SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

WHOLESALERS TO EXPORT MEDICINAL PRODUCTS

This guideline is intended to provide recommendations to wholesalers intending to apply to SAHPRA for a licence to export medicinal products. It represents South African Health Products Regulatory Authority's current thinking on the exportation of medicinal products by a wholesaler. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information. SAHPRA is committed to ensure that all medicinal products exported by wholesalers will be of the required quality, safety and efficacy. It is important that wholesalers 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 Chief Executive Officer (CEO) and the website.

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CHIEF EXECUTIVE OFFICER (CEO)

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GUIDELINE FOR THE EXPORTATION OF MEDICINAL PRODUCTS BY WHOLESALERS

NOTE: This guideline outlines the format and data requirements for preparation and submission of an application for exportation of medicinal products by a wholesaler, and should be read in conjunction with the Medicines and Related Substances Act, 1965 (Act 101 of 1965), and General Regulations.

1 INTRODUCTION

The registration of Medicines and Scheduled substances in South Africa is governed by the provisions and requirements of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) (hereafter 'the Act'), and the Regulations and Guidelines published in terms thereof.

This Guideline describes the information required for the licensing of wholesalers who intend to export medicinal products (i.e. medicines, scheduled substances, medical devices and *in vitro* diagnostics). The information submitted will be evaluated in terms of the provisions of the Act.

The aim of this Guideline is to assist wholesalers in the preparation of documentation for the application to be licensed to export medicinal products Whenever there is doubt, wholesalers are advised to consult South African Health Products Regulatory Authority (SAHPRA) for confirmation and/or clarification before completing and submitting an application. Wholesalers should always refer to the **current** version of the relevant guideline for ***Wholesalers to Export Medicinal Products*** before completing the application form.

2 GENERAL

2.1 Policy and Objectives

2.1.1 To ensure that wholesalers who intend to export medicinal products submit an application for the exportation of medicinal products.

2.1.2 To ensure that there is a standard way of inspecting wholesalers who intend to export medicinal products.

2.1.3 The Holder of a Certificate of Registration (HCR) is responsible for all aspects related to the quality, management and control of all exported medicinal products.

2.2 Scope

2.2.1 This guideline applies to all wholesalers who are intending to export medicinal products.

2.3 Definitions

The definitions provided below apply to words and phrases used in these guidelines. Applicants should also consider the definitions as prescribed by the Medicines and Related Substances Act 101, 1965 as amended and the Pharmacy Act, 1974 (Act 53 of 1974).

certificate of release a certificate compiled and issued by the wholesaler wishing to export prior to moving the products; the certificate should contain verification of all the required checks performed (documentation etc.) before the products are exported

contract business agreement for the supply of goods or performance of work for a specified or agreed time at a specified or agreed price;

2.3 Definitions - continued

contractor a company or person under contract**:** a company or person with a formal contract to do a specific job, supplying labour and materials and providing and overseeing staff if needed;

courier company a company employed to deliver messages, packages and mail**;**

distribution the procuring, purchasing, holding, storing, selling, supplying, or movement of pharmaceutical products, with the exception of the dispensing or providing pharmaceutical products directly to a patient or his or her agent. This activity of distribution is performed by wholesalers and /or distributors.

distributor Holder of Certificate of Registration/Marketing Authorization or prospective Holder of Certificate of Registration of pharmaceutical products.

good distribution practices (GDP)Good Distribution Practices are that part of quality assurance that ensure that the quality of a pharmaceutical products is maintained through adequate control throughout the numerous activities which occur during the distribution process.

good trade and distribution practices that part of quality assurance that ensure that the quality of a pharmaceutical products is maintained through adequate control throughout the numerous activities which occur during the trade and the distribution process.

holder of certificate of registration (HCR) a person who holds the certificate of registration of a pharmaceutical product and who is responsible for said pharmaceutical product throughout its whole life cycle.

importation the act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone);

