Universidade de Aveiro Secção Autónoma de Ciências da Saúde
Ano 2014/2015

ALINA MARIA MOREIRA DE FIGUEIREDO

REGISTO DE MEDICAMENTOS NOS PALOP, COM ENFOQUE NOS SEGUINTES PAISES: ANGOLA, CABO VERDE E MOÇAMBIQUE

MEDICINES REGISTRATION IN PORTUGUESE-SPEAKING AFRICAN COUNTRIES, FOCUSING IN THE FOLLOWING COUNTRIES: ANGOLA, CAPE VERDE AND MOZAMBIQUE

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor Bruno Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro

Thesis presented to the University of Aveiro to fulfil the requirements for the degree of Master in Pharmaceutical Medicine, conducted under the scientific guidance of Professor Bruno Gago, Invited Associate Professor of the Autonomous Section of Health Science, University of Aveiro

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“A rock pile ceases to be a rock pile the moment a single men contemplates it, bearing within him the image of a cathedral”

(Flight to Arras, 1942, Antoine de Saint-Exupéry)

palavras-chave

Assuntos regulamentares, Registo de medicamentos,Legislação, PALOP, Indústria farmacêutica.

Resumo

O presente trabalho propõe apresentar a perspectiva regulamentar do registo de medicamentos nos PALOPs – Países Africanos de Língua Oficial Portuguesa, respectivos requisitos regulamentares, dificuldades e oportunidades, com enfoque nos seguintes países: Angola, Cabo Verde e Moçambique.

Esta tese tem como finalidade aprofundar e sistematizar os conhecimentos no que respeita ao registo de medicamentos nos países seleccionados. A perspectiva regulamentar é enquadrada no contexto do sector da Saúde e seu desenvolvimento e das Agências Nacionais Reguladoras dos países em desenvolvimento, no continente africano.

A informação utilizada foi recolhida dos sítios Web do Ministério da saúde de cada país e/ou autoridade reguladora dos medicamentos, organismos internacionais competentes e bibliografia referente aos PALOPs e outros países africanos.

Os sistemas de saúde actualmente existentes nos países referidos são alvo de uma análise SWOT, com discussão dos pontos fortes e oportunidades de melhoria para cada um. As autoridades regulamentares dos países africanos em desenvolvimento enfrentam problemas de falta de recursos financeiros e humanos, existindo no entanto um esforço de melhoria nomeadamente na adoção de legislação de forma a garantir um controlo mais apertado dos medicamentos que são colocados no mercado.

O registo de medicamentos é um processo fundamental no que respeita à avaliação dos medicamentos com vista à sua colocação no mercado, procurando minimizar o uso de fármacos de baixa qualidade, ineficazes ou falsificados. As autoridades dos países em desenvolvimento enfrentam o desafio de avaliar fármacos sem a mesma ter sido realizada previamente por outras autoridades mais experientes, necessitando simultaneamente de técnicos qualificados para esse efeito. Como resultado têm sido observados nos últimos anos esforços na implementação de procedimentos, adoção de orientações internacionais e na formação de pessoal qualificado. Tem sido adotado em alguns países o processo de registo por reconhecimento da avaliação feita por autoridades mais experientes.

keywords

Regulatory affairs, Medicines registration procedure, Legislation, PALOP, Pharmaceutical Industry

abstract

This work aims to present the regulation perspective on the medicines registration in PALOPs – Países Africanos de Língua Oficial Portuguesa (Portuguese-speaking African countries), their regulatory requirements, constraints and opportunities, focusing on the following countries: Angola, Cape Verde and Mozambique.

This thesis has as purpose to deepen and systematize knowledge with regard to the registration procedure of medicines in the selected countries. Regulatory perspective is framed in the context of the health sector and its development and national regulatory agencies in developing countries in Africa.

The information used was gathered from the Ministry of Health Websites in each country and/or regulatory authority of medicines, international entities and bibliography regarding the PALOP and other African countries.

Health systems existing in referred countries are subject to a SWOT analysis, with discussion of the strengths and improvement opportunities for each one. The regulatory authorities of developing countries in Africa face problems of lack of funding and human resources but there is an improvement effort by several countries including the adoption of legislation in order to ensure a tighter control of medicines that are placed on the market.

The drug registration is a crucial process in the evaluation of medicinal products with the purpose to place them on the market, seeking to minimize the use of low quality drugs, ineffective or counterfeit. The authorities of developing countries face the challenge of evaluating drugs without prior evaluation by more experienced officials, and simultaneously requiring qualified personnel for this purpose. As a result have been observed in recent years efforts to implement procedures, adoption of international guidelines and training of qualified personnel. It has been adopted in some countries the registration process by recognition of the evaluation made by more experienced authorities.

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Acronyms

AIDS - Acquired Immune Deficiency Syndrome

ANVISA - Agência Nacional de Vigilância Sanitária (National Agency of Sanitary Vigilance)

API - Active Pharmaceutical Ingredient

ARFA - Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares

CHMP - Committee for Medicinal Products for Human Use

CIBS-INS - Comité Institucional de Bioética para a Saúde do Instituto Nacional de Saúde (Institutional Bioethics Committee for Health of the National Institutes of Health)

CNBS - Comité Nacional de Bioética para a Saúde (National Bioethics Committee on Health)

CRP - Collaborative Registration Procedure

CTD - Common Technical Document

DGFM - Direcção Geral de Farmácia e Medicamentos (General Directorate of Pharmacy and Medicines

DNME – Direcção Nacional de Medicamentos e Equipamentos (National Directorate of Medicines and Equipments)

ECV - Escudo de Cabo Verde (Cape Verde currency)

EFTA - European Free Trade Association

EMA - European Medicines Agency

EML - Essential Medicines List

EMPROFAC - Empresa Nacional de Produtos Farmacêuticos (National company of Pharmaceutical products)

EU - European Union

EUR - Euro

FARMED - Fórum das Agências Reguladoras dos Países do Espaço Lusófono (Forum of regulatory agencies of the countries of Lusophone Space)

FDA - United States Food and Drug Administration (also: USFDA)

FDC - Fixed dose combinations

GCP - Good Clinical Practice

GDP – Gross domestic product

GMP - Good Manufacturing Practice

HIV - Human Immunodeficiency Virus

ICH - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IMT - Instituto de Medicina Tradicional (Traditional Medicine Institute)

IND - Investigational New Drug (Application)

INN - International Nonproprietary Names

KOLs – Key Opinion Leaders

KW - Kwanza (Angola's currency)

MA - Marketing Authorisation

MAH - Marketing Authorisation Holder

MINSA - Ministério da Saúde de Angola (Angola's Ministry of Health)

MISAU - Ministério da Saúde de Moçambique (Mozambique's Ministry of Health)

MNC - Multinational companies

MRA – Medicines Regulatory Authority

MZN - Novo Metical (Mozambique currency)

NGOs – Non Governmental Organizations

NTA – Notice to Applicants

NMRA - National Medicines Regulatory Authority

PALOP - Portuguese-speaking African countries

PEPFAR - US President's Emergency Plan for AIDS Relief

PIL – Product Information Leaflet

SmPC – Summary of Product Characteristics

SSFFC - Substandard/spurious/falsely-labelled/falsified/counterfeit medical products

TRIPS - Trade-Related Aspects of Intellectual Property Rights

WHO - World Health Organization

Chapter 1 - Introductory Chapter

General introduction

According Universal declaration of Human rights, in article 25: “Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services...”

Access to healthcare by citizens, the protection and promotion of public health is an essential governmental task taken over partially by national medicines regulatory authorities (NMRAs). Assuring that good quality, safe and effective medicines are placed on the market allowing the patients to have access to it is the purpose of these Health Authorities. This is made by the implementation of national drug legislation and adoption of international laws. It is the responsibility of each country to set up a system for regulating not only medicines and traditional medicine but also the entire pharmaceutical sector in order to address this situation.

A country with an inefficient system or no system at all for medicine control allows the use of inefficacious and low-quality medicines, leading to treatment failures, worsening of side effects and may conduct to drug resistance.[1]

The regulation of medicinal products comprises different functions and activities whose scope and “modus operandi” may vary from country to country. Generally, these regulatory functions may include the following: licensing of professionals and practices; medicinal products evaluation and registration; inspection activities; quality control; providing independent information and controlling promotion and advertising; and surveillance and notification of adverse reactions. The main goal of regulation is to ensure the quality, safety and efficacy of medical products, as well as the relevance and accuracy of product information through effective implementation of these functions.[2]

Regulation of medical products requires countries several challenges: to develop a comprehensive legal basis (legislation and regulations), to provide technical guidance (guidelines, norms, standards, specifications and procedures); setting appropriate and adequate organizational entities such as a National Medicines Regulatory Authority that coordinates and supervises the regulatory system; to provide adequate numbers of qualified and skilled professionals competent to design and/or implement robust tools, either technical or scientific and legal provisions; to provide adequate and sustainable funding mechanisms; and carry out monitoring and evaluation.[2]

Effective regulation of medical products also requires political commitment, public adherence and interactions with various stakeholders (e.g. NMRAs, manufacturers, traders, consumers, health professionals, researchers, customs, civil society, politicians and government).

An NMRA deals with several challenges, one of the most important is to ensure that the pharmaceutical products they need are registered in their country. The process to reach this step can be named as “registration”, “marketing approval”, “marketing authorisation” or “product licensing”, and entails the evaluation by competent authority of product information that is submitted by the manufacturer (product application for requesting Marketing authorisation). The purpose of this documentations and its assessment is to make sure that the medicine is safe and effective for use by patients.[3]

In developing countries, such as African ones, national medicines regulatory authorities (NMRAs) have to deal with very limited funding, lack of adequate trained staff and expertise to perform these activities.

