SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

GUIDELINE TO THE SCHEDULING OF MEDICINES

This guideline is intended to provide guidance to applicants on the scheduling of substances submitted for registration as medicines. It represents the South African Health Products Regulatory Authority's current thinking on the safety, quality and efficacy of medicines and takes into account the country's obligations in terms of international agreements. It is not intended as an exclusive approach. The Authority reserves the right to request any additional information to establish the scheduling status of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the CEO and the SAHPRA website.

First publication released for Industry comment	October 2013
Due Date for Comment	January 2014
Version 1- Final Version	June 2014
Version 2 – Alignment with SAHPRA	July 2019
Implementation date	06 November 2019

CEO OF SAHPRA

TABLE OF CONTENTS

		Page
1	**INTRODUCTION**	3
1.1	Scope of the Guidelines	3
1.2	Information for Applicants	3
1.2.1	General	3
1.2.2	Language	3
1.2.3	Where to send applications	3
1.3	Principles of Scheduling	4
1.4	Brief description of the Schedules	4
2	**GENERAL GUIDELINES FOR CATEGORISATION IN THE SCHEDULES**	10
3	**APPLICATIONS FOR SCHEDULING OF MEDICINES OR SUBSTANCES**	12
3.1	Applications for Registration	12
3.2	Products submitted for registration where a change in scheduling status is requested	12
4	**APPLICATIONS FOR CHANGING THE SCHEDULING CLASSIFICATION (RESCHEDULING) OF A MEDICINE OR SUBSTANCE**	13
4.1	Applications for rescheduling of selected indications, strengths, routes of administration or pack sizes	13
5	**UPDATE HISTORY**	13
	Appendix: Format for applications for rescheduling	13
	1 Cover/title page	13
	2 Declaration by Applicant	13
	3 Table of Contents	13
	4 Summary	14
	5 Body of Application	14
	6 Other Relevant Information	15
	7 Bibliography	15
	8 Copies of referenced material	15
	9 Appendices if required	16

1 INTRODUCTION

1.1 Scope of the Guidelines

These guidelines are intended to provide information and guidance on the criteria and procedures applied by SAHPRA when evaluating the scheduling status of a medicine or substance for human or veterinary use.

These guidelines should be read in conjunction with the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended, and the supporting Regulations.

As these guidelines are constantly evolving, due to harmonisation initiatives as well new scientific developments, applicants are advised to always consult the latest information available. SAHPRA endeavours to keep abreast of such developments and to keep its requirements, procedures and policies in line with "best international practice".

1.2 Information for Applicants

1.2.1 General

The scheduling of medicines and products containing substances already listed in the Schedules as well as those substances not yet contained in the Schedules (new chemical entities) are normally managed as part of the medicine registration process. Three broad types of applications are considered by SAHPRA:

- applications for the registration of a medicine, which may include applications for the scheduling of a new chemical entity or applications for registration of a product containing a substance already listed in the Schedules (in accordance with such listing);
- applications for re-scheduling a substance that has already been listed in the Schedules;
- applications for listing a substance in the Schedules for prescribing by an authorised prescriber other than a medical practitioner or dentist.

Applications for the registration of a medicine may only be made by manufacturers or importers of medicines. However, applications for re-scheduling of a substance may be made by any person or organisation. Applications for listing a substance for prescribing by an authorised prescriber other than a medical practitioner or dentist would usually be made by a statutory health council,, but could also be made by an individual or organisation. In addition, requests to reconsider the scheduling status of a substance may be submitted by individuals, private sector firms, organisations, law enforcement agencies or specific departments of directorates within the public sector. The processing of all applications may only proceed once all requirements, outlined in this document, are complied with. The application will be considered complete only if the submission is in the proper format, with the required data, the correct number of copies and the prescribed application fee, if applicable.

Once an application has been received, it will be logged in, acknowledged, and processed for evaluation. From this point on, time lines will be followed as determined by SAHPRA for the evaluation and these will be communicated to the applicant.

At no stage will the applicant be permitted to communicate directly with an evaluator. All queries and concerns must be communicated through the regulatory authority to allow for these to be logged in and processed.

1.2.2 Language

In terms of Regulation 22 of Act 101 of 1965, all applications and supporting data submitted to the South African Health Products Regulatory Authority must be presented in English. Any documents in languages other than English must be accompanied by a translation.