Medicines Act the Medicines and Related Substances Act, 1965 (Act 101 of 1965);

must bound by legislative requirements

ownership Commercial ownership: a normal trade activity)
Regulatory ownership: the HCR remains the regulatory owner of the product, throughout the whole life cycle of the product

Pharmacy Act the Pharmacy Act, 1974 (Act 53 of 1974);

pharmaceutical product any medicine intended for human use or veterinary product administered to food producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

product recall a process for withdrawing or removing of specific batch/batches –of a pharmaceutical product from the pharmaceutical distribution chain/market for reasons relating to deficiencies in quality, safety or efficacy, including but not limited to defects in the product or complaints of serious adverse reactions to the product. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency.

2.3 Definitions - continued

qualification an action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification.

quality the degree to which a set of inherent properties of a product, system or process fulfils requirements;

quality assurance a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use,

quality management all management activities and functions involved in determination of quality policy and its implementation through means such as quality planning and quality assurance;

quality management system an appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

quality manual a detailed document that sets forth practices and sequence of activities aimed at translating an organization's quality policy into operational results, or conformance to standards (such as a ISO 9000 series);

quality policies principles, rules and guidelines formulated or adopted by an organization to reach its long-term goals;

quality records documents recording specific information relating to a procedure or work instruction. Quality records are proof that an organization is complying with its procedures and policies;

quality risk management a systematic process for the assessment, control, communication and review of risks to the quality of a pharmaceutical product across the product lifecycle;

quarantine the status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal;

risk the combination of the probability of occurrence of harm and the severity of that harm;

Scheduled substance any medicine or other substance prescribed by the Minister of Health under Section 22A of the Medicines Act;

Service Level Agreement (SLA) a negotiated agreement designed to create a common understanding about services, priorities and responsibilities;

shelf-life The shelf-life is used to establish the expiry date of individual batches. It is the length of time required for:

- the least stable API to degrade to the specified, motivated and approved or proposed, fraction of the labelled quantity,
- some element of pharmaceutical elegance to drop to an unacceptable level, or
- an arbitrary minimum of two years, unless otherwise determined by SAHPRA.

2.3 Definitions - continued

should	that something is suggested or recommended, but not required.
site	foreign site or site exported to means the wholesaler or agent site in that country to which the products are exported to
Site Master File	a document prepared by the distributor containing specific and factual Good Distribution Practices (GDP) information about the control of distribution operations of pharmaceutical products carried out at all sites handling the product during its life cycle before it reaches the end user;
Standard Operating Procedure	(SOP) is an authorized, written procedure giving instructions for performing operations not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection);
supplier	a person or entity engaged in the activity of providing or making available products or services along the supply chain;
supply chain	a system of organizations, people, technology, activities, information and resources involved in moving a product or service from supplier to customer;
transit	the period during which pharmaceutical products are in the process of being carried, conveyed, or transported across, over or through a passage or route to reach the destination;
vehicle	trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means which are used to convey /transport products;
vendor	anyone who provides goods or services to a company; and "supplier" has a corresponding meaning;
vendor / contractor audit	evaluation of the ability of the manufacturer, applicant or contractor to deliver a quality service, pharmaceutical product.;
verification	the act of reviewing, inspecting, testing, checking, auditing or otherwise establishing and documenting whether items, processes, services or documents conform to specified requirements;
withdrawal	the total withdrawal of a pharmaceutical product from the market.
wholesaler	those organizations performing the activities of distribution, in compliance with cGWP

2.4 Application Procedure

2.4.1 Eligibility to apply to be licensed by SAHPRA as a wholesaler who is authorized to export medicinal products will be limited to wholesalers who are in possession of a valid GWP licence and comply with GWP.

