requirements for prescription drugs. Thus, the proposed product cannot be authorized as a prescription drug based on this submission.

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

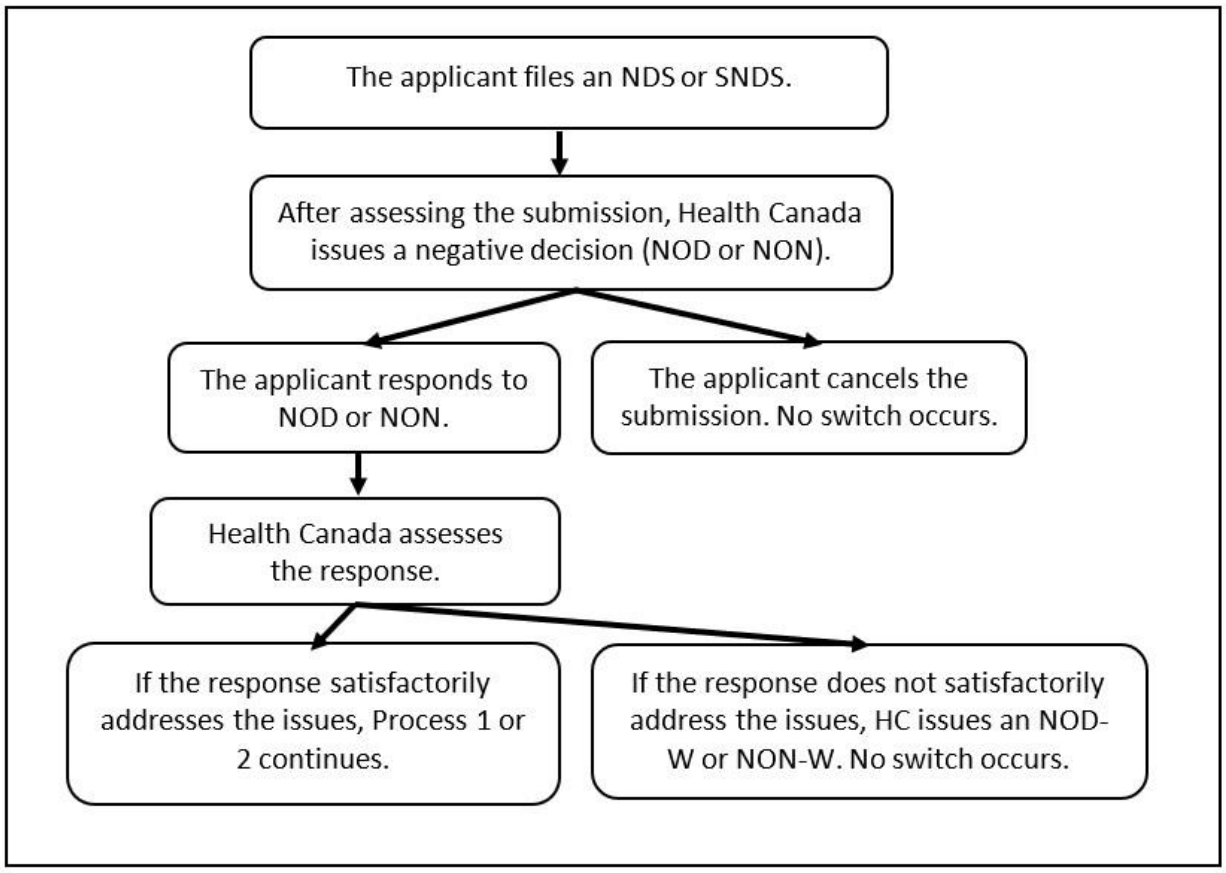
3) If the applicant responds, Health Canada assesses the response.

    - 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.

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

For more information on NODs, NONs, NOD-Ws and NON-Ws, consult the guidance document Management of Drug Submissions and Applications.

Flowchart 3: The assessment of the submission leads to a negative decision



Some other examples of where a switch may fail include:

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

7. Requesting a pre-submission meeting (all switches)

Before filing an NDS or an SNDS, the applicant is strongly encouraged to request a pre-submission meeting with Health Canada.

This is an opportunity for the applicant to ask questions related to the adequacy of their evidence in support of the proposed switch and the request for market authorization. For example, before undertaking clinical trials or consumer use studies, the applicant is encouraged to meet with Health Canada. Pre-submission meetings are also an opportunity to discuss Risk Management Plans (RMPs), if relevant to the switch.

Note that it is possible for a company to have more than one pre-submission meeting.

For information on requesting pre-submission meetings for an NDS or SNDS, consult:

- Section 7 of the guidance document Management of Drug Submissions and Applications; and
- the web page Common Electronic Submissions Gateway.

For Rx to NPD switches, in the pre-submission meeting, the applicant will meet with staff from:

- the Natural and Non-prescription Health Products Directorate (NNHPD) who assess NPDs;
- the Marketed Health Products Directorate; and
- other areas (e.g., clinical bureaus within the Pharmaceutical Drugs Directorate (PDD)) when needed based on the nature of the product and the proposed switch.

For Rx to NHP switches, in the pre-submission meeting, the applicant will meet with staff from:

- the NNHPD who assess NPDs;
- the NNHPD who assess NHPs;
- the Marketed Health Products Directorate; and
- other areas (e.g., clinical bureaus within the PDD) when needed based on the nature of the product and the proposed switch.

For all switches, staff from the NPD assessment area will lead pre-submission meetings.