1.2.3 Where to send Applications

Applications may be submitted at the SAHPRA reception; CSIR Campus, Meiring Naude Road, PRETORIA, 0001 where these will be logged in and acknowledged. All correspondence should be addressed to the CEO of Medicines. Applications received in any manner other than as stated above will not be considered for processing.

1.3 Principles of Scheduling

In terms of the Medicines and Related Substances Act (Act 101 of 1965), a 'Scheduled substance' is defined as follows: “means any medicine or other substance prescribed by the Minister under section 22A”. Section 22A(2) empowers the Minister of Health “on the recommendation of SAHPRA”, to make the Schedules referred to in that section, Section 37A also empowers the Minister, again on the recommendation of SAHPRA, to amend the Schedules by notice in the Government Gazette. The official Schedules shall therefore always be those that have been published in the Government Gazette or amended by subsequent notice in the Gazette. All medicines are subject to a scheduling process on the basis of the substances (active pharmaceutical ingredients) they contain.

The sale and supply of medicines in South Africa is governed by section 22A of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), read together with the supporting Regulations. Control over access to medicines and substances are therefore regulated by the process of scheduling, and the control measures provided for in the Act and Regulations. Scheduling allows for different levels of regulatory control over pharmacologically active substances, whether in the form of active pharmaceutical ingredients, naturally-occurring products or extracts thereof, or finished pharmaceutical products (medicines). In addition, these legal provisions enable South Africa to comply with its obligations in terms of the Single Convention on Narcotic Drugs (1961), the Convention on Psychotropic Substances (1971) and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988), to which it is a signatory.[1]

The primary consideration in scheduling a substance is its safety profile, in relation to the therapeutic indications for its use. Substances may be listed in one or more of eight Schedules.
However, substances may also be listed in more than one Schedule, based on dosage form, route of administration, strength, indication, dose, duration of treatment or a combination of these factors.
Where a substance or medicine has been listed in more than one Schedule, the other Schedule(s) in which it is listed is/are indicated in parentheses after the inscription in a particular Schedule. Where exceptions are included in an entry, these have been emphasised by printing the word —**except** in bold type.

DESPITE THIS, IT IS NOT POSSIBLE TO LABEL ANY SINGLE PRODUCT (AS DISTINCT FROM *SUBSTANCE*) WITH MORE THAN ONE SCHEDULE STATUS. WHERE APPLICANTS WISH TO MARKET PRODUCTS WITH DIFFERENT SCHEDULES, THIS WILL REQUIRE DIFFERENT MARKET AUTHORISATIONS AND ALSO DIFFERENT PROPRIETARY NAMES.

1.4 Brief Description of the Schedules

Section 22A of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) provides for a graduated system of control over sale and supply of substances, ranging from access via any retail outlet, at one extreme, to outright prohibition, at the other.

1.4.1 Schedule 0

Although no list of Schedule 0 substances is provided in the Schedules, a preamble states that “This Schedule includes all substances or mixtures of substances subject to registration in terms of the Act and which are not listed in any of the other Schedules”.

1 Details of the conventions can be obtained from the website of the International Narcotics Control Board at http://www.incb.org/

Section 22A(3) states that “Any Schedule 0 substance may be sold in an open shop.”

In order to qualify for Schedule 0 status, a substance must be known to be substantially safe in use, without routine necessity for advice or counselling by a healthcare practitioner. Medicines containing one or more substances, none of which bears a Scheduling status higher than Schedule 0, are indicated for minor diseases or symptoms which can be easily recognised by the patient and which do not require medical diagnoses or monitoring. As a result, Schedule 0 substances may be sold in an open shop (i.e. any setting, including general dealers). Such substances may also be sold in a pharmacy.

However, a holder of a section 22C(1)(a) dispensing licence may not provide any medicine to a patient unless that act is preceded by proper diagnosis and prescription (in terms of General Regulation 18(7)(f)).