2.4.2 The application submitted should be authorized by the Responsible Pharmacist as listed on the current Wholesale Licence. This pharmacist should be a full-time employee of the wholesaler and must submit the following:

- Proof of registration with the South African Pharmacy Council (SAPC) as the Responsible Pharmacist in terms of the Pharmacy Act, 1974 (Act 53 of 1974)

2.4.3 An updated Site Master File (SMF) for the wholesaler must be submitted.

2.5 Confidentiality/Secrecy

2.5.1 The confidentiality of information submitted to SAHPRA is governed by Section 34 of the Act.

2.5.2 SAHPRA, committee members or staff of the secretariat may NOT

a) Disclose to any person, any information acquired in the exercise of powers or performance of functions under the Act and relating to the business affairs of any person, except
- for the purpose of exercising his/her powers, or for the performance of his/her functions under the Act, or
- when required to do so by any competent court or under any law, or
- with the written authority of the CEO, or

b) Use such information for self-gain or for the benefit of his employer.

2.5.3 SAHPRA may insist on written confirmation of the identity and affiliation of an individual making enquiries telephonically, or in person. No information shall be disclosed telephonically unless the Medicines Control Officer can confirm that the enquirer is entitled to receive such information.

2.6 Language

2.6.1 In terms of Regulation 22(4) of the Act, all applications and supporting data submitted to SAHPRA should be presented in English (British).

2.7 Where to Submit Applications

2.7.1 Applications should be posted to the office of the Chief Executive Officer (CEO), CSIR Campus, SAHPRA Reception, building 38, Meiring Naude Road, Brummeria, Pretoria 0001, where they will be logged in.

2.7.2 All correspondence should be addressed to the office of Chief Executive Officer (CEO).

3 QUALITY MANAGEMENT SYSTEMS

3.1 Quality Risk Management

3.1.1 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of medicinal products.

3.1.2 It can be applied both proactively and retrospectively.

3.1.3 The quality risk management system should ensure that:

a) the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

b) the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

3.2 Personnel

3.2.1 The wholesaler must have an organization chart.

3.2.2 People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities.

3.2.3 Their duties may be delegated to designated deputies of a satisfactory qualification level and experience.

3.2 Personnel - continued

3.2.4 The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

3.2.5 There must be sufficient qualified personnel to take responsibility for the additional responsibilities related to the exportation of products. An adequate number of personnel, with the necessary qualifications and practical experience, must be appointed so that the responsibilities placed on any one individual should not be so extensive as to present a risk to quality. It may be necessary that an additional pharmacist must be appointed, by the wholesaler, on a full-time, permanent, basis to manage and control the activities related to the exportation of medicinal products.

3.3 Premises and Equipment

3.3.1 Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

3.3.2 Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid mix-ups, contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of medicinal products.

3.3.3 Storage Areas:

a) Storage areas should be of sufficient capacity to allow orderly storage of medicinal products, including products in quarantine, released, rejected and returned.

b) Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions for a specific medicine are required (e.g. temperature, humidity) these should be provided and monitored.

c) Receiving and dispatch bays should protect materials and medicinal products from inclement weather. Receiving areas should be designed and equipped to allow containers of these products to be cleaned where necessary before storage.

d) Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing physical quarantine should give equivalent security.

e) Segregated areas should be provided for the storage of rejected, recalled or returned medicinal products.

f) Highly active materials or medicines i.e. narcotics should be stored in safe and secure areas. In addition, this should be controlled by means of a scheduled substance register.

3.4 Documentation

3.4.1 Good documentation constitutes an essential part of the quality assurance system.

3.4.2 Documents should be designed, prepared, reviewed and distributed with care.

3.4.3 Records providing a history of each batch of medicinal product, including its distribution, and all other relevant circumstances pertinent for the quality of the product should be maintained for a specified period of time.

3.4.4 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the distribution of medicinal products are traceable.

3.4 Documentation - continued

3.4.5 If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions. Access should be restricted by passwords or any other means and the results of entry of critical data should be independently checked.