8. Assembling the NDS or SNDS (all switches)

Submission type

The applicant assembles an NDS or an SNDS requesting the switch and the market authorization for the proposed product. The type of submission required depends on the specific situation. Refer to Table 1 for help in determining which type of submission to provide.

Table 1: Determining submission type

Product to be switched	Situation	Type of submission to file
None, as no authorized prescription drug product exists	The applicant's proposed switch is not related to a currently authorized prescription drug product. However, the switch relates to a medicinal ingredient already on the PDL.	File an NDS as per section C.08.002 of FDR.
A "Division 1" prescription drug product	The proposed switch relates to the applicant's currently authorized Division 1 prescription drug product.	File an NDS as per section C.08.002 of the FDR as, in most instances, this switch represents a change in the conditions of use in Canada (namely, the sale of the product in a non-prescription setting without practitioner oversight) for which safety and effectiveness have not been established.
A "Division 8" prescription drug product	(a) If the switch of the applicant's prescription drug product is successful, there will be two products on the market: • the authorized Division 8 prescription drug product for some of its original conditions of use; and • the proposed NPD or NHP for other conditions of use.	File an NDS, as per section C.08.002 of FDR, for the proposed NPD or NHP, as it will be an additional product introduced to the market. (Future changes to the NPD or NHP can be tracked against the new authorization separate from the prescription drug market authorization.) If the switch is successful, the applicant will also need to file an SNDS for their authorized prescription drug product to reflect that some of its conditions of use have been removed.
	(b) If the switch of the applicant's prescription drug product is successful, the authorized Division 8 prescription drug product (with or without changes) will become an NPD or NHP. In other words, there would be no prescription drug product on the market at the end of the process.	File an SNDS, as per section C.08.003 of the FDR.

Submission content

In the NDS or SNDS, the applicant includes:

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

8.1 Evidence of safety, efficacy and quality

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

8.1.1 The applicant proposes a switch of an authorized prescription drug product without changes

Generally, in this type of switch, the product's safety, efficacy and quality have already been demonstrated in the submission(s) for the authorized prescription drug product. (The only condition of use that changes is the context in which the product is going to be sold.)

At a minimum, the applicant provides:

- the most recent Health Canada-authorized Product Monograph or Prescribing Information for the prescription drug product;
- a Product Monograph for the proposed product;
- any available post-market information (refer to section 22);
- if available, any more recent clinical trial data investigating the safety of the product or medicinal ingredient under similar conditions of use along with the appropriate clinical overviews/summaries; and
- consumer use studies.

8.1.2 The applicant proposes the switch of an authorized prescription drug product that includes additional changes to its conditions of use

The conditions of use of an authorized prescription drug product are specified in the Product Monograph or Prescribing Information. If the applicant proposes changes to the conditions of use and/or the chemistry and manufacturing as part of the switch, additional evidence will be required.

Examples of how the proposed NPD or NHP could differ from the authorized prescription drug product include changes to the indication, maximum single and/or daily dose, strength of the dosage unit, route of administration, dosage form, formulation, manufacturing, and target population.

The nature of the changes to the product and the conditions of use will determine what supportive evidence is required. For example, a new indication would require evidence from Phase III clinical trial(s). If applicable, the applicant can build on the data previously submitted to Health Canada for the authorized prescription drug product.

The applicant is encouraged to seek guidance from Health Canada on the need for and scope of the data that would be required.

8.1.3 The applicant proposes a switch and does not own a related authorized prescription drug product

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

8.1.4 Outdated data

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

8.1.5 Further information

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

- the applicable guidance documents on the web page Guidance Documents – Applications and submissions – Drug products; and
- Health Canada (e.g., in a pre-submission meeting).

8.2 Principles and factors assessment for inclusion in the NDS or SNDS

When completing the PDL Principles and Factors Assessment, the applicant should follow the guidance provided in sections 20 to 22. This is key for a successful switch.

The applicant should use the template for the assessment document found in Appendix 3 and include the completed assessment in the NDS or SNDS.

8.3 Labelling for inclusion in the NDS or SNDS

For both Rx to NPD switches and Rx to NHP switches, the applicant follows the requirements regarding labelling of NPDs when preparing the labels for inclusion in the NDS or SNDS. This includes providing a Canadian Product Monograph.

Consult the relevant documents on labelling and Product Monographs.

As discussed in section 21, 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 ensure 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, consult the guidance document Labelling Requirements for Non-prescription Drugs.

For Rx to NHP switches, the applicant should include a Product Facts Table in their consumer use studies and in the NDS or SNDS, if the Product Facts Table is required on the final NHP label. For information on Product Facts Table requirements, flexibilities and exemptions, consult the guidance document Labelling of Natural Health Products.

9. Formatting and filing an NDS or SNDS (all switches)

In terms of the format of the submission, the applicant should follow the instructions in the guidance document Management of Drug Submissions and Applications.

Applicants should also include 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 a prescription drug product that is being switched and it was authorized as the result of a paper submission, Health Canada encourages the applicant to re-submit electronically any relevant evidence from the earlier submission(s) in their switch submission. This will facilitate the review.

For more information on filing, consult:

- the web page Common Electronic Submission Gateway; and
- the guidance document Management of Drug Submissions and Applications.

10. Paying fees (all switches)

All applicants pay cost-recovery fees for the assessment of the information submitted in their NDS or SNDS.