As already mentioned, the role of an MRA is, among others, to coordinate and supervise medicines sector in order to protect public health. MRA is responsible to ensure adequate evaluation and control of all medicines in circulation in their country, including regulating and monitoring their clinical development, manufacture, approval for marketing, distribution, procurement, import, export, supply, sale and promotion.[3]

During many years Africa regulatory authorities for medicines focused mainly on providing populations with access to a wide range of affordable essential medicines, usually generics or well established use medicines. Due to lack of financial resources, neither the government nor the citizens can afford high-priced medicines, and innovative pharmaceutical companies are rarely interested in marketing their medicinal products in developing countries. As a result of several factors, African medicines regulatory authorities had limited experience in evaluating and approving new drugs. Also due to lack of resources and qualified personnel, control of the drug circuit is not as effective as it should and circulating substandard and counterfeit medicines may not be detected and consequently can be distributed and dispensed.

Similarly, quality of medicines could not also be addressed and monitored adequately by the NMRAs because of their restricted resources. Usually Regulatory authorities in developing countries rely on registration by stricter regulatory authorities in developed countries.

A 2004 WHO study reported that 90% of African MRAs lacked sufficient capacity to guarantee the quality, efficacy and safety of medicines in their country.[1] A survey carried out by

WHO about the status of MRA in African region showed that from the countries that filled the questionnaire, 66% have MRAs represented by the directorate of pharmacy, 34% have MRAs represented by an autonomous public agency, while medicines legislation in 37% of the countries is either ill-suited or non-existent.[3]

To enable agencies in developing countries to purchase high-quality, safe and efficient medicines at reasonable prices address, WHO established the prequalification programme in 2001. This approach improved the situation in developing countries tremendously. Nevertheless, prequalification does not result in a national marketing authorisation and consequently required medicines are still not accessible for all patients via the regular distribution chain. This is why WHO started a pilot project in 2012 to foster drug registration in developing countries. This collaborative registration procedure (CRP) not only aims to accelerate the authorisation process but also focuses on capacity building at the NMRA. Trainings, workshops and joint activities extend expertise as well as experience of local assessors and inspectors.

There was also another change in the picture recently: African MRAs are now being required to conduct first assess of novel products that have not previously been reviewed by more experienced regulatory authorities. One reason for this shift is the development of new products intended specifically for developing countries diseases such as malaria or leishmaniosis, new vaccines targeting malaria, HIV/AIDS, tuberculosis (TB), rotavirus and African strains of pneumonia and meningitis, etc. On the other hand, agencies like Food and Drug Administration (FDA) and European Medicines Agency (EMA) decreased their regulatory supervision of products that were for export rather than domestic use.

The Food and Drug Administration does not require US manufacturers to follow full Investigational New Drug Application (IND) procedures if the clinical trials materials are not intended for domestic use and the European Medicines Agency adopted a new regulation (726/04) stating that vaccines for exclusive use outside the European Union are not to be licensed in Europe.[3]

Both the FDA and European MRAs may also not review clinical development plans for such products. Some Western regulators are also no longer renewing licenses of older vaccines, which are still in wide use in Africa but have been replaced in Western markets by later-generation vaccines.

These changes mean that several new medicines will be submitted to African regulatory assessment and registration, without previous evaluation by western authorities.

Another important concept in developing countries, due to financial constraints, is the existence of a list containing essential medicines (EML – essential medicines list). WHO defines essential medicines as those that satisfy the priority health care needs of a population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available in functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. These drugs are considered as safe, effective and of high quality. Efforts are focused on their correct prescription and rational use of drugs. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.[4] A thorough selection of a limited range of essential medicines results in a higher quality of care, better management of medicines (including improved quality of prescribed medicines), and more cost-effective use of health resources. There are a number of studies that have documented the impact of clinical guidelines and lists of essential medicines on the availability and proper use of medicines within health care systems. As an example, Cape Verde publishes periodic list of medicines, although it isn't truly one essential medicines list but a list of INN - International Nonproprietary Names, names of drugs whose market availability is ensured by the state and its producing and importing companies. Nevertheless Cape Verde foresees the publication of an Essential Medicines List.

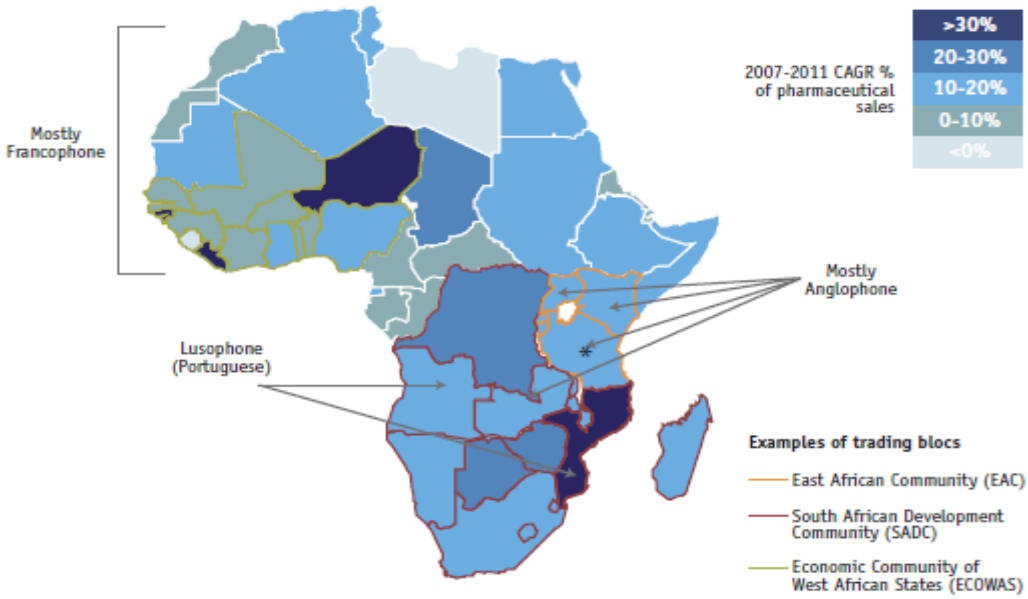
Objective

As a regulatory affairs technician, the regulatory area is the field of my daily work and also area of interest. Given the market developments, trends in consumption of medicines and evolution of medicines price, the mapping of the national health system in emerging countries, specifically in which concerns to the regulatory perspective for medicinal products, became an important challenge in order to consolidate the actual environment in an unique source.

It is expected that the potential economic development and increasing investments in health care (whether by states or by humanitarian organizations) lead to an improvement in the quality of health care provided to the population and also an increase in the equipment,

medicines or other pharmaceutical products, needed in the provision of health care. All this reasons make expectable an increase in the consumption of medicines and health goods.

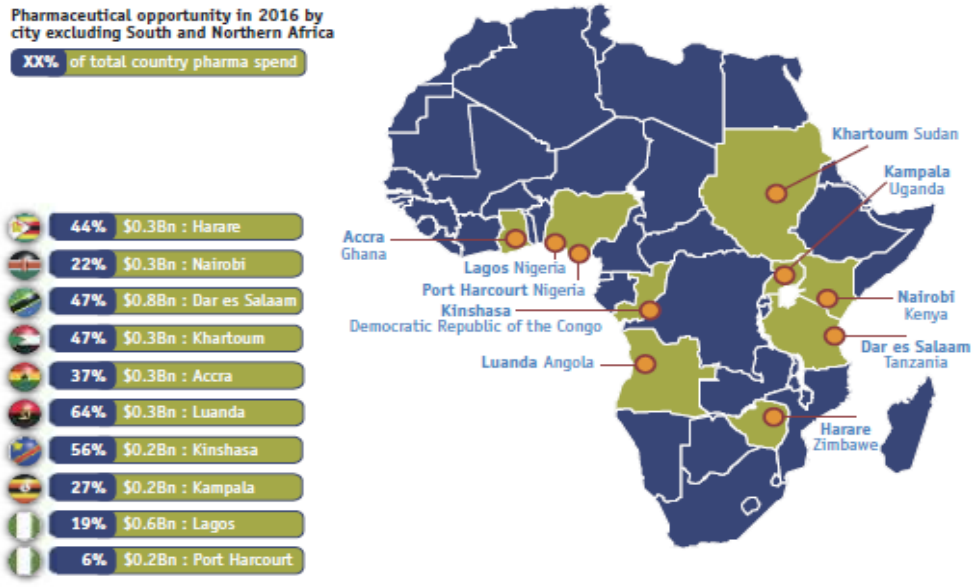
The following pictures support this grown in consumption in emerging countries, particularly in Africa.



* Tanzania is in both the EAC and the SADC.

Source: IMS Health Market Prognosis, Sept 2012, excluding Gabon, Cameroon and The Republic of Congo which use the 2007-2011 CAGR of pharmaceutical import data – UN Comtrade – code 30.

Figure 1 - Heterogeneity in Africa in Pharmaceutical growth, language and trading blocks[5]



Source: IMS Health Market Prognosis, Sept 2012. World Bank 2009: Reshaping Economic Geography. Canback Global Income Distribution Database. World Bank Databank.