General Regulation 45(2)(a) states that “Medicines which do not contain a scheduled substance and medicines which contain a substance appearing in Schedule 0 or Schedule 1 may be advertised to the public”

1.4.2 Schedule 1

Section 22A(4) states that:

“Any Schedule 1 substance shall not be sold-

(a) by any person other than-

(i) a pharmacist, or a pharmacist intern or pharmacist's assistant acting under the personal supervision of a pharmacist;

(ii) a manufacturer of or wholesale dealer in pharmaceutical products for sale to any person who may lawfully possess such substance;

(iii) a medical practitioner or dentist, who may-

(aa) prescribe such substance;

(bb) compound and dispense such substance only if he or she is the holder of a licence as contemplated in section 22C(1)(a);

(iv) a veterinarian who may prescribe, compound or dispense such substance;

(v) a practitioner, nurse or a person registered under the Health Professions Act, 1974, other than a medical practitioner or dentist, who may-

(aa) prescribe only the Scheduled substances identified in the Schedule for that purpose;

(bb) compound and dispense the Scheduled substances referred to in item (aa) only if he or she is the holder of a licence contemplated in section 22C(1)(a);

(b) to any person apparently under the age of 12 years except upon a prescription issued by an authorised prescriber and dispensed by a pharmacist, pharmacist intern or pharmacist's assistant or by a veterinarian or a person who is the holder of a licence as contemplated in section 22C(1)(a), or on a written order disclosing the purpose for which such substance is to be used and bears a signature known to the seller as the signature of a person known to such seller and who is apparently over the age of 12 years;

(c) unless the seller, other than a manufacturer or wholesale dealer in pharmaceutical products, enters in a prescription book required to be kept in the prescribed manner, the prescribed particulars of such sale.”

Schedule 1 substances must therefore be known to be substantially safe in use, but might require advice or counselling by a pharmacist or other healthcare practitioner in order to ensure safe use. Products containing Schedule 1 substances are indicated for minor diseases or symptoms.

As with Schedule 0 substances, the advertising of medicines containing Schedule 1 substances to the public is permitted by General Regulation 45.

Substances which may be prescribed by persons other than medical practitioners and dentists will be identified and will be annotated or otherwise differentiated in their inscriptions in each Schedule, from Schedule 0 to Schedule 6. However, in order to gain access to prescribing authority, such persons will also need to be registered as such by their professional council (as provided for in section 22A(14)(b)).

1.4.3 Schedule 2

The control over Schedule 2 to 6 substances is provided for in section 22A(5) of the Act, which reads as follows:

"Any Schedule 2, Schedule 3, Schedule 4, Schedule 5 or Schedule 6 substance shall not be sold by any person other than-

(a) a pharmacist, pharmacist intern or a pharmacist's assistant acting under the personal supervision of a pharmacist, who may sell only Schedule 2 substances without a prescription;

(b) a pharmacist or a pharmacist intern or pharmacist's assistant acting under the personal supervision of a pharmacist, upon a written prescription issued by an authorised prescriber or on the verbal instructions of an authorised prescriber who is known to such pharmacist;

(c) a manufacturer of or wholesale dealer in pharmaceutical products for sale to any person who may lawfully possess such substance;

(d) a medical practitioner or dentist, who may-

(i) prescribe such substance;

(ii) compound or dispense such substance only if he or she is the holder of a licence as contemplated in section 22C(1)(a);

(e) a veterinarian who may prescribe, compound or dispense such substance;

(f) a practitioner, a nurse or a person registered under the Health Professions Act, 1974, other than a medical practitioner or dentist, who may-

(i) prescribe only the Scheduled substances identified in the Schedule for that purpose;

(ii) compound and dispense the Scheduled substances referred to in subparagraph (i) only if he or she is the holder of a licence contemplated in section 22C(1)(a)."

In order for a substance to be listed in Schedule 2, it must be known to be substantially safe in use but require advice, counselling and management or monitoring by a pharmacist or other health professional. While medicines containing such substances may be indicated for minor disease or symptoms which can be recognised by the patient, these will require verification by a pharmacist but not an initial medical diagnosis or medical management. Schedule 2 medicines are therefore available without a prescription, but require a greater level of control than Schedule 1 medicines.

Additional control measures are provided for in section 22A(6) of the Act, which reads as follows:

"Any sale under subsection (5) shall only take place on condition that-

(a) all the prescribed particulars of every sale shall be recorded in the prescribed manner in a prescription book or other permanent record required to be kept in the prescribed manner;

(b) the authorised prescriber who has given verbal instructions to a pharmacist to dispense a prescription shall within seven days after giving such instructions furnish such pharmacist with a prescription confirming such instructions;

(c) in the case of verbal instructions the treatment period shall not exceed seven days;

(d) if a prescription is not presented for dispensing within 30 days of issue it shall not be dispensed;