This includes applicants seeking an Rx to NHP switch, which must begin under the FDR in light of subsection 2(2) of the NHPR and can only move to the NHPR if the NDS or SNDS results in the medicinal ingredient being removed from the PDL.

Note that **the content** of the NDS and SNDS 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 as well as chemistry and manufacturing data but 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*.

For more information on fees, fee categories and fee mitigation measures, consult the relevant sections of the guidance document Guidance on evaluation fees for human drugs and disinfectants.

11. Health Canada screens the submission for deficiencies

Health Canada screens submissions and if there are deficiencies, issues the applicant a Screening Deficiency Notice (SDN). For more information, consult the guidance document Management of Drug Submissions and Applications.

12. Health Canada assesses the NDS or SNDS

12.1 Assessment

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 requirements of the FDR for market authorization; and
- the PDL principles and factors do not apply to the product.

12.2 Internal decision-making process for PDL amendments

If the applicant has successfully demonstrated the items listed in section 12.1, the department's scientific staff will propose to the Prescription Drug Status Committee (PDSC) that the PDL be amended for the switch.

The PDSC is an internal committee of scientific and medical experts. Its role is to make recommendations on all proposed PDL amendments to the Director General (DG) of the PDD who has the delegated authority from the Minister of Health for decisions on amendments to the PDL.

The committee's core members are from the NNHPD, the Marketed Health Products Directorate, the PDD, the Veterinary Drugs Directorate and the Biologic and Radiopharmaceutical Drugs Directorate. Members from other directorates participate as needed.

If the PDSC agrees with the proposal to amend the PDL, it recommends this course of action to the DG of PDD. The DG makes the final decision on initiating the process for the PDL amendment for the switch, taking into consideration the recommendations of the PDSC.

13. Health Canada consults the public

If the DG endorses the switch proposal, the amendment process begins. This includes a consultation as required by section C.01.040.4 of the FDR. (For more information on the PDL and the PDL amendment process , consult the document Questions and Answers - Prescription Drug List.)

For switches, Health Canada consults the public and other stakeholders on the proposed amendment to the PDL. Health Canada does this by posting a Notice of Consultation on the Government of Canada website.

In this notice, Health Canada outlines the proposed amendment to remove the medicinal ingredient or the medicinal ingredient for certain conditions of use from the PDL. For example, a medicinal ingredient could be removed from the PDL for only some indications or at lower doses. The notice also includes the rationale for the switch, the conditions of use and a list of affected products.

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. The reason for this is that until the PDL is modified:

- the product would still be considered a prescription drug and
- the Minister would not be able to conclude that the NPD labelling, etc., meet the FDR requirements for market authorization.

14. Health Canada announces its intention to amend the PDL

After the 75-day 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 with the proposed amendment;
- modify the proposed amendment; or
- no longer pursue the proposed amendment.

14.1 Proceed

If the results of the analysis support a decision to proceed with the amendment process, Health Canada publishes a Notice of Intent. This notice specifies the date, six months later, when the amendment of the PDL will occur. The six-month transition period is a delayed implementation period in accordance with the international Technical Barriers to Trade (TBT) Agreement.

The transition period also provides market authorization holders of other affected products with time to comply with the upcoming new regulatory requirements (e.g., revised labelling). For more details, refer to section 19.7.

For Rx to NHP switches:

- In addition to publishing the Notice of Intent, Health Canada sends the applicant a Notification of Potential Reclassification. This notice explains that should the PDL amendment occur, their proposed product would no longer fall under the FDR. Upon receiving this notice, if the applicant has concerns about the potential reclassification, they should share them with Health Canada.

- Applicants will also receive a Notice of Reclassification to remind them of this change in classification following the PDL amendment, should it occur. Refer to section 18.2.1 for further details.

14.2 Modify

If the proposal needs to be modified, depending on the nature of the modification, Health Canada either:

- continues the PDL amendment process with a modified version of the proposed amendment; or
- conducts a new consultation.

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 before publishing a Notice of Intent or a new Notice of Consultation.

14.3 Stop

If the analysis results in Health Canada deciding not to pursue the amendment, Health Canada:

- communicates this decision to the applicant; and
- issues a notice to the public indicating that Health Canada will not amend the PDL.

Note: The next sections of the document are for the scenario where Health Canada has decided to proceed with the PDL amendment.

15. Filing the PLA (Rx to NHP switches only)

After Health Canada posts the Notice of Intent, the applicant provides a PLA to obtain a NHP Product Licence and an NPN. This can be either during or after the six-month transition period, as Health Canada is willing to contemplate whether the PLA would meet the NHPR requirements prior to the PDL amendment. However, decisions under the NHPR can only be made after the PDL is amended and the NHPR apply to the product.

The applicant provides a PLA as outlined in Natural Health Products Management of Applications Policy. There are currently no fees for the assessment of the PLA. The cost-recovery program for NHPs is under development.

The applicant completes the web-based PLA form (including the label). This involves accurately reflecting the information in the latest version of the labelling (including the Canadian Product Monograph) agreed to by Health Canada during the NDS or SNDS assessment.

The applicant should neither resubmit the evidence that was submitted as part of the NDS or SNDS nor resubmit the PDL Principles and Factors Assessment. This information, already with Health Canada, will be considered as part of the PLA.

Instead, the applicant indicates in the cover letter of the PLA that evidence in support of the NHP Product Licence is contained in their NDS or SNDS. The applicant also includes the control number assigned to the NDS or SNDS in the cover letter.