Figure 2 - Excluding northern and south Africa, Ten major Sub-Saharan African cities make up ~12% of the $30 billion opportunity in 2016[5]

Growth perspectives foreseen for timeframe 2012 – 2016 also support potential development in African countries. Angola and Mozambique presents high figures.[6]

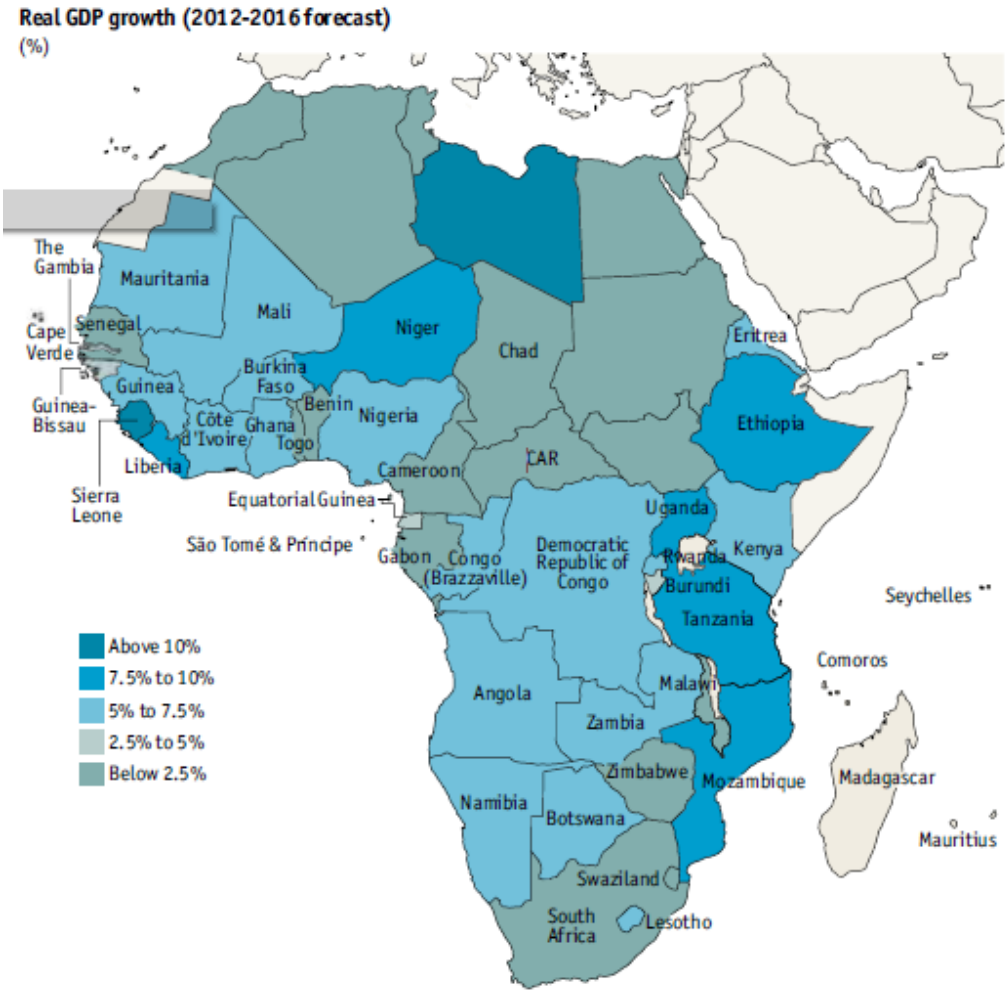


Figure 3 – Real GDP Growth (2012 – 2016 Forecast)[6]

On the other hand the existence of some neglected diseases like sleeping sickness, human African trypanosomiasis, visceral leishmaniosis, Chagas' disease or malaria or the high prevalence of diseases like AIDS makes necessary to ensure equitable access to effective therapeutic drugs[3], at the same time that aims to avoid the existence of counterfeit or falsified medicines. A counterfeit medicine is a medicine that is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include products with the correct ingredients or the wrong ingredients, lacking active ingredients, with incorrect quantities of active ingredients, or fake packaging.[7]

The process of registration of medicines has the purpose of provide evidence of quality, safety and efficacy of medicines before they can be made available to the patients who needed.

The assessment process is technically challenging, the difficulty been different depending on the type of medicines, from generic drugs, to new formulations and fixed dose combinations (FDCs). Novel drugs and biological products such as vaccines are the most difficult to assess.[3]

The option of select PALOPS as focus of study is related with the language similarities, cultural and historical proximity which may represent strategic advantage to the entrance in these markets.

Due to this proximity partnerships have been stablished between competent authorities of PALOP countries, and culminated in the setting up of FARMED - *Forum das Agências Reguladoras dos Países do Espaço Lusófono* (Forum of regulatory agencies of the countries of Lusophone Space).

FARMED aims, by cooperation between countries, to create a convergent way of acting to promote a ensure access to safe, effective and quality medicines, as well as contributing for sustainable development of pharmaceutical area and overcoming obstacles to this development. All regulatory agencies from Portuguese speaking countries (Lusophone countries) adhered to FARMED, and despite the diversity of systems, characteristics and means, have the will to come together around common goals of protecting public health and protection of citizens. [8]

Concerning medicines policy, FARMED contribute to promote dialogue between regulatory agencies, creating a regulatory convergence framework and establishing privileged access conditions to the medicine within the Portuguese-speaking world, respecting the specificities of each country. It represents the main instrument of discussion and definition of collaborative strategies among agencies and the interaction between them and their regulated and other relevant partners, focusing on the transparency of its activities. The statement of commitment to the founding principles was signed in May 2013.[8]

Learning purposes

With this thesis I intend to perceive and deepen the knowledge about developing countries health systems, regulatory entities, and the existing legislation in regulatory framework as well as to know and understand the mechanisms and procedures involved in placing a medicinal product on the market, under regulatory perspective.

Considering that it would become extensive one approach to all PALOPS, I've selected as the object of study the countries of Angola, Mozambique and Cape Verde, and a larger emphasis will be given to medicines registration process in the countries under study.

Chapter 2 – Search Method

As sources of information We've initially researched each Ministry of Health website, structure, available legislation and existing procedures. In cases were Pharmaceutical Products are regulated by a specific entity (ARFA in case of Cape Verde), this was the preferential search driver.

In a second phase I've searched at international websites namely WHO, Organisation for Economic Co-operation and Development, consulted legal diplomas and some bibliographic references regarding PALOPs and African countries.

Chapter 3 - PALOP - Portuguese-speaking African countries

PALOP – acronym for Portuguese-speaking African countries, also referred Lusophone Africa, is constituted for the following countries: Angola, Cape Verde, Guinea-Bissau, Mozambique and São Tomé and Príncipe.[9]

Besides having a common language, the five former colonies belonging to Portugal share a strong "cultural identity, a similar system of governance and a long tradition of contacts and exchanges amongst themselves"[10].

Based on the historical ties that bind Portugal to these countries has been developing some agreements at the level of higher education focusing mainly on scholarships and jobs, by the competent authorities in those countries and with the Portuguese authorities, including through the operation of joint committees, and also in other areas such as culture, economy, diplomacy and preservation of Portuguese language. It was also created a legal database called Legis-PALOP, representing a project of providing knowledge platform and share legal information among African Portuguese Speaking Countries and all who wish to know these laws.[11]

According to WHO, the cost of medicines represents a significant portion of total costs in health systems. In developing countries, including PALOPS, the focus of this thesis, expenditure on medicines accounts for a major proportion of health costs. This means that access to treatment is heavily dependent on the availability of affordable medicines.[12]

Despite medicines trade is growing rapidly, and still according to WHO data, most of it takes place between wealthy countries, with developing countries accounting for just 17% of imports and 6% of exports. It is estimated that one-third of the developing world's people are unable to receive or purchase essential medicines on a regular basis. Based on WHO analysis, the availability of access to medicines depends on several elements:

- Rational selection and use of medicines
- Affordable prices
- Feasible financing
- Trusty health and supply systems.

From the mentioned, affordable prices, is the most affected by globalization. Strategies to increase cost-effectiveness of medicines include:

- Reducing taxes, and promoting pricing policies.
- Boosting competition for products from several sources.
- Promote use of generic medicines including generic substitution.

- Good acquirement practices.
- Fairness in pricing and competition for single-source products. Equity in the measures established for price determination ensures that the price of a drug is fair, equitable, and affordable. The ones who agrees with equity pricing claim that the poor people should pay less for essential medicines.
- Differential pricing (also called tiered pricing) means the sale of the same good to different buyers at different prices, with the aim of improving the affordability of drugs while generating revenue for the pharmaceutical industry. Differential pricing has reduced the cost of many anti-retroviral HIV/AIDS therapies by up to 90% in low-income countries, although they continue to be sold at market price in developed countries.
- Price information and therapeutic substitution.
- Encouragement of competition, by using safeguards consistent with the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), such as parallel importation and compulsory licensing.[12]

  Parallel imports: Parallel importation is a lawful form of trade based on the principle of free movement of goods within the internal market. However, it is necessary to reconcile the uncompromising defense of Public Health with the legitimate interests of economic agents involved. The medicine object of parallel import is subject to a marketing authorization, which is supported by information provided by the State Agency source member, requested by the authority that evaluates the parallel import, along with other requirements set out in legislation. By allowing the reintroduction of price competition, parallel importation and compulsory licensing both provide safeguards against a patent holder charging excessively high prices in a particular market, enhancing the affordability and availability of medicines.

Compulsory licensing: is when a government allows someone else to produce the patented product or process without the consent of the patent owner. It is one of the flexibilities on patent protection included in the world trade organization agreement on intellectual property — the TRIPS Agreement.

Patent protection is one incentive for the research and development of new drugs. However, there is also concern that the TRIPS agreement, which grants extensive patent rights to pharmaceutical companies, will prevent developing countries from producing or buying generic drugs that usually cost much less than brand name drugs. The United Nations Development

Programme has questioned the compatibility of the TRIPS agreement with human rights law because of its impact on access to essential drugs in low-income countries.
WHO has recently added several anti-retrovirals to the Model List of Essential Drugs, increasing arguments that they should be available at reduced price.

In the following chapters we will detail the health system and existing procedures to place a medicinal product on the markets of Cape Verde, Angola and Mozambique.

Chapter 4 - Cape Verde

Having a surface area of 4,033 km2, Cape Verde is an archipelago of volcanic origin, formed by ten islands and eight islets. The archipelago is divided in groups of Windward and Leeward and administratively into 17 counties (cities). The resident population is about 531 046 inhabitants, mostly young people. The population growth rate, depending on migratory flows, stood in the decade 1990-2000, at approximately 2.4%. Average life expectancy is 71 years, being 69 years for men and 74 for women. The Constitution of Republic in 1990, Cape Verde has a multiparty system and the country known since then undergone major changes in terms of democratization, economic liberalization, decentralization and civil society involvement.

The Cape Verde economy is essentially of services, with the tertiary sector to occupy 64% in the composition of GDP, while the primary sector has only 13%, despite employing 47% of the labor-national work. In 2000 GDP per capita was estimated at US $ 1,354. [13]According to the Human Development Index, the country, which in 1999 was ranked in 105th position among 174 countries ascended in 2000 to 91th place due to the relatively favourable social indicators presented.

