LAMPIRAN A

GUIDELINE ON REGISTRATION OF MEDICINAL GASES

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National Pharmaceutical Regulatory Agency
Ministry of Health Malaysia

Table of Contents

1. Objectives

This guidance document describes the procedures and documentation requirements for submitting application to register a medicinal/medical gas product in Malaysia. The intention of publishing this guideline is to facilitate the applicant through understanding the registration procedures and requirements which will ensure a more efficient registration process. Registration of medicinal gas products is to ensure that medicinal gases approved for the local market are safe, effective and of quality. This guidance document should be read in conjunction with the Drug Registration Guidance Document (DRGD).

2. Legal Basis

Any gas or mixture of gases intended for the administration to patients for medicinal purposes (e.g. anaesthetic, therapeutic, diagnostic or prophylactic) are referred as medicinal gases.

According to the Sale of Drugs Act 1952 (SODA) 1952, a 'drug' includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for a medicinal purpose. Under the Control of Drugs and Cosmetics Regulation (CDCR) 1984, Regulation 7(1), no person shall manufacture, sell, supply, import or possess or administer any product unless –
(a) the product is a registered product; and
(b) the person holds the appropriate licence required and issued under these Regulations.

As medicinal gases are drugs within the meaning of Section 2, SODA 1952, it will be regulated by Drug Control Authority (DCA) as tabulated in Table I: MDDCI and Combination Products Classification Decision, DRGD. Therefore, similar acts, regulations and regulatory framework pertaining to the manufacturing, authorization and placing on the market for drugs (pharmaceutical products) will apply to medicinal gases.

3. Classification

Medicinal gases are gases or gas mixtures intended for the administration to patients for medicinal purpose such as anaesthetic, therapeutic, prophylactic and diagnostic use. (MS 2675-1:2017)

Medicinal gases are classified into two categories as below :

a) Medicinal gases classified as a medicinal product / drug (regulated by DCA)
Gases or gas mixtures which mode of action is achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for hypoxia (oxygen gas).

b) Medicinal gases classified as medical device (regulated by Medical Device Agency, MDA)
Gases or gas mixtures which mode of action is achieved primarily by physical in nature and not achieved primarily based on pharmacological, immunological or metabolic action

in/on the body, such as gases for insufflation of the abdominal cavity for laparoscopy and gases for removal of warts (e.g. liquid nitrogen).

4. Scope

4.1 The scope covers medicinal gas classified as a medicinal product/drug and in cylinders intended for inhalation, which manufactured in a filling plant from bulk liquid gas.

4.2 This guideline does not apply to other types of gases such as:
a) Gases classified as medical devices
b) Gases that are manufactured, mixed and handled (including extemporaneous preparation) in hospitals for own patients use.
c) Gases for animal use (veterinary)
d) Gases use for cosmetic/aesthetic purpose
e) Gases use in laboratory (e.g. gas for freezing of tissue samples, calibration gas)
f) Recreational gases (e.g. oxygen gas for diving, mountain climbing)
g) Industrial gases

4.3 This guideline also does not apply to cylinders on its own (empty cylinders).

5 Definitions

5.1 Medicinal Gas Active Pharmaceutical Ingredient

Medicinal gas active pharmaceutical ingredient (API) is any gas/substance intended to be an active substance for a medicinal gas product. Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (as for example in an air separation plant).

Medicinal gas API including bulk liquid gases in containers/tankers are not subjected to registration by the DCA.

However, API information (as stated in *TABLE 1: REGISTRATION REQUIREMENT FOR GENERIC MEDICINAL GASES PRODUCT*) should be submitted as part of registration requirements.

5.2 Medicinal Gas Product

Medicinal gas product (classified as a medicinal product/drug) means medicinal gas finished product that has undergone all stages of production and quality control, including packaging in its final container and labelling. Gases falling under the definition of medicinal product and filled in gas cylinders in a manufacturing plant is considered as medicinal gas product. Medicinal gas product is released to the market by Authorised Person and can be used directly by healthcare professionals or by the patients themselves, such as

Finished pharmaceutical products including medicinal gas product must be registered with DCA. Appropriate evidences of safety, efficacy and quality which are in compliance with the conditions stated in Section 6 of this guideline must be provided.

6. Registration Procedures and Requirements

In general, registration procedures (including timeline and processing fees) and general requirements for medicinal gases are similar to other pharmaceutical products as described in DRGD. Guideline on Filling the Online Application Form for Product Registration via Quest System is available in DRGD. Specific requirements for registration for medicinal gases are listed as below.