Applicants wishing to obtain their product licence and NPN promptly after the PDL is amended should provide their PLA within 60 days of the publication of the Notice of Intent being published.

16. Health Canada verifies the PLA (Rx to NHP switches only)

Health Canada verifies the PLA to confirm it:

- meets the requirements of the NHPR; and
- reflects the latest version of the labelling agreed to by Health Canada for the NDS or SNDS.

17. Health Canada amends the PDL

After the six-month transition period, Health Canada amends the PDL. Health Canada then posts the Notice of Amendment on the Government of Canada website to announce that the amendment to the PDL has occurred.

18. Health Canada issues the market authorization

18.1 Rx to NPD switches

18.1.1 Situations requiring a new DIN

A new DIN is required 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 a subset of the conditions of use of the prescription drug product, such that after the switch is complete there will be both the prescription drug product and the NPD on the market.
    - The new DIN would belong to the new NPD.
- There will be only an NPD on the market after the switch is complete and a DIN was previously assigned to the prescription drug product, but the switch changes one or more specific attributes (e.g., dosage form).
    - For more information on the specific attributes that necessitate a new DIN or revised Drug Notification Form, consult the guidance document Regulatory Requirements for Drug Identification Numbers (DINs).

In the last situation, if a new DIN is required, 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.

18.1.2 Market authorization (Rx to NPD switch)

Health Canada sends the applicant a Drug Notification Form (DNF) in relation to the new NPD. Health Canada also issues the applicant an NOC for the NPD and an acknowledgement of the final approved version of Canadian Product Monograph. With the issuance of both a DIN and an NOC, the product is market-authorized.

18.2 Rx to NHP switches

18.2.1. Resolution of the NDS or SNDS

After the PDL is amended, Health Canada issues the applicant a Notification of Reclassification outlining the following:

- The PDL has been amended.
- The applicant's proposed product is no longer a drug regulated under the FDR (refer to section 3 of the NHPR) and, therefore, the NDS or SNDS on switch hold will not be subject to further review.
- The proposed product is now subject to the NHPR.

In cases where no prescription drug product will remain on the market after the amendment, Health Canada also cancels the DIN(s) for the prescription drug product.

18.2.2 Market authorization (Rx to NHP switch)

After the PDL is amended, Health Canada issues a Product Licence and assigns the NPN if the applicant has:

- appropriately reflected in the PLA the latest version of the labelling (agreed to by Health Canada) for the NDS or SNDS; and
- complied with all the requirements of the NHPR.

The timing for issuance of the market authorization for an applicant who has met the requirements depends on when they applied. Specifically:

- If the applicant submits their PLA **within** 60 days of the publication of the Notice of Intent and assuming all other requirements are met, Health Canada issues the Product Licence and assigns an NPN shortly after the PDL is amended.
- If the applicant submits their PLA at any point **after** the 60 days (including after the PDL amendment), the applicant risks not receiving their Product Licence and NPN until some time after the PDL amendment.

19. Additional information

19.1 Timelines for the switch process

Table 2 shows the timelines for the different stages of the switch process.

The timeframes shown for parts B and D are for straightforward cases. These timeframes may need to be longer for complex cases (e.g., when major concerns are raised during the consultation).

Table 2: Timelines for the stages of a successful switch process

Stage in the process	Timeline
A. From the submission filing date to Health Canada having reviewed the NDS or SNDS submission and written a summary document for the PDSC	Appendix 3 of the guidance document Management of Drug Submissions and Applications sets out the performance standards for the assessment of submissions.
B. From the end of submission review to Health Canada posting of the Notice of Consultation	3 months
C. PDL consultation period	75 calendar days
D. From the end of the consultation period to Health Canada posting the Notice of Intent indicating the PDL will be amended	1 month
E. From Health Canada posting the Notice of Intent to Health Canada posting of the Notice of Amendment (i.e., the transition period)	6 months
F. From Health Canada posting the Notice of Amendment to Health Canada issuing the market authorization	1 or 2 business days for the NOC in the case of Rx to NPD switches. 1 or 2 business days for the NHP Product Licence in the case of Rx to NHP switches if the applicant applied early, etc. (Refer to section 18.2.2 for more details.)

19.2 Reconsiderations

Applicants wishing to request a reconsideration of a negative decision (e.g., a NON-W or NOD-W) issued by Health Canada with respect to the market authorization request for an Rx to NPD or Rx to NHP switch should consult the guidance document Reconsideration of Decisions Issued for Human Drug Submissions and Natural Health Products.

19.3 Switches involving products with multiple medicinal ingredients on the PDL

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

- prepare only one PDL Principles and Factors Assessment; and
- include information about each of the medicinal ingredients on the PDL under each of the subheadings indicated in the template (Appendix 3).

19.4 Switches involving medical devices

For a product classified as a drug-device combination product according to the Drug/Medical Device Combination Products Policy, the applicant is encouraged to contact Health Canada to discuss switch requirements and applicable authorizations.

When a switch involves the use of 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, if the use of the proposed product relies on the use of a particular medical device, 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
- understand the device output, where applicable.

Any human factors or usability assessments using the medical device components and formally conducted with health care professionals or specialized health technicians should be repeated with representative consumer test groups. This is done to confirm that the medical device design remains optimal for the new user population.

The proposed product would not be suitable for self-care and a switch if the following both apply:

- The proposed product can only be used in conjunction with the medical device.
- The device cannot be used without practitioner intervention.

