December 24, 2012

Notice

Our file number: 12-119951-937

Release of Draft Guidance Document: *Determining Prescription Status for Human and Veterinary Drugs*

Health Canada is pleased to announce the release of the Draft Guidance Document - *Determining Prescription Status for Human and Veterinary Drugs* for a 75-day stakeholder consultation.

As part of the *Jobs, Growth and Long-term Prosperity Act* (Bill C-38), which received Royal Assent on June 29, 2012, the Government amended the *Food and Drugs Act* to give the Minister of Health certain powers, including the power to establish a list that sets out prescription drugs.

Subsequent to changes to the *Food and Drugs Act*, the *Food and Drug Regulations* require amendments to replace Schedule F with an administrative process, the Prescription Drug List. On December 22, 2012, Health Canada published in *Canada Gazette*, Part I (www.gazette.gc.ca) a regulatory proposal to amend the *Food and Drug Regulations.* This proposal establishes a list of prescription drugs and includes broad principles for determining prescription status for human and veterinary drugs. The proposed amendment can be found at the following link: http://www.gazette.gc.ca/rp-pr//1/index-eng.html.

The draft guidance document *Determining Prescription Status for Human and Veterinary Drugs* supports the regulatory proposal by explaining the broad principles and factors that Health Canada considers when deciding whether a drug would be best sold as a prescription or non-prescription product. The principles and factors are derived from Health Canada's existing policy document *"Factors for Listing Drugs in Schedule F"* (reposted 1999). The draft guidance is designed to help the public, industry and healthcare professionals, including veterinarians, as well as other stakeholders, better understand and predict when a drug will be authorized as a prescription or non-prescription product.

This draft document applies to both human and veterinary drugs regulated under the *Food and Drugs Act*. It applies to all additions and removals from the proposed list of prescription drugs. This document does not explain the approach to decisions on whether a drug should be a controlled substance regulated under the *Controlled Drugs and Substances Act*. Once finalized, this guidance document will replace the policy *"Factors for Listing Drugs in Schedule F"*.

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Comments on the draft guidance should be provided to Health Canada, preferably in electronic format using the attached template, within 75 days from the date of this notice. The comments provided during the stakeholder consultation period may be made available upon request. Health Canada will consider comments made on the regulatory proposal published in *Canada Gazette, Part I* in conjunction with comments made on the guidance.

Should you have any questions or comments regarding the content of this guidance, please contact:

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Draft Guidance Document: Determining Prescription Status for Human and Veterinary Drugs
Published for External Consultation on December 24, 2012

In order to seek clarification between user's comments, we ask that you include your name, telephone number, full mailing or email address. If you chose to provide the personal information, it will not be shared with other parties and will not be used for any purpose other than the ones listed above. The following personal information that you provide in this form is protected under the *Privacy Act* at: http://laws.justice.gc.ca/en/P-21/index.html).

Comments submitted by: <full name>, <company/association name (if applicable)>
Telephone number: <telephone number>
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Email: <email address>
Date: <date of comment submission>

Comment Number	Section / Line Number*	Comment and Rationale	Proposed Revised Text
1			
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*Please refer to the Adobe Portable Document Format (PDF) version of the document to ensure accuracy in line numbers.

Health Canada Santé Canada

DRAFT GUIDANCE DOCUMENT

Determining Prescription Status for Human and Veterinary Drugs

This guidance document is being distributed for comment purposes only.

Published by authority of the
Minister of Health

Draft Date	2012/12/24

Health Products and Food Branch

Canada

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

Également disponible en français sous le titre : *L'ébauche de la linge directrice : Détermination du statut de vente sur ordonnance pour médicaments destinés aux humains et aux animaux*

FOREWORD

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

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

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

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

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1. Introduction

Health Canada is publishing this document to be transparent about the principles and factors that it considers when deciding whether a drug would be best sold as a prescription or nonprescription product.

This document is also designed to help the public, industry and healthcare professionals, including veterinarians, as well as other stakeholders, better understand and predict when a drug will be authorized as a prescription or nonprescription product.

2 Policy Objective

In determining prescription status, Health Canada's objective is to make drugs available in a way that will best prevent harm and optimize benefits, in the interest of protecting and promoting health and safety.