6.1 New Drug Product

New Drug Product (NDP) is defined as any pharmaceutical products that have not been previously registered in accordance with the provisions of the Control of Drugs and Cosmetics Regulation 1984. This is also applicable to innovative gases and/or innovative gas mixtures.

NDP medicinal gas requirement are listed in Appendix 3 Guidelines on Registration of New Drug Products, DRGD.

6.2 Generic Product

Generic Product (GP) is a product that is essentially similar to a currently registered product in Malaysia (Appendix 5, DRGD), where a reference (innovator) medicinal gas product has been registered in Malaysia.

For certain medicinal gases such as oxygen, carbon dioxide, nitrous oxide, nitrous oxide/oxygen mixtures and medical air, reference to a registered innovator product can be exempted if 'well-established use' can be demonstrated such as :
a) It can be proved that the gas or gas mixture has been used for the proposed indication and administration route for at least 10 years
b) The safety and efficacy (including indication and dosage) are well documented in the scientific literature and generally acknowledged
c) The quality of product is according to the pharmacopoeia

Registration requirements for generic medicinal gas product are listed in Table 1.

7. Inspection and Licensing Requirements

Inspection and licensing of manufacturing premises or facilities, importers and wholesalers of medicinal gases on the basis of compliance with Good Manufacturing Practice (GMP) as well as Good Distribution Practice (GDP) are vital element of drug control. Compliance to GMP is prerequisite for the application of a manufacturing license as well as product registration. All manufacturers are warrant to comply with PIC/S Guide to Good Manufacturing Practice for Medicinal Products and related Annexes.

Every importers/wholesalers responsible for placing the medicinal gases in the market shall ensure that the products are stored, distributed and subsequently handled appropriately according to any directives or guidelines issued by the Senior Director of Pharmaceutical Services in accordance with the provisions of Regulation 29 of the CDCR 1984.

8. Post-Registration Requirements

The product registration holder (PRH) shall implement continuous monitoring through post-marketing activities once the product is registered as stipulated in the DRGD.

8.1 Pharmacovigilance

The PRH is responsible to ensure that an appropriate system of pharmacovigilance is in place, and appropriate action is taken, when necessary.

The PRH should have in place written procedures describing the handling of all adverse drug reactions (ADRs) related to their products. The system and procedures in place must be adequate for receipt, handling, evaluation and reporting of adverse drug reactions (ADRs) to the NPRA within the stipulated timelines detailed in the Malaysian Pharmacovigilance Guidelines.

The minimum information required for ADR reporting purposes is:
a) an identifiable patient,
b) name of a suspect medicinal product,
c) an identifiable reporting source, and
d) an event or outcome that can be identified as a reasonable suspected causal relationship.

8.2 Quality Monitoring

The PRH needs to establish a system to ensure products marketed are in accordance to the standards and requirement of the Authority.

Product registration holder, licensed manufacturer, importer and wholesaler must have a systematic product complaints handling procedure and relevant records must be available.

Quality and safety issues of the product should be reported to the relevant Authority.
Product registration holder, licensed manufacturer, importer and wholesaler needs to have an effective product recall procedure that includes the appropriate corrective and preventive action.

9. Glossary

Medicinal gas active pharmaceutical ingredient
Any gas intended to be an active substance for a medicinal gas product. (PIC/S)

Medicinal gas product
Medicinal gas finished product that has undergone all stages of production and quality control, including packaging in its final container and labelling. (DRGD)

10. References

Adapted from :

Swissmedic Administrative Ordinance Authorisation of Medicinal Gases, 2014

Taiwan FDA Appendix 4 : Documents for the Application for Drug Review and Registration of Generics including Medical Gas

Other references :

PIC/S Guide to Good Manufacturing Practice for Medicinal Products and Related Annexes

EMA Guideline On Medicinal Gases: Pharmaceutical Documentation (Including Recommendation on Non-Clinical Safety Requirements for Well Established Medicinal Gases, July 2008

Guideline on Good Distribution Practice

MS 2675-1 : 2017 Medical Gas System - Part 1: Code of Practice for the Design, Installation, Validation and Verification