For additional guidance on what to submit related to the medical device in a switch submission, contact the Medical Devices Directorate by email: meddevices-instrumentsmed@hc-sc.gc.ca .

19.5 GMP, DEL and SL requirements

In addition to obtaining a product market 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.

19.5.1 Rx to NPD switches

Prescription and non-prescription drugs are subject to:

- DEL requirements as per Part C, Division 1A of the FDR; and
- GMP as per Part C, Division 2 of the FDR.

If the applicant or other parties conducting licensable activities (e.g., fabrication or importation) on the applicant's behalf 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 before they sell 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).

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

For more information, consult the following:

- The EL web page
    - For guidance on DEL requirements, consult Guidance Document on Drug Establishment Licences (GUI-0002).
    - For information on the fees associated with a DEL application, consult guidance document Fees for the Review of Human and Veterinary Drug Establishment Licence Applications.
- The GMP web page
    - For guidance on GMP requirements for drug products, consult Good Manufacturing Practices Guide for Drug Product (GUI-0001).

19.5.2 Rx to NHP switches

Normally at the beginning of an NDS or SNDS review, Health Canada screens the submission for the DEL, GMP compliance rating or DEL applications as outlined in the notice Submission Filing Requirements - Good Manufacturing Practices (GMP) / Drug Establishment Licences (DEL). However, because an Rx to NHP switch moves the product from FDR to the NHPR, Health Canada defers this screening until later in the assessment process.

To market the NHP in Canada, the switch applicant or other parties who are carrying out activities such as manufacturing 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, for the activities of manufacturing, packaging, labelling and/or importing.

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

- If they have the relevant and active SL, no further action is required.
- If they have a DEL but no SL, they apply for an SL via a streamlined pathway as described in section 2.1.1 of the Site Licensing Guidance Document.
- If they do not have an SL or DEL, they apply for an SL as described in the *Site Licensing Guidance Document*.

The applicant or other parties must obtain an SL before marketing the NHP. Performance standards for SL issuance are listed in Table 1 of section 3.1.1 Application completion timelines of the *Site Licensing Guidance Document*.

For additional guidance on the SL and NHP GMP requirements, consult the web page Guidance Documents – Legislation and guidelines – Natural health products.

If the Rx to NHP switch involves an authorized prescription drug product that will become an NHP with the prescription drug product no longer being marketed, the FDR DEL requirements continue to apply to the prescription drug product:

- until it is no longer sold; or
- until the date the PDL is amended, whichever occurs first.

Once one of these two criteria is met, the DEL holder may submit a request for DEL cancellation.

Note 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.

19.6 Intellectual property

For information on the data protection provisions of the FDR or on the *Patented Medicines (Notice of Compliance) Regulations*:

- consult the guidance documents Data Protection under C.08.004.1 of the *Food and Drug Regulations* and *Patented Medicines (Notice of Compliance) Regulations*, respectively; or
- contact the Office of Patented Medicines and Liaison by email: opml-bmbl@hc-sc.gc.ca .

19.7 The impact of a switch on other prescription drug products

In Canada, a successful switch results in an amendment to the PDL . This can have an impact on other **prescription** drug products (e.g., on generic versions of the reference drug product). Companies that are not the initiator of the switch need to assess if a proposed amendment to the PDL would mean their products will also no longer be prescription, and prepare themselves accordingly.

Where the switch results in the medicinal ingredient being entirely removed from the PDL, the affected companies would no longer be able to sell their products as prescription drug products. However, they could file a submission/application to obtain their market authorization as a non-prescription status product (NPD or NHP).

Where the switch results in the medicinal ingredient being removed from the PDL for certain conditions of use only, the affected companies' options depend on whether their prescription drug product matches these conditions of use exactly or has been authorized for other conditions of use as well. Health Canada will provide companies with details on all their options before launching the consultation.

Note that the submissions or applications from affected companies 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 being amended to remove a medicinal ingredient or a medicinal ingredient for specific conditions of use. Companies that do not have a related prescription drug product affected by the switch may wish to market a new NPD or NHP with this medicinal ingredient and under the specified conditions of use.

Conditional on a PDL amendment, these companies would file either an NDS or an Abbreviated New Drug Submission (ANDS) for an NPD or a Class III application for an NHP to obtain a market authorization. As long as the proposed new product aligns with the PDL amendment, these submissions/applications can follow the normal submission process with the regular requirements. They are not "switch submissions".

20. The PDL principles and factors assessment

The applicant should complete a PDL Principles and Factors Assessment following the template provided in Appendix 3.

In this assessment, the applicant should provide summaries of evidence and rationales demonstrating that none of the PDL principles and factors apply 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.

In the text that follows, Health Canada outlines points for the applicant to consider when developing the evidence and rationale. 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.

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. Where there is no additional information to detail, the applicant should state: "All the information related to this principle is included under Factors 1.1 to 1.8."

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:

- a description of how the condition is diagnosed;
- an assessment of the ease with which a consumer would be able to self-diagnose based on available evidence and/or new evidence (e.g., consumer use studies);

- an assessment of the risks associated with a misdiagnosis; and
- possible risk mitigation measures that would decrease the seriousness of the potential health consequences if the condition is misdiagnosed.

Describing the diagnosis

The applicant should outline how the condition 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 based on well-recognized symptoms, as well as their severity and duration.

If the symptoms 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 is able to self-diagnose the condition correctly. For more information on consumer use studies, refer to section 21.