3 Terminology

The following description of terms is provided only for the purposes of helping the reader understand this document. Official definitions are provided in other documents such as the *Food and Drugs Act* and its associated *Regulations*.

adverse reaction - Adverse reactions (also known as side effects) are undesirable effects that can sometimes occur with drug use. They can include minor reactions such as a mild skin rash or serious events such as a heart attack.

disease - The use of the word disease is meant to include diseases, disorders, abnormal physical states, or the symptoms or signs associated with them.

drug - In this document, the word drug includes natural health products, biologics [for example (e.g.), vaccines and gene therapies], pharmaceuticals and radiopharmaceuticals.

nonprescription product - A drug that can be obtained by the general public without a prescription.

patient - A patient can be a human, an animal or a group of animals (e.g. herd of cattle).

practitioner - Practitioners are people who have the right to prescribe drugs for humans or animals, according to provincial and territorial laws.

prescription status - If a drug has prescription status, several restrictions apply including that the drug can only be sold to a member of the general public if they have a prescription from a practitioner for that drug.

4 Scope and Application

This document applies to both human and veterinary drugs regulated under the *Food and Drugs Act*. It is intended to replace the policy *"Factors for Listing Drugs in Schedule F"* (reposted 1999). It applies to all additions and removals from the proposed list of prescription drugs.

While the principles and factors are relevant to applications for switching drugs from prescription to nonprescription status, this document does not cover the detailed application process nor the data requirements for such switches.

Additionally, this document does not explain the approach to decisions on whether a drug should be a controlled substance regulated under the *Controlled Drugs and Substances Act.*

5 Background

In 2012, the Government of Canada announced its plan for a simpler and quicker process for making changes to the Canadian list of prescription drugs. Currently, the list of prescription drugs is found in Schedule F to the *Food and Drug Regulations*. Making changes to Schedule F involves a lengthy regulatory process. Under the proposed new process the list of prescription drugs will be easier to update, as it will not be in the *Regulations*.

To put this new process in place, a legislative change to the *Food and Drugs Act* was first completed. Now, a regulatory amendment to the *Food and Drug Regulations* is required.

In addition to making the new process possible, the proposed regulatory amendment explains how decisions are made to add or remove a drug from the prescription drug list. Specifically, the proposed amendment outlines three broad principles that are considered in making these decisions.

The three proposed broad principles for determining prescription status are:

- *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 intended to be used; or
  (ii) to monitor the disease, disorder or abnormal physical state or its symptoms in respect of which the drug is intended to be used, or to monitor the use of the drug;

- *the level of uncertainty respecting the drug, its use or its effects justifies supervision by a practitioner; or*

- *use of the drug can cause harm to human or animal health or a risk to public health and the harm or risk can be mitigated by a practitioner's supervision.*

The proposed broad principles encompass factors that Health Canada has considered in making decisions about prescription status for over 20 years. These factors were listed in a policy entitled "*Factors for Listing Drugs in Schedule F"*. This more detailed document will replace that policy.

Health Canada is providing this document to explain the three principles and the associated factors in order to make the decision-making process more transparent.

6 General Approach

Health Canada's main goal in evaluating whether a drug would be better sold as a prescription or nonprescription product is protecting health and safety.

When Health Canada receives a new market authorization application for a natural health product, biologic or pharmaceutical drug, in addition to evaluating the data to determine whether the drug should be authorized for sale on the Canadian market, Health Canada also considers whether it is best sold as a prescription or nonprescription product.

Further, companies can submit an application specifically to request that their product, which was previously authorized as a prescription drug, be considered for sale without a prescription. These are referred to as "switch submissions" because it is a request to 'switch' a product from prescription to nonprescription. Health Canada evaluates these applications as well to see if sale as a nonprescription product would be appropriate.

When Health Canada decides whether a drug should be prescription or nonprescription, it considers the three principles and their associated factors as they apply to a particular drug. Drugs are assessed on an individual basis; a drug is evaluated with respect to its specific use, dose, route of administration, target population and species, etc.

If none of the principles and factors apply, then a drug will be a nonprescription product. Nonprescription products include natural health products, some biologics and some pharmaceutical drugs. While the federal government may make a drug a nonprescription product, the provinces and territories have the option to further restrict its conditions of sale.

If any of the principles or factors applies to a drug, that is considered sufficient for the drug to be given prescription status. In many cases, there will be several factors that apply to a drug that is a prescription drug.

Some of the descriptions of the factors in the next section may apply more specifically to human drugs and others to veterinary drugs. In some cases drugs with the same medicinal ingredient will be prescription for both humans and animals, while in others, drugs are prescription for one but not the other. The main reasons for this are that drugs can have different uses in humans and animals and sometimes the drug treatment involves greater risk to humans or to a particular animal species.