3.4.6 Electronically stored records should be protected by back-up transfer on magnetic tape, microfilm, paper or any other means. It is particularly important that the data are readily available.

3.5 Contracts

3.5.1 Contracted activities must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a medicinal product of unsatisfactory quality.

3.5.2 There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party.

3.5.3 The contract must clearly state the way in which the authorized person should release each batch of medicinal product for exportation and should exercises his/her full responsibility.

3.5.4 The contract between the Contract Giver and the Contract Acceptor should specify each party's respective responsibilities addressing *inter alia* the management and control of quality complaints, advertisements, recalls, pharmacovigilance, rejected and quarantined medicinal products.

3.5.5 Technical aspects of the contract should be drawn up by competent persons with suitable knowledge.

3.5.6 The wholesaler and the HCR must enter into a contractual agreement which allows for the exportation of the HCR's medicinal products.

3.5.7 The wholesaler must gain authorization from the HCR, on an annual basis, to allow for the exportation of the HCR's medicinal products.

3.5.8 A contract must be in place between the wholesaler and the foreign site to which the medicinal products will be exported.

3.5.9 The contract between the wholesaler and the foreign site must clearly stipulate the responsibilities of the wholesaler and the foreign site with regard to the management, control and implementation of quality complaints, recalls, pharmacovigilance, returned and rejected goods, quarantine products and handling of counterfeits.

3.6 Complaints and Product Recalls

3.6.1 All complaints and other information concerning potentially defective medicinal products must be carefully reviewed according to written procedures.

3.6.2 In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively medicinal products known or suspected to be defective from the market.

3.7 Self-Inspection

3.7.1 Self-inspections should be conducted in order to monitor the implementation and compliance with Good Wholesaling Practice principles and to propose necessary corrective measures.

4 REQUIREMENTS TO BE MET BY THE WHOLESALER INTENDING TO EXPORT

The wholesaler must meet the following requirements in order to be considered eligible to export medicinal products:

4.1 Legal Requirements

4.1.1. The wholesaler must be licensed by SAHPRA.

4.1.2. In addition to the Wholesale Licence, the companymust apply to export medicinal products.

4.1.3. The wholesaler must provide a list of the medicinal products that are intended to be exported. Information included on the product list must include the name of the relevant HCR, the product name, registration number and schedule of the medicinal product.

4.1.4. The wholesaler who intends to export must, on an annual basis, update the lists of medicinal products intended for export and must notify SAHPRA accordingly.

4.2 Release

4.2.1 All medicinal products to be exported must be released by the HCR in accordance with its quality system.

4.2.2 The release of medicinal products for exportation must be performed by the HCR and records must be kept by the wholesaler.

4.3 Foreign Sites

4.3.1 Exportation of medicinal products will only be permitted through those ports of entry deemed to be appropriate by the regulatory authority, government agency or Department of Health in the country to which the medicinal products will be exported.

4.3.2 Medicinal products may only be exported to countries which have a regulatory authority, government agency or Department of Health in place.

4.3.3 In countries where a Regulatory Authority is in place, the certificate of registration of the product must be obtained from that authority.

4.3.4 The appropriate authorization in a case where there is no Regulatory Authority should be obtained from the Department of Health of the country to which the medicinal products are intended to be exported. The authorization should include the following:

a) The authorization must make provision for appropriate marketing approval of the exported medicinal products in the country to which the products will be exported, by the foreign regulatory authority, government agency or Department of Health.

b) The authorization must confirm that the exportation of the medicinal products to the said country does not conflict with the regulatory requirements of the country.

4.3.5 The wholesaler is responsible for performing customer validity by validating the foreign sites to which medicinal products will be exported.

4.3.6 Foreign sites to which medicinal products will be exported, must submit a current SMF to the wholesaler, who in turn is responsible for submitting the SMF to SAHPRA. (Please refer to SAHPRA Guideline 4.08: Guideline for Preparation of Site Master File)

4.4 Exportation of Medicinal Products

4.4.1 Medicinal products which are intended to be exported must be labelled appropriately on the outside of the shipping package.