1.4.3 Schedule 2 continued

(e) in the case of a Schedule 2 substance, such substance may not be supplied to any person apparently under the age of 12 years except upon a prescription issued by an authorised prescriber and dispensed by a pharmacist, pharmacist intern or pharmacist's assistant or by a veterinarian or a person who is the holder of a licence as contemplated in section 22C (1) (a), or on a written order disclosing the purpose for which such substance is to be used and bears a signature known to the seller as the signature of a person known to such seller and who is apparently over the age of 12 years;

(f) in the case of a Schedule 2, Schedule 3 or Schedule 4 substance, such sale may be repeated if the person who issued the prescription has indicated thereon the number of times it may be dispensed, but not for longer than six months;

(g) in the case of a Schedule 5 substance, such sale shall not be repeated for longer than six months, and then only if the authorised prescriber has indicated on the prescription the number of times and the intervals at which it may be dispensed;

(h) where a Schedule 5 substance is used for-

(i) its anxiolytic, antidepressant or tranquillising properties it shall not be prescribed for longer than six months unless the authorised prescriber has consulted a registered psychiatrist, or, in the case of a psychiatrist, another psychiatrist before issuing a new prescription;

(ii) its analgesic properties it shall not be prescribed for longer than six months unless the authorised prescriber has consulted another medical practitioner, before issuing a new prescription;

(j) in the case of a Schedule 6 substance, it shall not be repeated without a new prescription being issued;

(k) in an emergency in which the health or life of a patient is at stake, a pharmacist engaged in wholesale practice may, on receipt of a telephonic or tele faxed or other electronic request, supply a Schedule 6 substance to a pharmacist, medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974, without a written order: Provided that-

(i) it shall be the responsibility of such pharmacist, medical practitioner, dentist, veterinarian, practitioner, nurse or other person to ensure that such pharmacist receives a written order within seven days.

(ii) the Schedule 6 substance shall be supplied in the smallest unit sales pack available;

(iii) a permanent record is made and kept of such supply.

(l) in an emergency a pharmacist may sell any Schedule 5 or Schedule 6 substance in a quantity not greater than that required for continuous use for a period of 48 hours, on the verbal instructions of a medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974, who is known to such pharmacist, but the prescriber who has given such verbal instructions shall within 72 hours after giving such instructions furnish to such pharmacist a written prescription confirming the instructions;

(m) in an emergency a pharmacist may sell a Schedule 2, Schedule 3 or Schedule 4 substance on a non-recurring basis for a period not exceeding 30 days in accordance with the original prescription in order to ensure that therapy is not disrupted if he or she is satisfied that an authorised prescriber initiated the therapy, with the intention that the therapy be continued, and that the particulars of such sale are recorded in a prescription book or other prescribed permanent record;

(n) a pharmacist may sell a greater or a lesser quantity of a Schedule 1, Schedule 2, Schedule 3 or Schedule 4 substance than the quantity prescribed or ordered, according to the therapeutic pack in the original container of such substance as supplied to him or her, but the quantity so sold shall not exceed or be less than, 25 per cent of the quantity specified in the prescription or order in question;

(o) any seller referred to in this subsection shall retain the prescription or order concerned for a period of not less than five years as from the date of such sale;

(p) a Schedule 6 substance may only be sold if the course of treatment does not exceed 30 consecutive days;

(q) the sale of a specified Schedule 5 or Schedule 6 substance by a manufacturer of or wholesale dealer in pharmaceutical products shall be recorded in a register which shall be kept in the prescribed manner, and shall be balanced so as to show clearly the quantity of every specified Schedule 5 or Schedule 6 substance remaining in stock as on the last day of March, June, September and December of each year, and such balancing shall be completed within the 14 days following each of the said dates;

(r) a pharmacist shall endorse on the prescription the date of sale and the quantity of the substance sold, and when it is repeated, the date of sale and the quantity of the said substance sold, and the last seller shall retain the prescription for a period of not less than five years as from the date of the last sale;

(s) any Schedule 1, Schedule 2, Schedule 3 or Schedule 4 substance for the treatment of any animal may be supplied by any person practicing a para-veterinary profession within the meaning of the Veterinary and Para-Veterinary Professions Act, 1982 (Act 19 of 1982), upon a written prescription issued by a veterinarian or on the verbal instructions of a veterinarian.

Some of these provisions only apply to medicines containing substances listed in the subsequent Schedules.