The next section describes in detail how Health Canada interprets the three principles and their associated factors in determining if a drug should be a prescription drug. The principles and factors are not necessarily independent of one another and some overlap exists between them.

Examples have been provided for further clarity. The drug examples have been chosen because they are good at illustrating the factor in question. The same drug might also be an example of other factors.

Further, some drugs may raise unique considerations not captured in the descriptions of the principles and factors provided below. In these rare cases, decisions are made with the protection of health and safety as the main goal and consideration.

7 Interpretations of the Principles and Associated Factors

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 intended to be used, or
(ii) to monitor the disease, disorder or abnormal physical state or its symptoms in respect of which the drug is intended to be used, or to monitor the use of the drug.

There are situations where practitioner supervision is needed to reduce the risk that the use of a drug would directly or indirectly harm a patient. In these situations, the involvement of a practitioner in the diagnosis, treatment and monitoring of the disease, including selecting and monitoring the use of the drug can help decrease the chances of harm occurring, as well as increase the benefits.

Factor 1.1 The Drug is Used in the Treatment of a Serious Disease Not Easily Diagnosed by the Public

Where the public could not easily diagnose the disease, the drug for the disease would typically be given prescription status. This includes cases where the public would likely misdiagnose a minor disease when in fact they have a serious disease. The drug for the minor disease would also be prescription.

These situations can arise, for example, where the symptoms (self-identified) or signs (observed in animals or humans) are common to a number of different diseases. The person who is experiencing these symptoms or the owner of the animal observing these signs, would not necessarily have the knowledge or experience to identify the disease correctly. Therefore, where practitioner expertise is needed in the diagnosis of the disease, the drugs used to treat the disease are typically prescription drugs. This will allow for proper diagnosis and drug selection.

Example - Practitioner involvement would be needed to diagnose muscular dystrophy. The diagnosis of this serious disease involves examination of the patient as well as tests such as a muscle biopsy or genetic tests. This is one of factors that results in drugs for muscular dystrophy being authorized as prescription drugs.

Example - Human patients with hypothyroidism [low thyroid function] can experience symptoms such as fatigue and sleepiness. Fatigue can be an early symptom of many minor diseases; as well as other serious diseases, including diabetes, leukemia; or conditions such as pregnancy. The diagnosis of hypothyroidism involves examination of the patient as well as tests such as blood levels and may require life-long follow-up. Obtaining appropriate treatment is important as the disease can be fatal if left untreated. Therefore, one of the reasons these drugs are prescription is that this disease could be easily misdiagnosed by the public.

Example - Practitioner involvement is needed to diagnose hyperadrenocorticism [Cushing's Disease] in dogs. The signs, such as hair loss, lethargy and frequent urination, are very similar to those of a number of other diseases. Many tests including those that require the use of blood and urine are typically needed to diagnose hyperadrenocorticism. One reason that trilostane, a drug used to treat this disease in dogs, is a prescription drug is because the public cannot easily diagnose this condition.

Factor 1.2 The Use of the Drug May Mask Other Diseases

Drugs are typically given prescription status when their use may mask or hide other serious diseases in humans or animals. Specifically, an individual may treat their own symptoms with a nonprescription product and obtain relief of those symptoms. However,

in obtaining relief, the individual is less likely to consult a practitioner. Similarly, an animal owner could treat the observed sign in their animals, and see an improvement in the animals leading him or her to be less likely to consult a practitioner. In the case where the symptom/sign was actually related to a serious disease, this is problematic. The self-treatment or the owner's treatment of the animals may delay diagnosis and treatment of the serious disease which may cause a negative impact on the health of that individual or the animals.

Therefore where a drug masks other illnesses, and results in:
(1) a lack of timely diagnosis and treatment;
(2) a significant worsening of the underlying disease; or
(3) otherwise putting at risk the chance of more successful therapy, the drug will likely be given prescription status.

Example - If a person had problems with erectile function and could buy a product for erectile dysfunction without prescription, there would be a danger of this drug masking an underlying disease. Taking this drug might help the erectile dysfunction however, erectile dysfunction can be a symptom of conditions such as hypertension, coronary artery disease, high cholesterol or diabetes mellitus. Therefore, the person may think they are fine once on the drug, but they still could have one of these underlying conditions which can be fatal. One of the reasons erectile dysfunction drugs are prescription drugs is concern that these drugs could delay proper diagnosis which could have significant consequences for a patient.