The applicant should indicate whether laboratory tests or other procedures involving a practitioner are required for diagnosis. If any of these are 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 19.4.

Risks associated with misdiagnosis

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

- the impact of a delay in using the appropriate treatment;
- the impact of the use of sub-optimal treatment; and
- 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 of a reoccurring condition where an initial diagnosis is required by a practitioner to ensure 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 independently conduct subsequent diagnoses and understand when they should stop treatment and consult a health care provider. The applicant also needs to address the risks of a consumer choosing not to consult 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 their 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:

- information on the product's mechanism of action, as this will help identify potential conditions which might be masked; and
- 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.

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.

The use of the product, as well as the condition itself, ought not to require practitioner supervision if the product is to obtain a non-prescription status as an NPD or NHP.

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

- Identify that they belong 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.
- 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.
- 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 section 21.

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 supervision of a practitioner. For more on medical devices, refer to section 19.4.

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

- Selecting of the correct product for the individual
- Managing adverse reactions
- Making decisions on dose adjustments and discontinuation
- Developing risk mitigation strategies for the individual
- Requesting or conducting any necessary testing before, during or following the use of the product
- Determining whether the treatment is being effective
- Adjusting the treatment and the monitoring in relation to comorbidities

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

Products for use in self-care should not require that a practitioner tailor the use of the product to an individual's unique circumstances or explain product information. Consumers should be able to easily understand the information and how to use the product.

Therefore, the applicant should demonstrate that the product's use does **not** involve:

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

Some examples of situations that would generally lead to the prescription status being maintained include where:

- the dose needs to be determined based on co-morbidities and/or test results;
- the product elicits tolerance requiring increasing doses to maintain efficacy;
- the product requires that a practitioner adjust the dose for the individual;
- the product elicits clinically significant withdrawal or discontinuation symptoms that require tapering or symptom monitoring upon product removal; and
- the product has complex risk statements (precautions, warnings, contraindications).

With respect to the degree of complexity of directions for use, risk statements, etc., results from consumer use studies can help demonstrate the consumer's ability to understand the instructions without assistance from a practitioner. For more information on consumer use studies, refer to section 21.

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:

- 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; and
- 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 content of the most recent Health Canada-approved Product Monograph or Prescribing Information for the prescription drug product, if that exists;
- a comprehensive overview of *in vitro*, pre-clinical and clinical studies;
- the market experience data (refer to section 22);
- the published literature;
- the safety assessments from other major regulatory authorities and any available safety information from the World Health Organization or other national or international health organizations; and
- information on the dose at which unintended and intended psychotropic drug effects occur for products that contain known psychoactive substances. (These effects can include, for example, 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.

Assessing 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 are available.

In terms of inaccurate dosing, the applicant should address overdosing as it pertains to the product's margin of safety and underdosing 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 individuals, children and the elderly. The applicant should include any risk mitigation measures that they have taken with respect to these sub-populations and the effectiveness of those measures.

In some cases, an NPD and a prescription drug product, or an NHP and a prescription drug product, 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 a 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 drug products, 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, unless there are effective risk mitigation measures in place.

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 safety results for all relevant clinical trials;
- drug-drug and drug-food interaction studies;
- available market experience data (refer to section 22); 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 may 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 section 21.

The applicant also needs to identify any special considerations for vulnerable sub-populations, such as pregnant and nursing individuals, 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 (i.e., substance use disorder).

Some products have the potential to induce psychoactive effects. These effects can be the primary (desired) effects of the product (e.g., sedatives) or secondary (unintended or undesired) effects. These effects include symptoms such as dizziness, anxiety, cognitive impairment or irritability. They also include 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 because 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 make it very difficult for a consumer to stop using the product.

For example, a consumer who no longer needs to use a product may continue to do so because an attempt to discontinue use had resulted in worsening symptoms. Oversight by a practitioner 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). Note that discontinuation symptoms are not confined solely to psychoactive ingredients.

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

- clinically significant psychoactivity requiring practitioner oversight; or
- 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. A mechanism of action rationale may also be sufficient to address this factor.

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. 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 they have instituted in relation 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 or a lack of adequate post-market data);
- a lack of full characterization of its pharmacological effects; or
- unknown consequences of its long-term use.

Where significant uncertainties exist, the product would generally maintain its prescription status.

Ideally, a product for self-care is well characterized. That is, in addition to its safety and efficacy profile, the pharmacodynamics, pharmacokinetics and 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.

The applicant should demonstrate that the proposed NPD or NHP has limited uncertainties that do not warrant oversight by a practitioner. The applicant needs to summarize where uncertainties and gaps in the information exist, including analysis on:

- the uncertainties and gaps in the data regarding the toxicology and safety of the product; and
- the uncertainties and gaps in the body of evidence supporting the product's safety and efficacy related 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. The applicant should also explain the reason(s) any remaining uncertainties and gaps would not justify the 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 volume of sales (population exposure).

The applicant should address all the elements outlined in section 22 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 general public. If the applicant has identified ways to mitigate potential dangers, they 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, they should include it in this part of the template. If the applicant does not have additional information, they should indicate in this section of the template that all the information related 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 taken.

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 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.

Generally, in these cases, the medicinal ingredient will be regulated as a controlled substance under the CDSA and its regulations, including being restricted to prescription-only status. This is in addition to being regulated under the FDR.

For non-CDSA substances, in order for the product to be switched to non-prescription status, the applicant should demonstrate that the product has a low likelihood for abuse.