Some additional demographic data about Cape Verde are presents hereafter:[14]

Table 1 – Cape Verde Demographic data

Population	**531,046 (July 2013 est.)**
Age structure	0-14 years: 31.2% (male 83,355/female 82,503)
	15-24 years: 21.8% (male 57,825/female 57,842)
	25-54 years: 37.3% (male 95,970/female 102,217)
	55-64 years: 4.5% (male 9,766/female 13,910)
	65 years and over: 5.2% (male 10,416/female 17,242) (2013 est.)
Median age	total: 23.5 years
Population growth rate	1.41% (2013 est.)
Birth rate	20.96 births/1,000 population (2013 est.)
Death rate	6.22 deaths/1,000 population (2013 est.)
Major cities - population	PRAIA (capital) 132,000 (2011)
Infant mortality rate	total: 25.13 deaths/1,000 live births

male	28.78 deaths/1,000 live births
female	21.38 deaths/1,000 live births (2013 est.)
Life expectancy at birth	total population: 71.28 years
Total fertility rate	2.39 children born/woman (2013 est.)
Contraceptive prevalence rate	61.3% (2005)
HIV/AIDS	adult prevalence rate 0.04% (2001 est.)
	people living with HIV/AIDS 775 (2001)
	deaths 225 (as of 2001)
Maternal mortality rate	79 deaths/100,000 live births (2010)
Health expenditures	4.8% of GDP (2011)
Physicians density	0.295 physicians/1,000 population (2010)
Hospital bed density	2.1 beds/1,000 population (2010)

4.1 General perspective of National Health System

The National Health System is characterized essentially by the presence of the public sector. The private sector, is mainly in the urban centers of Praia and Mindelo. The public sector has two central hospitals, 3 regional hospitals, 18 health centers, 20 health posts, 93 health centers and base 5 reproductive health centers. Management of Health is under the responsibility of the Ministry of Health, where is integrated Pharmacy General Direction, which is a central service, performing the role of regulation, guidance, implementation, evaluation and inspection of pharmacy, coordination and technical support for the management of medical-equipment. As an advisory body on drug policy there is the National Commission of medicines. [13]

Cape Verde presents a transition state where non-transmissible diseases tend to overcome transmissible diseases, in which concern health indicators.

The Ministry of Health is the government department which is responsible for formulating proposals on the definition of national health policy and the corresponding legislative measures to promote and monitor its implementation and evaluate the results. The health sector is increasingly demanded to guarantee to population the best possible level of physical, mental and social well-being, ensuring the protection and promotion of health on the one hand, and the prevention, treatment and rehabilitation of the disease, on the other.

Health policy shall comply with National Health Service principles, including the universality of access to services in all health care levels; Solidarity of all in ensuring the right to health and to contribute to the financing of health care; the defense of equity in resource distribution and use of services; protection of human dignity and the preservation of physical and moral integrity of users and providers; Safety of ethics and professional ethics in the provision of services [15].

Decree-law nº39/2010, of 27th of September - Organic Law of Ministry of Health, describes the requirements, principles and organizations of ministry of health. Cape Verde Ministry of health is constituted by several services, with the purpose of formulating health care policies, accomplishment of system regulation function and performance assessment.

Hereinafter is present Cape Verde organizational structure of ministry of health[16]:

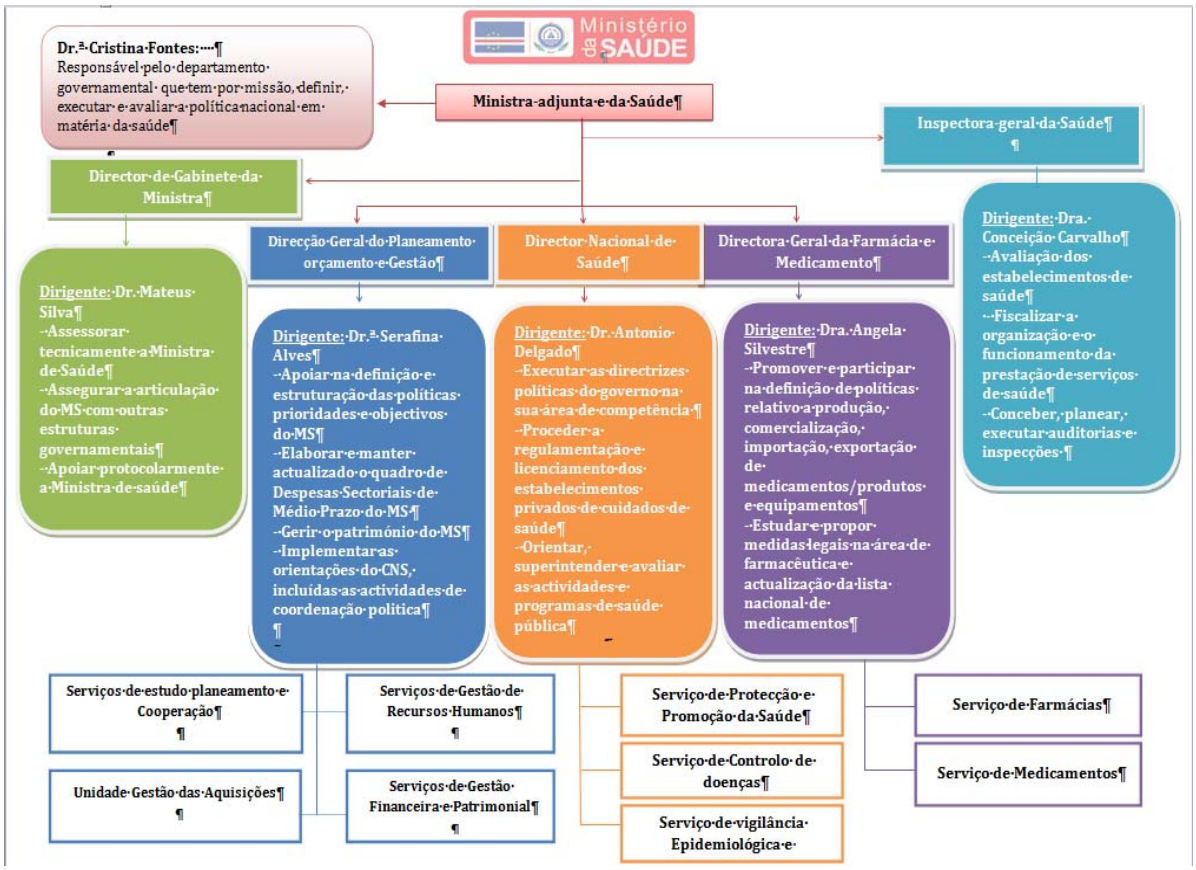


Figure 4 - Cape Verde organizational structure of ministry of health

General direction of pharmacy and medicines (DGFM) has, as main role, to promote and to take part in development of policies related to the production, marketing, importing, exporting of medicines /products and equipment's, study and propose legal measures.

DGFM is also responsible for the definition, regulation, fulfilment and assessment of national pharmaceutical policies with the goal of protecting public health, guaranteeing access by healthcare professionals and citizens to medicines and health products. These medicines should have ensured its quality, be safe and effective.

In Cape Verde pharmaceutical sector another organization exists: Agency for the regulation and supervision of pharmaceutical products (ARFA).[17] This entity is an independent national authority, responsible for technical and economic evaluation of food and pharmaceutical sectors. ARFA responsibilities' are enshrined in Decree-Law nº 22/2013 of 31st of May, articles 2 and 7, statutes of Agency for the Regulation and Supervision of food and pharmaceutical products.

ARFA is autonomous financially, administratively and regarding its heritage. Veterinary medicines, medical devices and medical equipment are not under ARFA supervision.

Publication of Decree-Law nº 22/2013 of 31st of May, regarding ARFA new statutes, introduced some changes in DGFM responsibilities, which started to be monitored by ARFA. Procedure of Marketing Authorisation and Pharmacovigilance fall within the scope of ARFA responsibilities'.

Summarising, ARFA is responsible for the regulation of products and pharmaceutical products; DGFM regulates the circuit, being responsible for licensing activities.

Cape Verde Law, within order nº 5/87 of 19th of January, created a national commission of medicines, with the following functions: NHS monitoring and consulting the government member responsible for health. At that time, it was composed of seven members, mostly leaders of the Ministry of Health, including the Pharmacy General Directorate; the Directorate General of Health and EMPROFAC. One of its main tasks is the preparation of National Drug List. It is currently under revision of their composition and operation.

4.2 Manufacture of medicines

Manufacture of medicines is regulated by decree-Law nº 59/2006. To manufacture medicines an authorization is needed from DGFM. This entity issues a certificate according OMS administrative provisions. Currently, procedure for requesting manufacture medicine authorisation is not detailed in proper regulation, however some requirements need to be

followed: payment fee, existence of appropriate facilities, compliance with GMPs (allowing the entrance of inspectors in the facilities whenever is needed) and having a Technical Director with proper qualifications.

Concerning medicines manufacturers, INPHARMA is, at the time being, the only manufacturer authorized to produce medicines in Cape Verde.

4.3 Distribution and Import of medicines

In private sector, most of the medicines consumed in Cape Verde, are imported by EMPROFAC, state-owned company created in 1979 by Decree-Law No. 51/79, aiming to: Streamlining the import; Wholesale distribution to public and private sectors; Standardization of national prices. It owns the import and wholesale distribution monopoly, EMPROFAC (National Company Import and Distribution of Pharmaceuticals). By Decree-Law No. 28/97, it became a private company with 100% public capital; is planned to be privatized in the short term as part of a global macro-economic global policy.

The large dependence on external, combined with other factors such as the small size of the market, territorial discontinuity and the economic fragility of the country affecting this area of services, causing ruptures with some frequency, which however doesn't reach significant expression in the availability of essential drugs.

The distribution of medicines in the public sector is ensured by EMPROFAC and the Laboratories Inpharma. The distribution is made by the Central and Regional Drugs warehouses, assigned to the DGFM. The distribution of the budget for medicines is made taking into account the population and the size of the health structures.[18]

Distribution of medicines depends on previous authorization by DGFM and is also needed authorization for medicines import. Manufacturing authorization holders are exempted of these authorizations.