Health Canada also considers whether the chances of delayed diagnosis and treatment can be reduced by information on the product label. For example, warnings could be included on a product label stating that after a certain period of time, if symptoms /signs continue in the patient, a practitioner should be consulted. In some cases, labelling can be sufficient to address the concerns of masking and in these cases the drug may not need to be prescription.

Factor 1.3 Practitioner Supervision is Necessary for Treatment and/or Monitoring

There are some diseases and drugs that require the involvement of a practitioner to achieve the best results in patient health, both in terms of reducing the potential harms and increasing the potential benefits. There are many parts of the treatment and monitoring where direct practitioner supervision can be needed.

Treatment can include the selection and administration of an appropriate drug. If the general public would not have the skills and knowledge to choose the right drug for the disease, then prescription status would be needed. Furthermore, development of appropriate risk mitigation strategies may require practitioner involvement.

Example - There are several classes of drugs for treating a person with hypertension [high blood pressure] depending on the cause of hypertension (age, poor adrenal gland function, kidney disease, etc.). A practitioner would be needed to select the appropriate drug or combination of drugs for treatment of this serious disease taking into account the cause of the high blood pressure and the person's condition (age, other medications, other illnesses, etc.). This is one of the factors that results in drugs for high blood pressure being authorized as prescription drugs.

Monitoring of some diseases and the impact of the use of some drugs can require practitioner expertise. In terms of monitoring, practitioner supervision could involve:

- changing the dose of the drug [amount of drug given], discontinuing drug use or switching drug treatment if the drug is not working or is causing adverse reactions;
- making sure that the drug continues to be the right treatment if the disease gets better or worse;
- instructing patients as to the tests that need to be conducted prior to or during treatment;
- ordering different tests, or testing more often, if the patient's condition changes;
- assessing the test results; and
- monitoring more closely a patient who also has other diseases that may affect their treatment.

Example - Clozapine is a drug for treating schizophrenia in humans. It can cause serious drops in a person's white blood cell levels. White blood cells are key in helping a patient fight off infections. If the levels of white blood cells get too low, there is a serious risk of death. For this reason, practitioners closely monitor the results of the patient's blood tests when treating with clozapine to ensure the patient is not experiencing this adverse reaction. Thus, one of the reasons clozapine is a prescription drug is because it requires practitioner supervision.

Factor 1.4 The Use of the Drug Requires Complex or Individualized Instructions

There are two main reasons why individualized instructions may be necessary: when the use of a drug needs to be tailored to a patient's specific circumstances or when the drug information cannot be easily understood by the general population.

A drug will typically be given prescription status when a practitioner is needed to provide instructions for using the drug that take into account the patient's individual circumstances. This could include the practitioner selecting the proper dose, changing the dose of drug during the course of therapy or adjusting the drug treatment to take into account the patient's age, weight, medical history, other medications, disease severity, test results, general health conditions (e.g., liver or kidney function), etc.

Example - Digitalis is a drug used for cardiac problems in humans. The dose that a patient should take is calculated based on patient weight and previous response to the drug. This dosing is not something that a layperson would likely have the knowledge to determine on their own. This is one of the reasons digitalis is a prescription drug.

Example - Methimazole is used to treat hyperthyroidism [overactive thyroid function] in cats. The treatment requires selecting the dose based on factors such as animal weight, appetite and blood test results. The veterinarian will give the animal owner individualized instructions for the particular cat in question.

In other cases, the information about the drug is hard to understand because the details are so numerous or complex that it would be difficult for the average person to understand them if they were just written on the label. This includes information such as the directions for use, contraindications [when you should not use the drug], interactions with other drugs, warnings and precautions. Where this information cannot be easily understood and followed by the patient or animal owner, then the drug would typically be a prescription drug.

In these cases, making the drug prescription means that a practitioner can then go over the information with the patient and answer questions to make sure the information is clear. Furthermore, the practitioner can also identify for the patient which information would be relevant to their particular situation.

Example - Certain life-threatening fungal infections can be treated with itraconazole capsules. The information related to this product is complex. For instance, there is a long list of contraindications for this drug, which include many drug-drug interactions. Furthermore, there are warnings pertaining to problems that may occur that a patient could not self-assess such as changes in liver function. The involvement of a practitioner can help identify the contraindications and warnings that apply to the particular patient as well as the appropriate precautions that need to be taken. Because practitioner involvement is necessary for comprehension and use of the drug-related information, and because of other factors that apply to this drug, itraconazole capsules are prescription drugs.