General Regulation 45(2)(b) states that "Medicines which contain a substance appearing in Schedule 2, Schedule 3, Schedule 4, Schedule 5 or Schedule 6 may be advertised only for the information of medical practitioners, dentists, veterinarians, pharmacists and other persons authorised to prescribe or in a publication which is normally or only made available to persons referred to therein". No product containing a Schedule 2 substance may therefore be advertised to the public.

1.4.4 Schedule 3 and 4

From Schedule 3 to Schedule 6, medicines containing such substances can only be obtained on the prescription of an authorised prescriber. Schedule 3 and 4 substances are indicated for use in disease or conditions which require professional medical, dental or veterinary diagnoses and management.

As listed above, repeat prescriptions for Schedule 2, 3 or 4 substances are limited to a maximum of 6 months' supply. There are no differences between the control measures applicable to Schedule 3 and 4 substances.

Section 22A(6)(l) provides for emergency access to Schedule 2 to 4 substances: "in an emergency a pharmacist may sell a Schedule 2, Schedule 3 or Schedule 4 substance on a non-recurring basis for a period not exceeding 30 days in accordance with the original prescription in order to ensure that therapy is not disrupted if he or she is satisfied that an authorised prescriber initiated the therapy, with the intention that the therapy be continued, and that the particulars of such sale are recorded in a prescription book or other prescribed permanent record".

As with Schedule 2 substances, Schedule 3 and 4 substances may not be advertised directly to the public.

1.4.5 Schedule 5 (and specified Schedule 5)

In order to be listed in Schedule 5, substances must be known to have a low to moderate potential for abuse or dependence, which necessitates both medical diagnosis and management, but also enhanced control of supply. Such substances may be listed in schedule IV of the 1971 Convention on Psychotropic Substances, which indicates more stringent international control. In addition, some Schedule 5 substances are listed as "specified Schedule 5", indicated by flagging with an asterisk in the Schedules. It is intended that enhanced record-keeping will be required for all specified Schedule 5 substances (such as the keeping of registers by all sellers).

1.4.5 Schedule 5 (and specified Schedule 5) continued

Repeat prescriptions for Schedule 5 and specified Schedule 5 substances are permissible, but are more stringently controlled by section 22A(6):

"(g) in the case of a Schedule 5 substance, such sale shall not be repeated for longer than six months, and then only if the authorised prescriber has indicated on the prescription the number of times and the intervals at which it may be dispensed;

(h) where a Schedule 5 substance is used for-

(i) its anxiolytic, antidepressant or tranquillising properties it shall not be prescribed for longer than six months unless the authorised prescriber has consulted a registered psychiatrist, or, in the case of a psychiatrist, another psychiatrist before issuing a new prescription;

(ii) its analgesic properties it shall not be prescribed for longer than six months unless the authorised prescriber has consulted another medical practitioner, before issuing a new prescription."

Emergency access to Schedule 5 or 6 substances is provided for in section 22A(6)(k), but with specific requirements: "in an emergency a pharmacist may sell any Schedule 5 or Schedule 6 substance in a quantity not greater than that required for continuous use for a period of 48 hours, on the verbal instructions of a medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974, who is known to such pharmacist, but the prescriber who has given such verbal instructions shall within 72 hours after giving such instructions furnish to such pharmacist a written prescription confirming the instructions".

Schedule 5 and specified Schedule 5 substances may not be advertised directly to the public.

1.4.6 Schedule 6

Schedule 6 substances may have a moderate to high potential for abuse or for producing dependence, which necessitates close medical management and supervision and strict control over supply. Such substances are listed in Schedules of the 1961 Convention on Narcotic Drugs (except those listed in Schedule III). The conditions under which Schedule 6 medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act and are suitably restrictive.

Section 22A(6)(i) prohibits the supply of a Schedule 6 substance on a repeat prescription, whereas section 22A(6)(o) limits the quantity dispensed to a maximum of 30 days' supply at the prescribed dose.

Schedule 6 substances may not be advertised directly to the public.

1.4.7 Schedule 7

Schedule 7 substances are not recognised for medical use and have an extremely high potential for abuse or producing dependency which renders their possession unjustifiable and undesirable, except for limited scientific purposes. This Schedule includes substances listed in Schedule I of the 1971 Convention on Psychotropic Substances. The advertising of Schedule 7 substances is accordingly prohibited.

1.4.8 Schedule 8

Access to a limited list of substances which have an extremely high potential for abuse or dependency, but some limited recognised medical uses, is provided for by this Schedule. Such substances are made available by the Director-General only to medical practitioners who have obtained special permission from the South African Health Products Regulatory Authority for such use and prescription. The advertising of Schedule 8 substances is prohibited.