4.4.2 A robust system, which supports full traceability of medicinal products, exported from the wholesaler to the foreign site, must be implemented.

4.4.3 Comprehensible and accessible records of each batch of medicine exported must be retained by the wholesaler and should include the following:

a) The generic name or international non-proprietary name
b) The strength and the dosage form
c) Name and the strength of each ingredient contained in the medicinal product
d) Trade name or proprietary name
e) Total quantities to be exported
f) Name and address of the wholesale (exporter)
g) Name and the address of the foreign site (consignee)
h) Country of the foreign site (consignee)
i) Route of dispatch
j) Date of dispatch
k) The medicinal product registration number in the importing country

4.4.4 Transport validation studies must be performed by the wholesaler for all medicinal products to be exported or alternative continuous temperature monitoring of each consignment of medicinal products to be exported, must be performed and the records thereof must be maintained and be made available.

5 REQUIREMENTS TO BE MET BY THE HCR

5.1 The HCR must be licensed by SAHPRA.

5.2 Medicinal products intended to be exported must be registered by SAHPRA.

5.3 The wholesaler and the HCR must enter into a contractual agreement which allows for the exportation of the HCR's medicinal products by the wholesaler.

5.4 The HCR must apply to SAHPRA for a CPP prior to any medicinal products to be exported.

5.5 The HCR must provide the wholesaler with certified copies of the registration certificates and certified copies of the CPP of each of the medicinal products that the wholesaler intends to export.

5.6 The HCR is responsible for releasing medicinal products for exportation.

5.7 The HCR is responsible for providing a certificate of release for each batch of each medicinal product released for exportation, to the wholesaler.

6 REQUIREMENTS TO BE MET BY THE FOREIGN SITE

6.1 The foreign site, to which the medicinal products will be exported, must be authorized by the local regulatory authority, government agency or Department of Health, to handle medicinal products.

6.2 A contract must be in place between the wholesaler and the foreign site.

6 Requirements to be met by the foreign site - continued

6.3 The South African wholesaler, issued with a licence to export, must ensure that the foreign site is capable of managing the receipt, storage and handling of the medicinal products, exported by the wholesaler, in a manner which is compliant with cGWP, by conducting regular audits at that site.

7 STANDARD OPERATING PROCEDURES

7.1 Standard Operating procedures (SOPs) must be in place and must clearly describe each procedure performed by the wholesaler.

7.2 The list of SOPs to be implemented by the wholesaler include but is not limited to the following procedures:

a) Contracts
b) Release of Product for Exportation
c) Authorization to Export to Foreign Site/s
d) Customer Validity
e) Receipt, Storage, Handling and Management of Medicinal Products
f) Management and Control of Batch Traceability and Record Keeping of each Batch of Exported Medicinal Product
g) Transport Validation
h) Management of Temperature Excursions and Non-Conformances
i) Quality Risk Management
j) Handling of Returned and Damaged Medicinal Products
k) Handling of Quarantined Medicinal Products
l) Recall Procedure
m) Destruction of Rejected Medicinal Products
n) Deviations
o) Handling of quality Complaints
p) Management and Control of Counterfeit Medicinal Products
q) Archiving of Documents

8 UPDATE HISTORY

Date	Reason for update	Version & publication
February 2015	First publication released for comment	v1 Feb 2015
20 May 2015	Due date for comment	
Oct 2015	Version 1 released for implementation	v1 March 2016
Oct 2015	Amendment of 6.3 New section “2.3 Definitions” included	v1.1 May 2016
Nov 2019	Authority: “MCC” to “SAHPRA” Authority logo: “MCC logo” to “SAHPRA logo” Council to SAHPRA Registrar of Medicines to Chief Executive Officer Director-General to CEO	v1.2 November 2019