Factor 1.5 Practitioner Expertise is Necessary to Administer the Drug or Oversee the Drug's Administration

In some cases practitioner supervision is necessary where it takes expertise to administer or oversee the administration of the drug. Practitioner supervision is advisable where the route of administration is complex. In these cases the drugs are typically authorized as prescription drugs.

Example - The administration of propofol, a general anaesthetic, requires that the patient be monitored (heart rate, blood pressure, etc.) before, during and after the drug is given. As such, practitioner supervision is necessary for its administration. Because of this factor, as well as others, propofol is a prescription drug.

This would also include situations where the person administering the drug may be harmed. In these situations, the drugs are typically authorized as prescription drugs.

Example - Tilmicosin, an antibiotic for cattle and sheep, can be fatal if injected accidentally into a human. If self-injection occurred, immediate emergency care would be needed. One of the reasons tilmicosin is a prescription drug is to ensure its safe use by a veterinarian.

Factor 1.6 The Drug has a Narrow Margin of Safety

For some drugs, the difference between a therapeutic (helpful) dose, and a toxic one, is very small, so it is critical that the patient receive precisely the right amount of drug to prevent serious consequences. Drugs that have this kind of narrow margin of safety are typically prescription drugs.

Example-Lithium is a drug used to manage manic episodes in individuals with bipolar disorder (manic depressive disorder) and it has a narrow margin of safety. If human patients take too much of the drug, it can be toxic, causing problems such as kidney and nervous system damage. If patients take too little, the manic episodes can reoccur. Practitioner supervision is required for this drug to make sure the dose of the drug is correct, through careful and regular monitoring of the blood levels of this drug and monitoring for side effects that may suggest that the blood levels are too high. In addition to meeting other factors, lithium meets the narrow margin of safety factor and is therefore a prescription drug.

Related to a narrow margin of safety is the impact of minor accidental misuse. If significant harm would occur if a patient or animal owner were to accidentally slightly exceed the dose; miss a warning or contraindication statement; use the drug a little longer than recommended; etc., Health Canada would consider making it a prescription drug.

Sometimes drugs have a narrow margin of safety only in particular subpopulations. These drugs will also typically be prescription drugs. Examples of subpopulations include children, pregnant women, seniors, humans or animals with certain genetic profiles, and particular animal species.

Example - Ivermectin, a drug for prevention of heartworm in dogs, has a narrow margin of safety in some, but not all, collie dogs. Special precautions are advised for collies as serious adverse reactions (such as seizures) can occur. This is one of the reasons Ivermectin is authorized as a prescription drug for dogs.

Health Canada will also take into consideration the effectiveness of labelling at excluding particular subpopulations who could be harmed by the drug. There may be some instances where labelling can be effective and the drugs may be permitted to be sold as nonprescription products.

Factor 1.7 The Drug has Potential or is Known to Cause Serious Adverse Reactions at Normal Therapeutic Dosage Levels

A drug would typically be authorized as a prescription drug if when used at a normal dosage level, it can cause serious adverse reactions or can result in serious interactions with food or other drugs. Practitioner involvement is required for communicating and managing the risks to patients.

Some drugs have potential or are known to produce serious adverse reactions in particular subpopulations (e.g., children, pregnant women, seniors, and particular animal species).These drugs will also typically be prescription drugs.

Example - Isotretinoin is a drug used to treat severe acne in humans that can not be treated successfully with other medications. At the normal dosage level, this drug can cause birth defects if it is used just before or during pregnancy. It is very important to make sure patients understand the risks and precautions of this drug. To further reduce risks, negative results on pregnancy tests are required prior to prescription refills. Therefore, one of the reasons for this drug being given prescription status is to ensure that a practitioner is involved in the selection of this treatment and communication of risks to the patient.

Example - Bisphosphonates are a class of drugs used, among other things, to prevent osteoporosis in postmenopausal women. In rare cases, at the normal dosage level, serious adverse reactions such as deterioration of the jaw bone have occurred in patients treated with bisphosphonates. This is one of the reasons bisphosphonates are prescription drugs.