Import of medicines to Cape Verde is regulated by the Decree-Law No. 51/79, of 9th of June. As told before, State owns the right of import specialties and chemical and pharmaceutical products as well as materials, medical and hospital equipment. Thus, the import and sale at wholesale distribution of human medicinal products, in the Cape Verdean market, are provided by the National Company for Pharmaceutical Products, EP - EMPROFAC.

4.4 Registration of medicines – Legislation

There are several laws and decrees published in Cape Verde in the area the pharmaceutical products and registration procedure. In the next paragraphs, are pointed out the documents to be considered under the registration of medicinal products:

- Decree-Law nº5/87 of 19th of January – Creates National Commission of Medicines
- Resolution nº 16/2003, of 28th of July – Defines the National Pharmaceutical Policy. It's currently under revision.
- Decree-law nº 59/2006, of 26th of December - This law is therefore intended to establish a more comprehensive discipline and full of matters relating to the introduction of the marketing authorization, registration (including renewals and variations), manufacture, import, export, marketing, to donations and advertising of medicines for human use.
- Decree-Law nº 39/2008, of 24th of November - Regulates the generating juridical and tax relations of the obligation to pay fees and other charges payable to the State, through the ministry of health, by the several operations inherent to licensing procedures for pharmacy and registration of medicinal products.
- Deliberation nº9/2014, of 18th of September 2014 - AIM regulation addressed to the applicant and on the general principles of the application of an authorization granted by another state, as provided for in Decree-Law No. 59/2006, as well as detailed explanation of these same procedures.
- Law nº 87/VIII/2015, of 14th of April - It is created the order of pharmaceutics in Cape Verde, and are also approved their statutes, published in annex to diploma.
- Law nº 41/VI/2004 of 5th of April – Basic Law on National Health System

4.5 Submission Procedure of a Marketing Authorisation (MA) Dossier

A medicine can only be introduced in the market of Cape Verde after an authorisation granted by a competent authority. Introduction and marketing of any medicines in national market needs previous authorisation by ARFA, either for medicines manufactured in the country or imported from abroad.

As described before, Marketing Authorisation is regulated by Decree-Law nº59/2006 of 26th of December, by resolution nº09/2014, of 6th of October and its annex Regulation of Marketing authorisation introduction (MAI) by recognition of MAI granted by other country. MA procedure includes scientific and technical assessment of MA dossier, to grant efficacy, quality and safety of medicines available in the market, based on the implementation of strict legal and scientific criteria.

For the scope of MA introduction is considered an individual medicine the following: "Product name + INN + Pharmaceutical form + Strength". In this way, different presentations of a medicine are part of the same marketing authorization. However, for each presentation is assigned a single national code.

In Cape Verde exist the following 2 Marketing Authorisation Procedures:

1. MA Complete Procedure

The complete AIM procedures are divided into two types:

i. Marketing authorisation procedures for innovative medicines

ii. MA procedures for generic medicines.

Regarding the standards and documents to submit a complete procedure MA, they are described in articles 4 to 23 of Decree-Law 59/2006 of 26 December. The structure of the MA application dossier through the complete procedure should follow the guidelines of the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), concerning the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD).

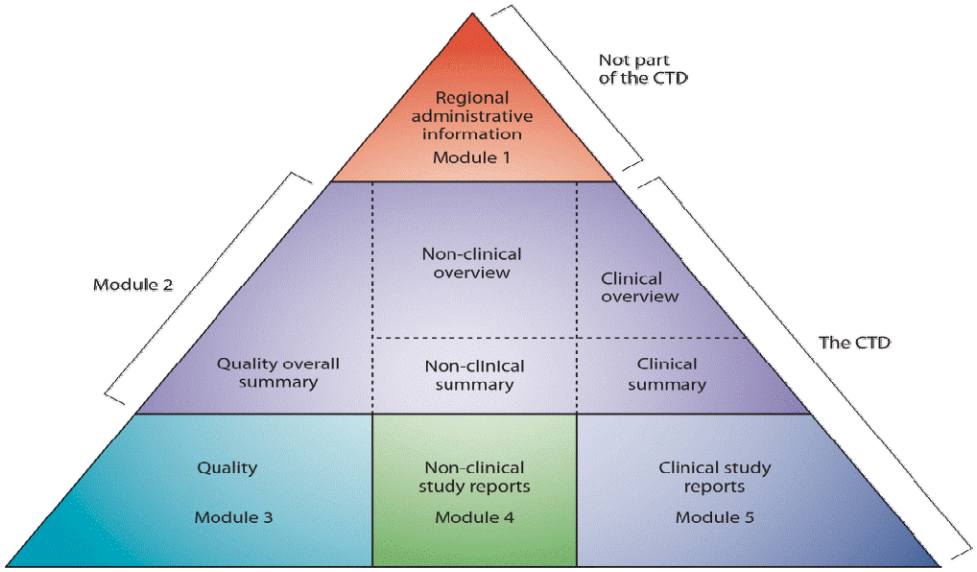


Figure 5 - CTD structure, from ICH website
(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/CTD_triangle.pdf).

2. Recognition procedure of MA granted by another country

If the medicinal product intended to be placed on the market in the Cape Verdean had a previous Marketing authorisation in a Country recognized by ARFA for this purpose, according to article 24 of Decree-Law nº 59/2006, of 26th of September and Resolution nº 09/CA/2014, of 6th of October, the marketing authorization is granted in Cape Verde by recognition of the marketing authorization issued in the State of reference.

In order to recognize the MA granted by another state, the minimum requirement should be fulfilled:

- Being an official authority (either a Ministry of Health service or an Agency or Institute), which makes the evaluation and grants the authorization of medicines, considering the rules and standards applicable and that guarantees the quality of medicines placed on the market;
- Ensure, through inspection activities, that GMP requirements are followed by manufacturers.

List of member states is included in the table 2. Portugal is one of the countries for which the recognition is authorized.

Table 2 - States table recognized by ARFA for the purpose of MA Granting for recognition of marketing authorization granted by other states

State	Authority
Germany	Federal Institute for Drugs and Medical Devices - BfArM
Germany	Paul Ehrlich Institute
Austria	Austrian Agency for Health and Food Safety - AGES
Belgium	Federal Agency for Medicines and Health Products - FAMHP
Brazil	Agencia Nacional de Vigilancia Sanitaria - ANVISA
Bulgaria	Bulgarian Drug Agency - BDA
Cyprus	Ministry of Health - Pharmaceutical Services
Croatia	Agency for medicinal products and medical devices of Croatia - HALMED
Denmark	Danish Health and Medicines Authority - SUND-HEDSSTYRELSEN
Slovakia	State Institute for Drug Control - SUKL
Slovenia	Agency for Medicinal Products and Medical De- vices of the Republic of Slovenia - JAZMP
Spain	Spanish Agency for Medicines and Health Products - AEMPS
United States of America	U.S. Food and Drug Administration - FDA
Estonia	State Agency of Medicines - RAVIMIAMET
Finland	Finnish Medicines Agency - FIMEA
France	National Agency for the Safety of Medicine and Health Products - ANSM
Greece	National Organization for Medicines - EOF

State	Authority
Netherlands	Medicines Evaluation Board
Hungary	National Institute of Pharmacy - OGYI
Ireland	Irish Medicines Board - IMB
Iceland	Icelandic Medicines Agency - IMA
Italy	Italian Medicines Agency - AIFA
Latonia	State Agency of Medicines - ZVA
Liechtenstein	Office of Health / Department of Pharmaceuticals
Lithuania	State Medicines Control Agency - VVKT
Luxembourg	Ministry of Health
Malta	Medicines Authority
Norway	Norwegian Medicines Agency
Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal	Autoridade nacional do Medicamento e Produtos de Saude I.P. - INFARMED
United Kingdom	Medicines and Healthcare Products Regulatory Agency - MHRA
Czech Republic	State Institute for Drug Control - SUKL
Romania	National Medicines Agency - ANM
Sweden	Medical Products Agency- LAKEMEDELSVERKET

We will now describe the main steps to submit a dossier by recognition of MA authorisation Granted by another State.

The application for marketing authorization must be submitted in digital format (CD-ROM, DVD-ROM or Pen drive) and can, additionally, be submitted in paper format. The requirement and application form must be sent necessarily on paper, as well as appear in digital dossier. The delivery can be made directly in the record of ARFA or by mail.

Marketing authorization application is constituted by the following documents:

- Cover letter
- MA Application form
- Copy of SmPC, PIL and Labelling texts in the origin country and translation to Portuguese language, if applicable
- Declaration stating that information provided in the dossier is the same as the approved in origin Country from which MA recognition is requested (PT language)
- List of variations approved in origin State (PT, EN or FR language)
- Applicant declaration stating that any changes in the medicine status, namely official decisions from competent authorities in other member states to recall the medicine from the market, will be communicated to ARFA (PT language)
- WHO certificate filled by competent authority of country from which MA recognition is requested (PT, EN or FR language, or its translation by competent entity, if applicable)
- Declaration about the existence of marketing data emitted by the competent authority of the country for which marketing authorization is requested recognition (PT, EN or FR language, or its translation by competent entity, if applicable)
- Declaration stating no changes on the benefit/risk balance filled by competent authority from the country where MA was granted (PT, EN or FR language, or its translation by competent entity, if applicable)
- List of safety alerts regarding the medicine, emitted by the competent authority of the country for which marketing authorization is requested recognition (PT, EN or FR language, or its translation by competent entity, if applicable)
- Specifications and analytical methods used in the quality control of the finished product (PT, EN or FR language)

Application form shall be accompanied by the annexes submitted in the same order and the same numbering defined in the Order Form, as follows:

Proof of payment

Proof of establishment of the applicant in the country where is located.

Letter of authorisation for communication on behalf of the applicant/MAH.

Authorisation to exchange confidential information between ARFA and competent Authority

Manufacturing Authorisation

Flow-chart indicating all manufacturing and control sites involved in the manufacturing process of the medicinal product and the active substance.

GMP certificate(s) or other GMP statement(s); Where applicable a summary of other GMP inspections performed.

European Pharmacopoeia Certificate(s) of suitability for Transmissible Spongiform Encephalopathies.

Written consent(s) of the competent authorities regarding GMO release in the environment.

Copy of Marketing authorization certificate granted in other(s) state(s)

Correspondence with European Commission regarding multiple applications.