For guidance on assessing the abuse potential of substances, consult the following notice which outlines Health Canada's expectations: Guidance on the Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity.

The applicant may need to provide 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 summary of market experience listing adverse events associated with abuse or abuse potential
- A review of available information to determine if abuse or diversion has been reported with the ingredient

In terms of the review of available information, it should include an extensive survey of various sources of information. This includes published peer-reviewed literature; grey literature (such as reports from international health organizations and media reports); etc. The applicant should also provide a list of all known street names of the product or its active ingredient(s) and include these terms in their search. The applicant's search strategy should be included in the submission.

The applicant should be clear on what effects are observed under normal conditions of use (the conditions for which the switch and market authorization are 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 addiction (substance use disorder).

21. 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:

- label comprehension studies;
- self-selection studies;
- actual use studies; and
- human factors studies.

Health Canada typically requests the applicant to provide one or a combination of these types of consumer use studies in switch submissions. The applicant is encouraged to discuss the need for consumer use studies with Health Canada before filing their submission.

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. For example, the United States Food and Drug Administration (US FDA) has developed the following documents:

- Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products (2010)
- Guidance for Industry: Self-Selection Studies for Nonprescription Drug Products (2013)
- Applying Human Factors and Usability Engineering to Medical Devices (2016)

Applicants can discuss their choice of methodologies at a pre-submission meeting.

21.1 Label comprehension studies

Central to justifying a switch is the demonstration that the labelling effectively supports the consumer using the proposed product without the involvement of a practitioner. 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 (e.g., the indication, dose and warnings) that relate to the safe and effective use of the product.

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 general population, that vary in age, sex and level of literacy. In some instances, studies may need to address other relevant populations, such as those with other underlying medical conditions or concomitant medications.

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); and
- 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. They should also provide an analysis of both quantitative and qualitative data to support and interpret study findings. The applicant should organize the results by age cohorts (such as adolescents and adults, where applicable) and literacy levels.

Generally, a pre-specified target threshold of 80% or higher is expected for the major communication elements relating to safety and efficacy depending on the level of risk. These label elements include, for example:

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

21.2 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 using:

- 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 that 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 submitted to Health Canada. They should also provide an analysis of both quantitative and qualitative data to support and interpret study findings.

21.3 Actual use studies

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

These studies provide information about:

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

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 diagnosing the condition, selecting the product and monitoring its use. The design and interpretation of the results of actual use studies are complex.

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

21.4 Human factors studies

Human factors studies may be necessary when the proposed switch pertains to a product used with a medical device or a prescription drug-device combination product. These studies provide evidence in support 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 user's ability to understand the packaging and labeling information;
- assess the user's ability 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 eliminating or mitigating potential use-related hazards.

22. Market experience

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.

22.1 Information to be provided

The applicant should provide information on the post-market use of the health product in Canada and in other countries as part of the submission for a switch, if available.

Ideally, this information should be related to the proposed NPD or NHP under the same conditions of use. When that is not available, the applicant should present information related 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:

- Any RMPs;
    - For more information on Canadian RMPs, consult the guidance document Submission of Risk Management Plans and Follow-up Commitments.
- A summary of identified and potential risks including adverse reaction data, if applicable, from the applicant's own safety databases (e.g., a summary of Canadian Adverse Reaction Reports);
- A summary of the safety signals discussed in the most recent Periodic Safety Update Report(s) (PSURs) and Periodic Benefit-Risk Evaluation Report(s) (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;
- Information on intentional misuse;

- A summary of all serious and non-serious medication incidents including intercepted medication errors, 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 chronological summary of available risk communications and recalls.

The applicant should analyze this data to determine whether the risks differ when the status of the product is prescription versus non-prescription, if applicable.

With respect to adverse reaction information:

- The applicant should obtain information on adverse reactions from the World Health Organization's Vigibase and the Canada Vigilance Database as well as from other international databases, where available. The applicant should include these findings in their analysis.

- When highlighting adverse reactions reported in clinical trials conducted since the product's first authorization, the applicant should also address the comparability of the trial product with the proposed NPD or NHP.

- The applicant should take into account the foreign regulatory requirements and procedures by which adverse reactions are collected 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 (such as, only mandatory in hospital settings).

22.2 Additional contextual information to be provided

Health Canada expects the applicant to contextualize the market experience information obtained from other key regulatory authorities (e.g., the European Medicines Agency (EMA) and the US FDA). This contextual information will be helpful when Health Canada evaluates the market data provided.

To this end, it is necessary to include the following details about the product and its regulation in these key jurisdictions:

- Foreign product information;

- Regulatory status;

- Level of health care professional involvement and consumer access;

- Foreign labelling and other risk mitigation measures; and
- Magnitude of product exposure

The following sections include further guidance on the different types of contextual information.

Foreign product information

The applicant should describe the degree of similarity between the foreign product(s) and the proposed NPD or NHP to be marketed in Canada. This includes addressing:

- recommended single and maximum daily dose;
- duration of use;
- route of administration;
- dosage form; and
- indications.

Regulatory status

Health Canada expects the applicant to provide information on the regulatory status of the product in the jurisdictions of the key regulatory authorities. In other words, the applicant should indicate whether the product has been classified as, for example, a prescription drug product, non-prescription product, behind-the-counter product or food supplement.

Level of health care professional involvement and consumer access

If there are key jurisdictions in which the product is not a prescription drug product (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 care 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 jurisdictions, the product may be freely available for purchase in all retail locations, while in others, its sale may be restricted 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 key 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 PBRERs.