TABLE 1 : REGISTRATION REQUIREMENT FOR GENERIC MEDICINAL GASES PRODUCT

Requirements	Notes
Part I Administrative Data And Product Information (Product Validation)	
1.3 Full Product Name	Product name shall consist of dosage form and strength (for single active ingredient product) e.g. X Brand Oxygen Medicinal Gas 99%v/v
2.1 Dosage Form	Medicinal gas
2.2 Dosage Form Description	Compressed medicinal gas
Active Ingredient	Percentage formula (v/v)
Excipient (if applicable)	
Product Validation – Other Information	
5 Ingredients of Animal Origin	If any
6 Manufacturer	
7. Is there any Contract Manufacturer Involved?	
8. Is this Product a Second Source Product?	
9. Is there any Repacker/Packer Involved?	
10. Is the Product Manufactured for Export Only?	For Export Only (FEO) products
11. Is the Product Under Patent Protection?	
12. Is this an Imported Product?	
13. Does this product contain any premix?	
14. Is this a Replacement Product?	
15. Does this product need Priority Review?	
16. Request for Data Exclusivity (DE)?	For New Drug only
17. Is this product Certified Halal?	
18. Does this product contain a medical device component?	If medicinal gas product is packaged together with medical device components, the medical device component should be complied with medical device requirements. Example of medical device components for medicinal gas : flow meter, pressure regulator, alarm.
Part I Section A	
A4 Product Description	Physical appearance of product and container. Physical state and the pressure of compressed gas.
A7 Indication	
A8 Recommended Dose	
A9 Route of administration	Inhalation
A11 Warning and Precautions	Including safety warning

A18 Instruction for Use	
A19 Storage Condition	
A20 Shelf Life	
A21 ATC Code	Refer to WHO ATC/DDD Index www.whocc.no/atc_ddd_index/
Part I Section B	
B1 Batch Size	Definition, size and manufacturing formula for standard batches
B2 Attachment of Batch Manufacturing Formula (BMF)	
Part I Section C Particulars of Packing	
Pack Sizes	Cylinder capacity (unit : m^3, L, kg) * For each capacity, the water capacity of the container (in L), the amount of gaseous product released at 1 atm and 15°C (in m3), and the weight of product stored (in g for compressed gases) are provided Type of material Filling pressure and filling weight Type of valve, type of valve outlet connection
Part I Section D Label, Package Insert and Patient Infomation Leaflet	
D1 Immediate Label	Refer to Table 2
D3 Package Insert	If any. Refer to Proposed Package Insert (DRGD).
D4 *Risalah Maklumat Ubat untuk Pengguna* (RiMUP)	For medicinal gas products which are self-administered by patients. Refer to Consumer Medication Information Leaflet (RiMUP) (DRGD).
Part I Section E	
E2 Contract Manufacturer and Repacker	
E3 Certificate of Pharmaceutical Product	For imported product only
E4 Certificate of Free Sales	For imported product only
E5 Certificate of GMP	
E6 Manufacturer	
E7 Other Manufacturer(s) Involved	If applicable
E8 Importer	
E9 Store	
E12 Analysis Protocol	
E13 Validation of Analysis Protocol	For Scheduled Poison only. Validation of non-compendial methods Verification of compendial method (if applicable)
E14 Supporting Documents	Including data to support 'well-established use' (Section 6)
E15 Worldwide Registration Status	For imported product only

Part II Section P **Medicinal Gas Product**	
P1 Description and Composition	Percentage formula, deliverable volume Density under standard conditions (e.g. 15°C, 1 atm)
P2.1 Information on Development Studies	Justification for the composition
P3.2 Manufacturing Process and Process Controls	Detailed description of the manufacturing process such as vaporization, filling to cylinders etc. Including procedures of pressure test and purging
P3.2.1 Manufacturing Process Flowchart	
P3.3 Control of Critical Steps and Intermediate	In process quality controls (IPQC) Before filling and after filling
P4.1 Specification of Excipients	Specifications and testing specifications for all excipients (if any)
P5.1 Specification of Finished Product	Specifications and testing specifications for the finished product Pharmacopeia monograph / in-house
P5.2 Analytical Protocol of Finished Product	If applicable
P5.4.1 Certificates of Analysis	Tests for identity, assay and purity Appearance of cylinders and label Cylinder pressure
P6 Reference Standards of Materials	
P7 Container Closure System (CCS)	Type of CCS (e.g cylinders) Supplier Specification, capacity, material and suitability of the primary container. Procedures for emptying, cleaning and filling the primary container. Procedures for maintenance and testing of the primary container (including procedures of pressure test and purging). Cylinder identification (according to MS 2583: 2014 Identification of Contents of Medical Gas Containers (First Revision) a) Cylinder marking b) Cylinder identification colours Cylinders traceability (e.g tracking system, reference code). Cylinders shelf life. Note: Cylinders should be complied with medical device requirements.