Example - Warfarin is a drug used to prevent clots in the blood. If human patients eat too much of certain foods (e.g., dark leafy green vegetables) while taking this drug, this can lead to haemorrhage [excessive bleeding]. Practitioners can review with patients the importance of these food-drug interactions and how to manage them so that problems can be avoided. For reasons including this potential for serious interactions, warfarin is a prescription drug.

Example - Follitropin beta is a drug which stimulates egg development in women and is often used in patients undergoing Assisted Reproductive Technologies such as in vitro *fertilization. Even when taken at normal dosage levels, follitropin beta can cause serious adverse reactions including lung problems. As a result of this and other applicable factors, the drug was authorized as a prescription drug.*

Health Canada will also evaluate whether labelling for some drugs can work to effectively warn the public of potential interactions and adverse reactions such that harm can be avoided. In some cases, prescription status may not be necessary if the risks can be avoided through labelling.

Factor 1.8 The Drug has Dependence and/or Addiction Potential

Some drugs have the potential to cause dependence and/or addiction and therefore would be considered for prescription status.

Example - Modafinil is a drug that is used for sleeping disorders and has the potential for dependence. This drug requires close monitoring of patients by a practitioner particularly where the patient has a history of drug or stimulant abuse. This is one of the reasons modafinil is a prescription drug.

Most drugs that may cause dependence and/or addiction are also regulated as controlled substances under *Controlled Drugs and Substances Act* and its associated regulations. The *Act* and its associated regulations impose additional requirements on activities such as record-keeping, storage and distribution, to limit the potential for diversion to the illicit market. Examples of controlled substances are morphine and methadone.

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

Drugs are authorized for sale by Health Canada when the drugs are evaluated to have benefits that outweigh the risks. Nonetheless, there may remain some uncertainties about the drug. In such cases where those uncertainties warrant further attention, Health Canada will typically give the drug prescription status. Uncertainties can relate to many issues such as a lack of experience with the drug, a lack of adequate post-market data regarding the drug’s use and effects, etc. By

giving the drug prescription status, Health Canada ensures that a practitioner is involved in, for example, monitoring any adverse reactions and long-term consequences of drug use, assisting patients in managing any adverse reactions, and reporting back on any adverse reactions.

Factor 2.1 There is Limited Market Experience with the Use of the Drug

There are several situations where there may be limited knowledge about the consequences of long term use of a drug:

a) Drugs new to the market
While many drugs that are new to the market are authorized for sale based on extensive clinical trial data, these trials are conducted on a limited subset of the population. More information about drugs is gained when these products are used in the broader population which may vary from the subset used in the clinical trials. Specifically, in the broader population, there would be people with other illnesses and medications, greater genetic diversity, greater range of ages, etc. With more long-term and widespread use, more information (e.g., about potential long-term toxicity or rare adverse reactions) is gained about the drug. But initially, less may be known about the long-term effects in the broader population and practitioner involvement means that they are there to assist patients in managing adverse reactions if any were to occur.

b) Drugs proposed for a new use
A drug may have been on the market but is now being proposed for sale with a change to its conditions of use (e.g, a new use, strength, dose, species, age group, or route of administration). In some cases, there may be gaps in the information regarding the long-term consequences associated with the new use. In these cases, prescription status would help to ensure practitioner oversight.

c) Drugs used in a small number of patients
Some drugs have been used only by a small number of patients. For example, drugs that treat rare diseases are used by very small target patient populations. In cases where the drug has not had widespread use or is only used in a small patient population, it can be more difficult to determine the long-term consequences of its use. If there are uncertainties that warrant further attention regarding long-term use, the drug will typically be prescription.

d) Drugs whose pharmacological effects are not fully characterized
For some drugs, there is not a complete understanding of their pharmacological effects, leaving some uncertainties about the long-term consequences of their use. Where the pharmacological effects and the long-term consequences of these

effects are not well established, the drugs are typically authorized as prescription drugs.

Limited experience with a drug can leave some uncertainties regarding the safety and efficacy of the drug. When there are uncertainties that warrant further attention, the drugs are typically given prescription status so that practitioners can monitor and manage any unanticipated effects.

Example - Natalizumab is first in a new class of drugs to treat multiple sclerosis. It is a monoclonal antibody which reduces nerve damage by decreasing inflammation in the brain. There are uncertainties about natalizumab, including concerns about side effects from its long-term use. Therefore, for these and other reasons, it is a prescription drug.