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 jurisdictions. The applicant should also provide information on the product exposure in vulnerable sub-populations, if available.

Appendix 1: Contact information

Applicants who have questions regarding switches should contact the NNHPD by email: nnhpd-dpsnso@hc-sc.gc.ca.

Appendix 2: Glossary

a) Acronyms

ANDS – Abbreviated New Drug Submission

CDFT – Canadian Drug Facts Table

CDSA – *Controlled Drugs and Substances Act*

DEL – Drug Establishment Licence

DG – Director General

DIN – Drug Identification Number

DNF – Drug Notification Form

DSM-5 –*Diagnostic and Statistical Manual of Mental Disorders,* 5th edition.

EMA – European Medicines Agency

FDR – *Food and Drug Regulations*

GMP – Good Manufacturing Practices

ICH – International Conference on Harmonisation

MDR – *Medical Devices Regulations*

MedDRA – *Medical Dictionary for Regulatory Activities*

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

PDD – Pharmaceutical Drugs Directorate

PDL – Prescription Drug List

PDSC – Prescription Drug Status Committee

PLA – Product Licence Application

PSUR – Periodic Safety Update Report

Rx – Prescription

RMP – Risk Management Plan

SL – Site Licence

SDN – Screening Deficiency Notice

SNDS – Supplement to a New Drug Submission

TBT – Technical Barriers to Trade

US FDA – the United States Food and Drug Administration

b) Definitions

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

Abuse: The use of a product for purposes other than for which it was prescribed (for example, using it for its reinforcing properties).

Addiction (substance use disorder): This refers to the compulsive and continuous use of a substance despite negative impacts to a person, their family, friends and others, typically involving cravings and impaired control over use.

Applicant: The company that is the applicant or sponsor that is initiating the request for an Rx to NPD or Rx to NHP switch.

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

Conditions: This 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: These 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: Difficulty discontinuing drug use due to unpleasant physical and/or psychological withdrawal effects.

Drug-device combination product: A therapeutic product that combines a drug component and a medical 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.

Intercepted medication error (near miss): An event that could have resulted in unwanted consequences, but did not because either by chance or through timely intervention the event did not reach the patient.

Market experience: Knowledge gained about an authorized product once it is being sold.

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

Non-prescription status: The default status of ingredients or products that are not prescription drugs, prescription drug products or products with prescription status. For example, NPDs and NHPs both have non-prescription status.

Practitioner: An individual who is entitled to treat patients with prescription drugs according to provincial or territorial laws and is practising their profession in that province/territory. Two common examples are doctors and dentists.

Product Facts Table: A table on the outer label of some NHPs that displays important information about the product in a standardized format so that the information is clear, consistent and legible for consumers.

Psychoactive effects: Effects of a substance or mixture of substances on the central nervous system that result in temporary changes in cognition, perception, mood and consciousness, which can lead to temporary changes in behaviour. Examples of these include dizziness, calmness, stimulation, anxiety, irritability, cognitive impairment, hallucinations, drowsiness and euphoria.

Serious adverse reaction: 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.

Submission filing date: The date that the submission is deemed administratively complete by Health Canada (i.e., once all elements and forms required for processing are completed and submitted to Health Canada).

Switch: A change of status from prescription status to non-prescription status.

Switch submission: For Rx to NPD switches, this term refers to the NDS or SNDS in which a switch is requested. For Rx to NHP switches, this term refers to the NDS and the PLA, or the SNDS and the PLA, in which the switch is requested.

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

c) Dependence, addiction, misuse and abuse terminology

The Government of Canada is proposing the use of new terminology related to substance use to minimize stigma and discrimination. For more information on the Government of Canada's guide to terminology, consult the web page Stigma: Why Words Matter.

In addition, Health Canada notes that the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) has moved away from using the term "addiction". The DSM-5 has also replaced the previous diagnostic categories of "substance abuse" and "substance dependence" with "substance use disorders". These changes suggest that use of these terms is evolving.

Health Canada has opted to use the terms "abuse", "dependence" and "addiction" herein. One of the reasons for this is 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 companies are clear on the search terms to use when collecting data for submissions.

Appendix 3: Template for the PDL Principles and Factors Assessment

Applicants should prepare their PDL Principles and Factors Assessment using the subheadings shown in the template. Applicants should include the assessment in Module 1.0.7 of the NDS or SNDS.

Applicants should ensure that in the assessment:

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

Table 3: 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.
[Insert the rationale and evidence related to Principle 1.]
Factor 1.1 The drug is used in the treatment of a serious disease not easily diagnosed by the public.
[Insert text.]
Factor 1.2 The use of the drug may mask other diseases.
[Insert text.]
Factor 1.3: Practitioner supervision is necessary for treatment and/or monitoring.

[Insert text.]
Factor 1.4: The use of the drug requires complex or individualized instructions.
[Insert text.]
Factors 1.5: Practitioner expertise is necessary to administer the drug or oversee the drug's administration.
[Insert text.]
Factor 1.6: The drug has a narrow margin of safety.
[Insert text.]
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.]
Factor 1.8: The drug has dependence and/or addiction potential.
[Insert text.]
Principle 2: The level of uncertainty respecting the drug, its use or its effects justifies supervision by a practitioner.
[Insert text.]
Factor 2.1: There is limited market experience with the use of the drug.
[Insert text.]
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.]

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