2 GENERAL GUIDELINES FOR CATEGORISATION IN THE SCHEDULES

In deciding the scheduling status of a medicine or substance, the primary emphasis is on evidence of safety in use and the requirements for professional advice and/or supervision of its use. In addition, the requirements for control over access, possession and supply, as stipulated in international agreements, are considered. The scheduling decision therefore involves the consideration of a number of factors, including:

- evidence for the toxicity of the substance and the safety in use;
- the proposed indication for the substance;
- the need for medical diagnosis, monitoring and medical management by a healthcare professional;
- the potential for abuse;
- the need for access to the substance.

However, there may be considerable interaction between the factors considered, as none is a simple binary quality of the substance (indicating the presence or absence of the factor). The factors need to be considered as a whole in order to reach a final assessment of the public health risk associated with a substance, and hence their optimal categorisations in relation to the available control measures.

In terms of the listing of substances to be prescribed by persons other than medical practitioners or dentists, the competencies of the prescriber category in question also have to be considered.

In order to meet the criteria for Schedule 1 status, the following characteristics would need to be demonstrated by candidate substances:

- There is a low and well-characterised incidence of adverse effects, interactions with commonly used substances or food and contra-indications;
- The risk profile of the medicine is well defined and the risk factors can be identified and managed by a consumer through appropriate packaging and labelling and access to consultation with a health professional if required;
- The use of the medicine at established therapeutic doses is unlikely to produce dependency and the medicine is unlikely to be misused, abused or illicitly used;
- The medicine is for minor ailments or symptoms that can easily be recognised and are unlikely to be confused by the consumer with other more serious diseases or conditions. Treatment can be managed by the consumer without the need for medical intervention. However, the availability of a pharmacist at the point of sale supports the consumer in selecting and using the appropriate medicine;
- The use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition;
- The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low;
- Safe and effective use of the medicine can be achieved by labelling, packaging, and/or provision of other information, with access to advice from a pharmacist.

In order to meet the criteria for Schedule 2 status, the following characteristics would need to be demonstrated:

- The risk profile of the medicine is well defined and the risk factors for adverse effects and interactions are known, identifiable and manageable by a pharmacist;
- The medicine is substantially safe with pharmacist intervention to ensure its safe and effective use. There may be potential for harm if the medicine is used inappropriately;

- The consumer may not be able to self-monitor the safe ongoing use of the medicine. The condition does not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management;
- The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use. An interaction between the pharmacist and consumer (patient) is necessary to reinforce and/or expand on aspects of the safe use of the medicine;
- Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or a pharmacist;
- The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition. Interaction between the pharmacist and the consumer (patient) is required to detect the risk of masking a serious disease or compromising medical management of a disease, and to deal with it appropriately;
- The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is an identified risk of misuse, abuse or illicit use, the risk can be minimised through monitoring by a pharmacist.

However, if any of the following characteristics are met, the substance will require scheduling as a prescription-only medicine (Schedules 3 to 6):

- The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention. Diagnosis, management or monitoring of the medical condition is such that it requires medical, veterinary or dental intervention before the substance is used;
- The use of the substance requires adjunctive therapy or evaluation. Adjunctive therapy could include other medicines, non-pharmacological measures, or specialised medicine delivery devices. Evaluation could include laboratory tests or additional clinical assessments;
- The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use;
- Control of access and duration of therapy by a medical, veterinary or dental practitioner is required;
- The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance;
- The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical, veterinary or dental intervention to minimise the risk of using the substance;
- The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical, veterinary or dental practitioner;
- The use of the substance has contributed to, or is likely to contribute to, communal harm. For example the development of resistant strains of microorganisms. Appropriate use, and/or the decision to continue treatment, requires evaluation by a medical, veterinary or dental practitioner;
- The experience of the use of the substance under normal clinical conditions is limited. Unexpected effects of the substance may only become evident after widespread use. Close monitoring of the patient is required by a medical, veterinary or dental practitioner to monitor for unanticipated effects.