Example - Raltegravir is used with other human drugs to treat Human Immunodeficiency Virus-1 (HIV-1) infections in some patients. The long-term effects of this drug have not been established. This is one of several reasons raltegravir is a prescription drug.

As experience grows, and more knowledge is gained about a drug, prescription status may no longer be necessary if the drug does not meet any of the other factors. In other cases, once more is known about the drug, new issues are identified with its use and effects such that prescription status would still be required.

Sometimes drugs are marketed in other countries before they are sold in Canada. As such, if the country has a well developed post marketing surveillance system, some information about the drug's use and effects may already be available. Health Canada will also consider this experience.

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

In some cases, making drugs prescription is a risk management decision to manage access to these products in order to protect the health and safety of individuals, animals and the public at large. Access is restricted with the help of practitioners.

Factor 3.1 There is Potential for Harm to Public Health

There are some drugs that if widely or improperly used would have the potential to cause public health concerns. In these cases, drugs are typically given prescription status to avoid or minimize future problems for individual patients and for the public.

For instance, where the drug could contribute to the development of resistant strains of micro-organisms [bacteria, viruses or fungi] or resistant strains of parasites, it would be

typically authorized as a prescription drug. This would also apply to drugs for veterinary use which are also useful in human medicine. Resistant strains create not only problems in terms of individual human and animal health, but also in terms of public health.

Example - Fluoroquinolone antibiotics are available only as prescription drugs because their unrestricted use in humans and animals could result in the development of resistance in bacteria. Patients who then are infected with the resistant bacteria could no longer be successfully treated with the fluoroquinolone antibiotics. Therefore, access to this group of antibiotics is restricted by making them prescription drugs.

Factor 3.2 There is Potential for Diversion or Abuse Leading to Harmful Non-medical Use

In the context of human drugs, a drug will likely be given prescription status if it has diversion or abuse potential that is likely to lead to harmful non-medical use. It is important that patient access to these drugs has practitioner supervision. In many cases, the medicinal ingredients in these products will also be regulated as controlled substances under the *Controlled Drugs and Substances Act* and its regulations.

Intentional abuse is not applicable in the veterinary context as the owner of the animal being treated controls how much of the drug the animal will get. However, veterinary drugs which are likely to be diverted to humans and whose use in humans could cause significant harm would likely be authorized as prescription drugs or could be regulated as controlled substances.

8 Exceptions

Health Canada considers the three principles and associated factors described above when determining whether a drug should be made available by prescription only. If one or more of these principles or factors apply, the drug typically will become a prescription drug. However, there are cases where, in the interest of an individual, public or animal health, exceptions are made. In these cases, a health and safety rationale for easier access to these drugs outweighs the benefits of the prescription controls. Under such circumstances, Health Canada will consider making an exception so that a prescription would not be required for the public to obtain access to the drug.

For instance, some exceptions have been made to ensure that some drugs are easily available to the public under emergency circumstances where it would not be possible to get a prescription in a timely manner.

Example - Nitroglycerin, a drug for angina [chest pain], is an exception and does not have prescription status. People normally get nitroglycerin with a prescription from their practitioner. However, in the event that a person is experiencing angina but cannot locate their nitroglycerin and is not close to a hospital, he or she is able to obtain it from a pharmacy as it is a nonprescription product. The nitroglycerin helps relieve the chest pain and limit further damage to the heart. This is an example of where there is easier access for emergency circumstances.

Example - Some people have such severe allergies to a substance (e.g., peanuts) that they carry on them auto-injectors filled with epinephrine. When they are accidentally exposed to the substance they can use the drug to prevent a life-threatening reaction. These epinephrine auto-injectors are available without a prescription so that if someone were to travel to another town or city in Canada and forget their epinephrine auto-injector, they could easily get a replacement at any pharmacy. This exception helps prevent health emergencies from occurring.

Exceptions have also been made where greater availability better served public health and obtaining individual prescriptions was not practical for the healthcare system.

Example - Every year, many people have to go to hospital due to influenza infections [the flu] and some die . Vaccinating the public on a large scale can reduce the number of people who become sick with the flu. Health Canada considered many facts including the nature of the drug and the involvement of healthcare professionals in the drug's administration, and concluded that being able to reduce the number of people who are affected and harmed by the flu outweighed the benefits of requiring a prescription. Therefore, an exception was made for flu vaccines and they were not made prescription drugs. In this way, large public vaccination campaigns can be undertaken to help protect individual and public health.