List of Mock-ups or Samples/specimens

List of proposed (invented) names and marketing authorisation holders in the concerned member states.

Copy of European Pharmacopoeia certificate of suitability (CoS), Active Substance master File or Drug Master File

Copy of EMA certificate for a Vaccine Antigen Master File (VAMF).

Copy of EMA certificate for a Plasma Master File (PMF).

Templates for several documents described above are available at ARFS web site.[19]

Cape Verde Publishes periodically publishes the following lists of medicines (updated every 3 years):

4.6 - Medicines life-cycle – Post Approval activities

An initial marketing authorization is valid for five years and is renewable for an unspecified period, unless if, due to pharmacovigilance reasons, it intends to limit the additional renewal period of five years.

After MA is granted and certificate is issued, Marketing Authorization Holder must place the medicine into the market during the next 12 months, with the exception of duly justified cases. In case there are no marketing records during that period, MA Holder should justify, by providing adequate documents, the reasons for not placing the medicine on the market, subject to MA revocation.

ARFA may extend this period, up to a total of 24 months. Request for extend the period for introducing the medicine on the market must be made by filling an application addressed to President of Administration Council of ARFA.

The application for renewal must be submitted by the MAH up to 90 current days before the expiration of the validity of Marketing Authorization. Renewal request should describe current status of pharmacovigilance data, this is, should demonstrate medicine safety during the period the medicine has been on the market. Renewal request should also evidence adaptation to the technical and scientific progress. The following documents should be submitted: [20]

- Cover letter (according template)
- Table of contents
- Renewal application form and annexes
- WHO certificate, and translation if applicable issued by competent authority in the origin country
- Proof of payment
- Periodic safety report (PSUR) filled in accordance with international guidance.
- PIL currently approved in the country of origin and certified translation to Portuguese language if applicable
- Labelling currently approved and certified translation to Portuguese language if applicable.

SmPC, PIL and Labelling copies approved in country of origin should only be submitted if changes are verified on the latest versions approved in ARFA.

ARFA may accept or refuse the renewal request, due to safety reasons, benefit-risk ratio, Non GMP compliance, etc. In case of refuse, should justify the reasons for the refusal.

Submission of variations to MA Dossier

Any changes that are implemented or intended to implement to a medicine with marketing authorization already granted shall be subject to approval of ARFA.

Instructions for submission variations are described in Deliberation No. 09 / CA / 2014, 6th of October, in the chapter 9 - Regulation for MA introduction in the market for recognition of marketing authorization granted by another state.

The submission of variations should be made after the granting of marketing authorization and whenever there are changes in medicinal product and / or whenever changes are made in MA dossier in the member state that is used as a reference for the application for recognition of MA. Marketing Authorization Holder should submit a variation request to MA terms. The period for replying to this type of application is 120 days. Variation application should be submitted with the following documents:

- Cover letter
- Summary of the variation submitted and justification
- Table of contents
- Variation application and annexes
- Certificate of a Pharmaceutical Product (CPP)
- Declaration on the existence of marketing data issued by Competent Authority in member state from where MA recognition was done
- Revision of any documents updated in the sequence of the variation to submit.

The variation request to be submitted to ARFA should be submitted only after variation approval in reference country, with exception of the variations identified below. Variation implementation depends on the final decision by ARFA. The types of variations needed to submit to authority are described in chapter 9 of Deliberation 09/2014.

For the following variations previous approval in reference country is not needed, however they need to be positive decision by ARFS before implementation:

- Inclusion of a another presentation
- Temporary suspension of manufacture
- Cancelation of medicine presentation
- Reactivation of manufacture
- Cancelation of medicine registration.[20]

Some variations like changes in excipients or changes in equipment are detailed in annexes 12 and 13. Templates for cover letter, payment of fees and variation application are provided and should be submitted accordingly.

Withdrawal from the market - The MAH may request the withdrawal from the market of his medicinal product by presenting a request to the ARFA's Presidency of Council of Directors, with appropriate justification, and taking into account the availability of alternatives therapies in the market.

4.7 Fees

The costs regarding Marketing authorizations applications are regulated by Decree Law No. 39/2008, of 24th of November. Payment of fees must be made by bank transfer to the following entity:

Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares – ARFA.

Transference details are provided in ARFA Website. The charges related to bank transfers shall be supported by the applicant.

MA payment of fees should be done for each product as follows:

"Product name + INN + + + Pharmaceutical form + Strength", regardless of different dosages and pharmaceutical forms are grouped into a single application.

Type of Procedure:

MA application for innovative drugs - 60.000 ECV (544,144 EURO (EUR))

MA application for a generic product – 25.000 ECV (226,727 EURO (EUR))

Renewal applications for innovative drugs – 30.000 ECV (272,072 EURO (EUR))

Renewal applications for a generic product – 10.000 ECV (90,691 EURO (EUR))

Variation applications for innovative drugs – 30.000 ECV (272,072 EURO (EUR))

Variation applications for a generic product – 10.000 ECV[21] ECV (90,691 EURO (EUR))[22]

4.8 Clinical investigation

According to Basic Law on National Health System, clinical trial should always be conducted under clinical supervision and responsibility. Rules for the conduction of clinical trials shall be published in specific diploma. Patient's informed consent, in the absence of national specific legislation, should follow GCP and international guidelines.

Conditions for clinical trials, investigation activities to be supported by state, should always observe as guiding principle, the protection and preservation of human life. Good clinical practices and international guidelines should be followed.

4.9 Pharmacovigilance

Law nº 41/VI/2004, of 5th of April – Basic Law on National Health System, foresees production, import, export and marketing of medicines and pharmacovigilance to be regulated by national law. In Cape Verde Pharmacovigilance is under responsibility of ARFA, through SNF – *Sistema Nacional de Farmacovigilância* (Pharmacovigilance National System).

Since 2009 ARFA has developed several activities in order to test the implementation of a pharmacovigilance system. In 2012, SNF was created, and nowadays, Cape Verde has available an application for notification of adverse reactions.[23] Upon the reception of an adverse reaction, the information is analysed by a team of drug safety experts in order to classify the reaction, characterizing the probability of the reaction / quality described problem is due to the medicine and integrate reporting in the international monitoring program coordinated by WHO by sending adverse reaction report to the Uppsala Monitoring Centre. According to ARFA, pharmacovigilance has as main objectives to identify adverse reactions and drug-related problems, identify their risks, establish regulatory measures and inform healthcare professionals and the general public.

Cape Verde has an integrated system for monitoring Pharmaceutical market, fulfilling several goals. The concept of creating SIMFAR - *Sistema Integrado de Monitorização do Mercado Farmacêutico* that is an Integrated Pharmaceutical Market Monitoring System, whose configuration and use is that of a "market observatory" underpins an integrated approach to technical and economic aspects of medicine, including the monitoring of access, price and stock,

and also for assessing the quality, safety, efficacy and effectiveness. ARFA is the entity responsible for the implementation of SIFAR.

SIMFAR objectives are to gather, process and make accessible the information on the market of medicinal and pharmaceutical products having the aim of monitoring and support studies and reports on the accessibility and use of medicines; provide information that can contribute to the implementation of inspection and surveillance activities; support policy formulation, decision making and evaluation of their impact. Integrate the support instruments for the implementation of quality systems, safety and efficacy of medicines and pharmaceuticals.

Chapter 5 - Angola

Angola is a country in southern Africa bordering with Namibia on the south, the Democratic Republic of the Congo on the north, and Zambia on the east; its west coast is on the Atlantic Ocean with Luanda as its capital city. The province of Cabinda has borders with the Republic of the Congo and the Democratic Republic of the Congo. With a total Area of 1,246,700 km², its coastline has around 1,600 km.

The country is divided in administrative divisions: 18 provinces, 163 municipalities and 557 communes, and the major cities are: Luanda (capital), Huambo, Lobito and Benguela.[24]

Republic of Angola independency happened in 11th of November 1975 and currently has a multiparty system.

A new currency, the kwanza (Kz), was introduced in December 1999, replacing the readjusted kwanza (Kzr), 1 EUR = 122 Kz (2012).

Angola has enormous reserves of oil, gas and diamonds, as well as considerable hydroelectric potential, varied agricultural land, good rainfall and considerable marine resources and have, as main mineral resources petroleum, diamonds, iron ore, phosphates, copper, feldspar, gold, bauxite, uranium.[25]

The epidemiological profile is characterized by a high incidence of infectious diseases such as respiratory diseases, diarrhea, HIV / AIDS and tuberculosis, and parasitic diseases such as malaria. The rates of vaccine-preventable diseases such as tetanus and measles, and malnutrition are still high, especially in children under 5 years. They also verified high levels of chronic non-communicable diseases, road accidents and violence. (Ministry of Health, 2012).

Some demographic data (2014)[26]

Table 3 – Angola Demographic data

Population	**19,088,106 (July 2014 est.)**
Age structure	0-14 years: 43.2% (male 4,206,929/female 4,043,618)
	15-24 years: 20.5% (male 1,992,955/female 1,923,932)
	25-54 years: 29.3% (male 2,822,164/female 2,777,147)
	55-64 years: 4% (male 370,181/female 389,885)

	65 years and over: 2.9% (male 259,637/female 301,658) (2014 est.)
Median age	total: 17.9 years
Population growth rate	2.78% (2014 est.)
Birth rate	38.97 births/1,000 population (2014 est.)
Death rate	11.67 deaths/1,000 population (2014 est.)
Major cities - population	LUANDA (capital) 5.068 million; Huambo 1.098 million (2011)
Infant mortality rate	total: 79.99 deaths/1,000 live births
male	83.74 deaths/1,000 live births
female	76.05 deaths/1,000 live births (2014 est.)
Life expectancy at birth	total population: 55.29 years
Total fertility rate	5.43 children born/woman (2014 est.)
Contraceptive prevalence rate	17.7% (2009)
HIV/AIDS	adult prevalence rate 2.3% (2012 est.)
	people living with HIV/AIDS 248,800 (2012 est.)
	deaths 12,600 (2012 est.)
Maternal mortality rate	450 deaths/100,000 live births (2010)
Children under the age of 5 years underweight	15.6% (2007)
Health expenditures	3.5% of GDP (2011)
Physicians density	0.17 physicians/1,000 population (2009)
Hospital bed density	0.8 beds/1,000 population (2005)

5.1 General perspective of National Health System (NHS)

The National Health Services (NHS) was established at independence in 1975. From 1975 to 1992, the principle of universal and free primary health care formed the basis of the Angolan national health system. Before 1992, universal and free primary health care formed the basic principles of the Angolan national health system. Since then, a law has been put in place (Law 21-B/92 of 28th of August on NHS), to allow the private sector to work alongside the public sector, for those who could afford it, as well as the introduction of user fees. Since then health care has been provided by both public and the private sector. World Health Organisation data ranked Angola's health system 181st out of 190 countries. The public healthcare system is used by around 90% of the

population in Angola but this is out of need rather than choice, since many cannot afford private health insurance.