Accordingly, in order for a higher degree of control to be imposed, as in Schedule 5, specified Schedule 5 or Schedule 6, one or more of the following characteristics would need to be demonstrated:

- Listing in Schedule IV to the United Nations Single Convention on Narcotic Drugs (1961) or in Schedule I to the United Nations Convention on Psychotropic Substances (1971);
- Taking into consideration the danger to the health of individuals and of the community (both immediate and imminent) associated with the use of the substance as compared to the therapeutic advantages of the substance, the benefits are substantially outweighed by the risks.

However, if the substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use, then a higher level of control is required through prohibition of use, possession, administration, prescription, sale or distribution, in order to prevent abuse, misuse or diversion into illicit activities. This may be achieved by listing in Schedule 7. With such substances, the dangers are such as to warrant limiting use to strictly controlled medical and scientific research. Exceptions can be provided for in terms of Schedule 8 status.

The same logic would be applied in considering an application for rescheduling. Therefore, in order to justify a rescheduling from Schedule 3 or 4 to Schedule 2 or 1, evidence would need to be provided to justify use without a prescription. If any of the following criteria were met, prescription status would need to be maintained:

- The substance is likely to present a direct or indirect danger to human health, even when used correctly, if used without supervision by a medical practitioner or dentist;
- The substance is frequently and to a very wide extent used incorrectly or inappropriately, and as a result is likely to present a direct or indirect danger to human health;
- The safety and efficacy of the substance has not yet been adequately described and requires further investigation.

Likewise, in order to justify a Schedule 0 status, evidence would need to be provided that show that the hazard to health, the risk of misuse and the need for special precautions in handling are small, and that wider sale would be a convenience to the consumer.

3 APPLICATIONS FOR SCHEDULING OF MEDICINES OR SUBSTANCES

3.1 Applications for Registration

Refer to section 5 of the General Information guideline.

3.2 Products submitted for registration where a change in scheduling status is requested

Although a substance might already be listed in the Schedules, it is possible that an application could be made for a new dosage form, or for a drug combination formulated for new indication for use. In such cases, the new product may qualify for the same scheduling status as was allocated to the active ingredient in other dosage forms or with different indications. Alternatively, SAHPRA may find it necessary to assign a different scheduling status, one appropriate to the dosage form or to the new indications for the substance.

If an applicant is of the opinion that the unique properties or limited indications of a product qualify it for a different scheduling status than that already listed in the Schedules, a rescheduling application should be made. The requested status should not merely be indicated on the proposed package insert.

The covering letter for the application should clearly indicate that a request for rescheduling is involved. Any new clinical or supportive data included in the CTD/ eCTD application form must also be incorporated in the application for rescheduling.

It is therefore advisable to submit a copy of the rescheduling request directly to the section dealing with scheduling so that the evaluation may be initiated simultaneously with the registration process.

4 APPLICATIONS FOR CHANGING THE SCHEDULING CLASSIFICATION (RESCHEDULING) OF A MEDICINE OR SUBSTANCE

4.1 Applications for rescheduling of selected indications, strengths, routes of administration or pack sizes

A product is normally assigned the highest scheduling status appropriate to any one of the registered indications of the product. If application is made to reschedule only selected indications of a specific product to a lower Schedule, a unique name and a separate registration dossier will also be required for such a product. It must be noted that dual scheduling on printed packaging is not permitted. Only products with indications, strengths, routes of administration and/or pack sizes applicable to the lower schedule will qualify for the lower scheduling status.

The structure of the application should be as follows:

Cover/title page
Declaration by Applicant
Table of Contents
Summary
Body of Application
Other Relevant Information
Bibliography
Copies of referenced material
Appendices if required

The application format is provided in the Appendix.

Applicants must provide:

(i) Three copies of the full application.

5 UPDATE HISTORY

Date	Reason for update	Version & Publication
Sept 2013	Initial Version	Version 1
June 2014	Implementation	Version 1
October 2019	Align with SAHPRA	Version 2

Appendix: Format for applications for rescheduling

1 Cover/title page

The cover / title page should indicate:

i. The subject of the application.

ii. The name and address of the applicant.

iii. The name of a contact person.

iv. The date on which the application was submitted.

2 Declaration by Applicant

Applications for a rescheduling decision must contain a declaration by the applicant certifying that to the best of the applicant's knowledge all information relevant to the application has been submitted and is true and accurate.

3 Table of Contents

The table of contents should tabulate and correlate the titles of each section and major subsections of the application with their appropriate page numbers.