P8 Stability Data	Not required for medicinal gas generated from the air such as oxygen. Specific storage conditions are proposed by the applicant and maximum product shelf life allowed is 3 years. Stability data is required for medicinal gas manufactured by chemical synthesis. Test condition : 25 ± 2°C or 30 ± 2°C, relative humidity (RH) not specified (closed container system)
Part II Section S **Medicinal Gas Active Pharmaceutical Ingredient (API)**	
S1.1 Nomenclature	
S1.2 Structure formula	
S1.3 General Properties	Physical properties
S2.1 API Manufacturer(s)	
S2.1.1 Other API Manufacture(s) involved	If any
S2.1.2 Name of Synthesis Route	Air separation, chemical synthesis.
S2.2 Description of Manufacturing Process and Process Controls	For Scheduled Poison only. Brief manufacturing process description / flow chart
S2.3 Control of Materials	For Scheduled Poison only.
S2.3.1a TSE Risk Free Statement	For Scheduled Poison only.
S2.4 Controls of Critical Steps and Intermediates	For Scheduled Poison only.
S3.1 Elucidation of Structure and other Characteristics	For Scheduled Poison only.
S3.2 Impurities	For Scheduled Poison only.
S4.1 Specification from API Manufacturer	
S4.2 Analytical Procedures	
S4.3 Validation of Analytical Procedures	For Scheduled Poison only. Validation of non-compendial methods Verification of compendial method (if applicable)
S4.4.1(i) Certificates of Analysis (COA) from API Manufacturer	
S4.4.1 (ii) Certificates of Analysis (COA) from Finished Product Manufacturer	
S4.5 Justification of Specification From API Manufacturer	For Scheduled Poison only.
S5. Reference Standards or Materials From API Manufacturer	For Scheduled Poison only.
S6 Container Closure System (CCS)	For Scheduled Poison only. Description only
S9 GMP Certificate	GMP Certificate or Declaration on Quality Management System (refer Template 1)
S10 Other information	If any

TABLE 2 : LABELLING REQUIREMENT FOR MEDICINAL GASES PRODUCT

Requirements	Notes
Product Name	
Dosage Form	Medicinal gas
Name of Active Ingredient (s)	
Strength of Active Ingredient (s)	
Batch Number	
Manufacturing Date	
Expiry Date	
Storage Condition	
Country's Registration Number	
Name & Address of Manufacturer	
Safety Label	Precaution/Warning
Pack Size (Unit/Volume)	
The words "Controlled Medicine / Ubat Terkawal"	For Scheduled Poison only

Notes :

a) Adhesive/stick on labels are allowed for medicinal gas cylinders.

b) Security Label (Hologram) may be exempted for medicinal gas product provided cylinders traceability system is available.

TEMPLATE 1 : DECLARATION ON QUALITY MANAGEMENT SYSTEM FOR MEDICINAL GAS ACTIVE PHARMACEUTICAL INGREDIENT (API) MANUFACTURER BY COMPETENT PERSON

PART A: PRODUCT DETAILS

Product Name	
Product Reference Number[1]	
Name of Medicinal Gas API	
Name of Medicinal Gas API Manufacturer	
Address[2] of Medicinal Gas API Manufacturer	
Name of Medicinal Gas Product Manufacturer	
Address[2] of Medicinal Gas Product Manufacturer	
Product Registration Holder	

PART B: DECLARATION BY COMPETENT PERSON

The undersigned hereby declare that:

i. I am authorized to release the finished product based on the predetermined specification and responsible to put the finished product in the market.

ii. The manufacturer and/ or supplier of the Medicinal Gas API is an approved supplier according to the finished product manufacturer's quality management system.

iii. I hereby reviewed the quality of the concerned Medicinal Gas API which is stated in Part A.

iv. I undertake to ensure that the Medicinal Gas API specified in Part A has been manufactured in accordance with the finished product manufacturer's quality management system.

v. I have reviewed the manufacturing process of the Medicinal Gas API which is received by the finished product manufacturer to be used as API in the manufacturing process of the concerned finished product.

vi. Each lot or batch of the Medicinal Gas API shall be tested against and comply with the specifications established by the finished product manufacturer for that Medicinal Gas API.

vii. I have reviewed the distribution activities conducted by the supplier for the Medicinal Gas API which is used as API in the manufacturing process of the concerned finished product.

PART C: NAME AND SIGNATURE OF COMPETENT PERSON RESPONSIBLE FOR THIS DECLARATION

This declaration is submitted by the following Competent Person[3] of the finished product manufacturer (stated in Part A):

Signature of Competent Person: ……. (Together with official stamp) Name: Designation: Date:	Signature of Superintendent: ……. (Together with official stamp) Name: Designation: Date:

1. *This refers to the reference number assigned to the finished product submitted for registration with National Pharmaceutical Regulatory Agency (NPRA).*
2. *State the site name(s) and address(es) in detail, including the building numbers (Lot No. or block no.) & country.*
3. *Competent person: The personnel who is responsible to release the finished product and placing the finished product in the market.*