The new constitution from 2010 states a government responsibility to promote universal and free primary health care.[27]

The system of provision of healthcare is classified on 3 levels:[28]

Primary Level: primary health care outreach, comprising medical centers, health centers, municipal hospitals, nursing offices and doctors' offices. It's the first contact point between population and health system.

Secondary level (intermediate): General hospitals; it's the reference for primary level units.

Tertiary level: mono or polyvalent hospitals, with provision of specialized and differentiated health care.

The following schemes the level of health care system:[29]

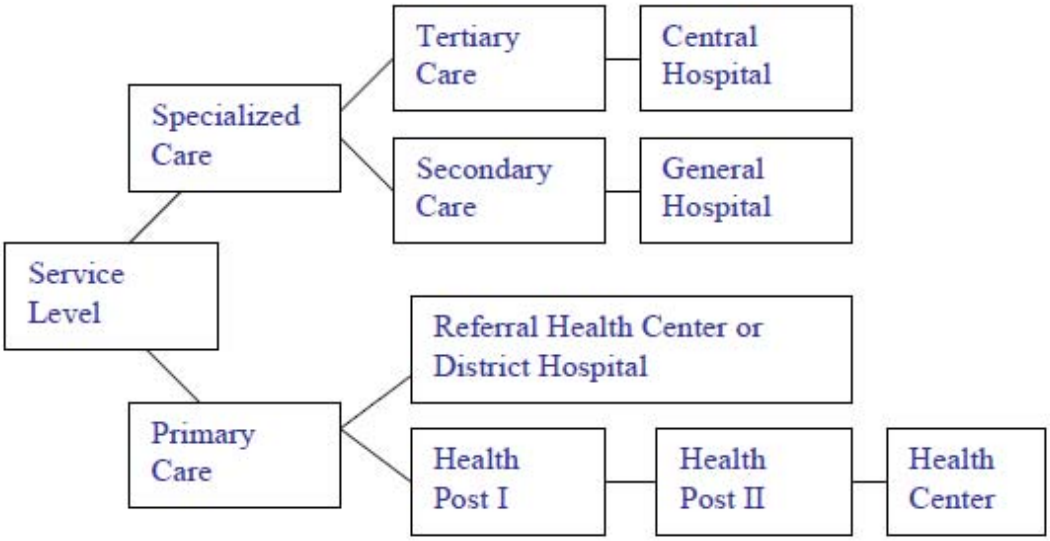


Figure 6 - Health service delivery levels in Republic of Angola

The Ministry of Health, abbreviated to MINSA, is the central administrative body of the state that executes, supervises and monitors the national health policy. It's responsible for developing and proposing a national health policy, ensuring their correct implementation, monitoring and periodic evaluation.

Their responsibilities are:

- Promote health development of the country in coordination with national partners and related sectors of the national and international communities;
- Promoting the control and the fight against endemic-epidemic diseases;
- Promote the health of the general population, and in particular of vulnerable populations, especially women and children, taking necessary measures to ensure equity and access to health care;
- Develop programs to solve specific health problems and submit them for approval by the Council of Ministers;
- Promote the development of human resources, participating in their planning, training and supervision of the exercise of health professions in collaboration with other relevant institutions;

Ministry of Health has developed a new district health strategy: *Revitalização do Sistema de Saúde a nível Municipal* that calls for shifting more resources to the primary health care system. It also emphasises that management responsibility should be moved to Angola's 164 districts. The policy is a commitment to improve primary health care services, and it has a pro-poor approach. The decentralisation of responsibility for primary care from the provincial to the district level constitutes a major transition for the provincial and district governments. In 2007 MINSA introduced provincial health maps, which are meant to inform health infrastructure investments and operational planning and decisions. Such maps have been completed for 11 out of 18 provinces. A new National Medicines Policy was updated and adopted in 2010.[27]

According to the document Angola Health system Assessment 2010, and which concerns Angola's policy on medicines and Medical Products: The National Medicines Policy was adopted in 2010 indicating the opportunity for significant improvement in medicines management. Stock-outs of medicines and commodities in the public sector to support service delivery remain a challenge. Currently, MINSA still manages the procurement and distribution, including the essential-

medicines-kit program, but problems include poor information systems, delayed national procurements, lack of an operational registration system, and limited quality assurance. In the face of these challenges, provinces are increasingly managing their own medicines outside of the kits system and at least one donor has resorted to a private distribution system.[29]

Hereinafter is presented Angola organizational structure of ministry of health.

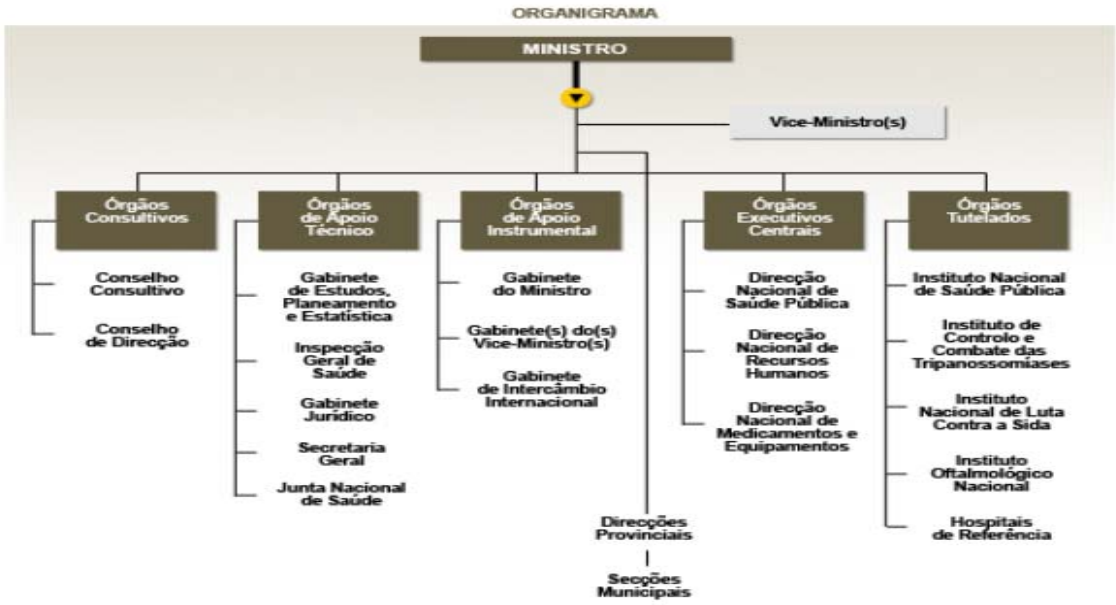


Figure 7 - Angola organizational structure of ministry of health

5.2 Manufacture of medicines

Article 3 of presidential decree nº 191/10, 1st of September classifies pharmaceutical stablishments accordingly the activities to be undertaken. Manufacture of medicines is included in the point *Production stablishements*.

In accordance with the Presidential Decree about the Exercise of Pharmaceutical activity, medicines manufacture comprises acquisition of active pharmaceutical ingredients and excipients, packaging materials, manufacturing activities, quality control, batch release and storage operations.

To open a pharmaceutical establishment, independently of the activity to develop, is necessary an authorisation granted by Ministry of Health through it's department DNME (National Directorate of Medicines and Equipments).

Manufacturing authorisation request should contains the following elements:

- Social denomination or name
- Head's office address
- Tax identification number
- Technical Director (DT) identification, scope of activities
- Manufacturing site address for the activities described above

Additionally, the following documents should also be presented:

- Proof of qualifications of Technical director
- DT Statement of responsibility
- Copy of Plant, facilities descriptive document
- Business licence copy issued by competent authority.

Similar requirements are demanded for pharmacies and for any pharmaceutical stablishment.
Once the manufacturing facility is finished, a request for inspection should be made to DNME.

This authorisation can be suspended or withdrawn in case of decree infringement. Accordingly licence to manufacture needs a previous requirements to ministry of health.
Manufacture of medicines should follow Good manufacturing practices and Good laboratory practices to be defined by Ministry of health dispatch.

5.3 Distribution and Import of medicines

Medicines distribution is made upon authorisation granted by Ministry of Health. According to the Regulation of Exercise of Pharmaceutical Activity, the licensing request for pharmaceutical activity should be directed to Ministry of Health, which trough DNME, grants the authorisation to distributors. By definition in the same document, distributors comprise any company that import, stores or distributes medicines with the purpose of wholesale distribution or direct sale.

Additionally to license, distributors installation also need a request to Ministry of Health (article 48 of Regulation of pharmaceutical activity). Once facilities are set, applicant should require an inspection to DNME.

Authorization to distribute medicines is granted after facilities approval and payment of a fee equivalent to 5 national minimum salaries. [34]

In 2012, was published the document "Standards for Good Storage and Distribution Practices of Medicines and Sanitary Products. This document set the rules and procedures intended to guaranteeing medicines quality and safety that are stored and distributed by public and private operators.

This document is composed by 3 parts:

Part I – Warehouse structures, location, external and internal physical structure including some rules for the definition of minimum areas, types of materials to be used in the facilities, types of equipment's namely racks and pallets, existence of temperature and humidity monitoring devices, refrigerators for sensitive drugs and also separated areas for reception, expedition and storage. Distributors warehouses should also have segregated areas for returns, specific categories of drugs or expired medicines.