4 Summary

The summary should contain a concise, clear statement of -

i. The purpose of the application, including any proposed change involved as well as the reason for the proposed change in scheduling status.

ii. The major points in the argument, including –

   a. The proposals arising from such argument.

   b. An overall summary of the toxicology, clinical data, post-marketing studies and pharmacoepidemiology of the compound.

The arguments must address the criteria listed in the guidelines for the categorisation of medicines or substances in the schedules.

Normally, this summary will not extend beyond a few pages. Tables are favoured as a means of condensing information. Studies reported in the summary should be cross-referenced to the reports in the main submission.

5 Body of Application

The body of the application should communicate the aims and justification of the proposal in a concise, clear and logical manner. Appropriate data and information must be supplied to demonstrate that the substance or product will be safe for the public when supplied and used in the proposed manner. Whilst the format of each application may vary the Committee recommends the use of a standard framework consisting of the following:

5.1 Purpose of the Application

5.2 General Background

5.2.1 Current Regulatory Status

Reference should be made to the current local regulatory status of the product or substance in terms of dosage forms registered, scheduling status and approved indications. If applicable, the registration number must be indicated.

5.2.2 International Regulatory Status

Classification / scheduling status in other countries where the product is registered, including information of the approved indications and dosage forms. The availability status should be clearly indicated in terms of e.g. prescription only, pharmacy only, general sales outlets. For regulatory authorities with which the SAHPRA aligns itself, refer to the General Information guideline.

5.3 Introduction of the data upon which the application is based

5.4 Technical Information

Additional information on the active pharmaceutical ingredient that was not submitted during the registration of the original product is required. Data that were submitted during the registration process may be summarized.

5.4.1 Physico-Chemical Properties of the Active Pharmaceutical Ingredient

i. Structural formula or any available information on the structure of the substance.
ii. All relevant chemical and physical properties.

5.4.2 Pharmacology

i. Any known information relating to the structural and pharmacological relationship to other drugs or chemicals
ii. The pharmacodynamic and pharmacokinetic profile
iii. Interactions, incompatibilities, side effects or adverse reactions
iv. Any recognized standard such as a pharmacopoeia monograph.

5.4.3 Clinical Data

i. Post-marketing reports
ii. Additional clinical reports
iii. Adverse drug reaction reports
iv. Epidemiology reports
v. Poisoning reports

5.4.4 Toxicology

i. Summary of the known toxicology of the product.
ii. Summary of the known metabolism of the product.
iii. Relevant details of any published or unpublished toxicological investigations of the product / substance

5.4.5 Safety Reports

i. A summary of animal studies that show low general toxicity and no relevant reproductive toxicity, genotoxic, or carcinogenic properties relevant to the experience/ exposure of the product.
ii. Information from post-marketing surveillance studies, clinical trials and published literature presenting the issue of drug safety. For OTCs: Considerable experience of patient exposure, including at least 2 years of use in the relevant or similar population.
iii. Information on adverse drug reactions. In the case of OTC medication the information should include experience without medical supervision in other countries. Variables such as numbers of patients treated, demographic details, indications for use and dose should be provided and taken into account in providing and interpreting the data;
iv. Drug interactions with food or commonly prescribed drugs.
v. Consideration of the consequences concerning misuse.

5.4.6 Occupational Health and Safety Information (If applicable)

A summary of occupational health and safety aspects.

5.4.7 Pharmaceutical Aspects

Any intended change in formulation, pack size, packaging, etc should be indicated. However, pharmaceutical data such as stability need not be included. This data must be evaluated as part of a registration application or amendment to the registration application.

5.4.8 Monitoring of the Public Health Impact

If evaluation of the public health impact is required proposals on how this will be managed should be given.

5.4.9 Education

If any specific education of professionals, distributors or users are required, details of a process to manage this is required.

5.5 Proposal

Indicate proposed schedule.

5.6 Discussion

Safety issues must be justified in relation to the schedule for which the application is made. For example: A motivation for rescheduling from Schedule 5 to Schedule 4 will focus on the absence of abuse potential.

5.7 Proposed Indication for Use

New indications are evaluated by the Clinical Committee as part of a registration application or an amendment to the registration application after registration. Only thereafter will the possibility of rescheduling be discussed.

5.8 Product Information and Presentation:

Presentation of the product:

i. Dosage form, strength and pack size
ii. Type of packaging
iii. Label warning or other information that can impact on safety
iv. Proposed package insert

Patient information leaflet **6 Other Relevant Information**

7 Bibliography

8 Copies of referenced material

9 Appendices if required