Part II – Rules for Good Practices of storage and distribution. Includes information about human resources needed and functions, rules and basic precautions for the reception of goods, the storage including precautions for temperature sensitive medicines, Returns (including complaints, falsified medicines, recalls, rejections), Stock control, distribution, transport, etc.

Part III – Rules for reception of Medicines and sanitary products donations, including principles for the donation and models to be filled in the reception of donated medicines.

According to Presidential Decree nº 180/10 of 18th of August, in chapter IV, only medicines registered in Angola can be acquired and commercialized. However the registration procedure wasn't yet implemented. Currently is needed Manufacturing authorisation, certificates of analysis and medicines labelled in Portuguese language.

Distribution authorization is granted for a 2 years period.
Business licence is granted for 5 years and includes medicines categories.

DNME published in 2012 an inquiry to identify and pre-qualify all suppliers of pharmaceutical products in Angola, included in attachment 2.

Any company that wishes to supply medicines to Angola's market, must fill this inquiry, and present it together with CPPs (certificate of a Pharmaceutical Product according to WHO requirements), for the products intended to be placed on the market. A paper copy and a CD containing this information should be provided to authority. This inquiry and its annexes corresponds to administrative and technical dossier that will be analyzed by DNME to evaluate manufacturers/laboratories, representatives and importers. Once this dossier is evaluated, DNME will issue a certificate, accepting this supplier for the purpose of licensing the entity.

Import procedure follows a non-automatic licensing procedure. Procedure to import medicines requires an authorization issued by DNME (invoice licensing) and the trade by importers licensed by DNME. Importers list exists at National Board of Customs and Trades.

Until 2013, pre-shipment inspection was mandatory, but since then it is optional (Presidential Decree nº 63/13 of 11nd of June).

Pre-shipment inspection follows appropriate procedure (described in Decree nº41/06 of 17th of July and by Executive Decree nº 124/06 of 11th of September – additional standards and relevant procedures ensuring implementation of IPE regulation. [34]

Imported medicines entrance either intended to private or public sectors is regulated by General Health Inspection in coordination with National Board of Customs and Trades.

5.4 Registration of medicines – Legislation

There are several laws and decrees published in Angola.

In the next paragraphs, are pointed out the documents to be considered under the registration of medicinal products:

Law nº 21-B/92 of 28th of August – National health system Basis Law.

Presidential decree nº 191/10, 1st of September – Regulation of pharmaceutical activity. This document aims to set the rules for the exercise of pharmaceutical activity in private and public domains, in all national territory.

Law nº 3/99, of 6th of August – Law about traffic and consumption of narcotic drugs, psychotropic substances and precursors.

Presidential decree nº 180/10 18th of August – National pharmaceutical policy. Definition of general basis for national pharmaceutical policy, to promote the quality, safety and efficacy of medicines in Angola, as well as promote rational use of medicines by patients and healthcare professionals.

Presidential decree nº 262/10of 24th November – approves Health national politics and repealing all legislation that contradicts the present presidential decree.

Identification and Pre-qualification for suppliers of Pharmaceuticals products in Angola, August 2012 – Rules weren't approved yet but are alreadybeing implemented).[34]

Presidential Decree nº 180/10, of 18th of August – General Basis for National Pharmaceutical Policy, foresees the promotion, protection and development of medicines production in national territory.

Standards on Best Practices for Medicines and Sanitary products Warehouse and Distribution, 2012 – these rules weren't approved have already started to being implemented. [34]

Identification and pre-qualification of Pharmaceutical products suppliers in Angola, August 2012 - these rules weren't approved have already started to being implemented. [34]

There are several laws and decrees published in Angola.

In the next paragraphs, are pointed out the documents to be considered under the registration of medicinal products:

Law nº 21-B/92 28th of August – National health system

Presidential decree nº 262/10of 24th November – approves Health national politics

5.5 Submission Procedure of a Marketing Authorisation Dossier

Marketing authorization procedure is laid down in Chapter II of National Pharmaceutical Policy document. This section refers to the registration process and selection of medicines in Angola. According to this document, obtaining marketing authorization is regulated in specific legislation namely in which concerns documentation to be submitted, validation procedures for MA application, medicines evaluation, shelf-life evaluation, and Marketing Authorization Introduction terms as well as duties and rights oh MA Holder.[30]

It is foreseen a rapid procedure for pharmaceuticals in emergencies or for reasons of public health. The documents needed for registration procedure shall be submitted to regulatory authority of the pharmaceutical sector, which may request technical reasoned opinion to the national technical committee of medicines.[30]

MA certificates are granted by regulatory authority, after approval by Ministry of Health, of the MA request. Nevertheless, updated legislation and regulation regarding the registration

procedure is still not available currently. One of the priorities published by MINSA is the creation of the national registration and approval of medicines. As one of MINSA purposes: The creation of the national registration and approval of drugs for its introduction in the market, and the control of its quality through the development of a specific laboratory are some challenges for the near future of the Ministry of Health (MINSA).

Presently, and until it has been published legislation regarding registration procedures, Manufacturers, Marketing Authorization Holders and Representatives or Entities that import pharmaceuticals products, should proceed with its identification as medicines and health product suppliers.

5.6 Medicines life-cycle – Post Approval activities

After granting of the marketing authorization, variations to MA terms and renewals need to be submitted to authority. MA Holder should conduct periodical inspections in hospitals, pharmacies and health centers, regarding medicines use and adverse reactions to its medicines, reporting to Regulatory authority any findings. [30]

Respecting MA validity and renewal, registration of a medicine is valid for a period of 5 years. The first medicines re-evaluation should be requested before the end of that period. [30]
Also for renewal procedures specific laws shall be published.

As part of medicines life-cycle with purpose to adapt MA dossier to current technical and scientific knowledge, the submission of variations is foreseen in Presidential decree nº 180/10 of 18th of August, Pharmaceutical national policy.

Since there is no registration procedure, withdrawal from the market requires publication of legislation. Withdrawal for investigational products should be conducted by the manufacturer under the clinical trial sponsor supervision.

5.7 Fees

Fees shall be defined by Ministry of health and Finances regarding registration procedure, variations and renewal procedures.

5.8 Clinical investigation

Law nº 21-B/92 – National Health System Basis Law and National Pharmaceutical Policy are the only official documents containing legislation regarding clinical trials. The law foresees governmental support for clinical investigation, and should be promoted cooperation between MoH, University Agostinho Neto and other public or private entities.

Since no specific regulation is currently published, there is no information about authorization procedure for clinical investigational or patients informed consent. International guides and GDPs should be followed.

According the existing National Health System Basis Law, clinical investigation undertaken on national territory should respect and safeguard human life. Rules for the conduction of clinical trials, stakeholder's responsibilities, etc., will be defined in specific legislation, not available currently.

Investigational medicines import is subject to presentation of: proof of authorization for clinical trial, issued by ministry of Health; existing pharmacological and toxicological documentation, Clinical trial protocol, identification of clinical trial centers and responsible investigators.

5.9 Pharmacovigilance

Implementation of a system for monitoring adverse reactions is foreseen in National Pharmaceutical Policy. Pharmacovigilance committees were created in several provinces.

Any change in the information provided in the inquiry to identify and pre-qualify all suppliers of pharmaceutical products in Angola should be communicated to DNME by supplier.

Chapter 6 – Mozambique

Republic of Mozambique is located in located on the east coast of Southern Africa, bordered by the Indian Ocean to the east, Tanzania to the north, Malawi and Zambia to the northwest, Zimbabwe to the west, and Swaziland and South Africa to the southwest. It is separated from Madagascar by the Mozambique Channel to the east. The capital and largest city is Maputo. The country is divided into 11 provinces: Niassa (capital: Lichinga); Cabo Delgado (capital: Pemba); Nampula (capital: Nampula); Zambézia (capital: Quelimane); Tete (capital: Tete); Manica (capital: Chimoio); Sofala (capital: Beira); Inhambane (capital: Inhambane); Gaza (capital: Xai-Xai); Maputo (capital: Matola); Cidade de Maputo (capital: Maputo).

Mozambique has a population of 20 069 738 inhabitants, 52% of whom are women.[31]
Mozambique is a member of the African Union, the Commonwealth of Nations, the Community of Portuguese Language Countries, the Latin Union, the Non-Aligned Movement and the Southern African Development Community, and is an observer at La Francophonie.
Having 801 590 Km^2, Mozambique is the size of the UK and France combined and has a 2 500 kilometre coastline. Most of the country comprises a low lying coastal plain. Two major rivers, the Limpopo and the Zambezi, flow through Mozambique and 200 kilometres of Lake Malawi coastline lies in the extreme North West. Maputo, in the South is the capital.
Mozambique currency is Novo Metical (MZN). 1 € ≈ 48 MZN[32]
Mozambique is endowed with rich and extensive natural resources such as hydroelectric power, natural gas, coal, minerals, woods and fish products. The country's economy is mainly based on agriculture, but the industry, mainly in the manufacture of food, beverages, chemicals, aluminum and oil, is growing. The country's tourism sector is also growing. South Africa is the main trading partner for Mozambique and the main source of foreign direct investment. Portugal, Brazil, Spain and Belgium are also among the most important economic partners of the country.

Some demographic data (2014)[33]

Estimates for this country explicitly take into account the effects of excess mortality due to AIDS; this can result in lower life expectancy, higher infant mortality, higher death rates, lower population growth rates, and changes in the distribution of population by age and sex than would otherwise be expected (July 2014 est.)

Table 4 - Mozambique Demographic data

Population	**24,692,144 (July 2014 est.)** ***note:*** **estimates for this country explicitly take into account the effects of excess mortality due to AIDS**
Age structure	0-14 years: 45.3% (male 5,627,116/female 5,566,260)
	15-24 years: 21.3% (male 2,566,298/female 2,689,695)
	25-54 years: 27% (male 3,113,095/female 3,553,266)
	55-64 years: 3.5% (male 404,988/female 448,814)
	65 years and over: 2.9% (male 332,013/female 390,599) (2014 est.)
Median age	total: 16.9 years
Population growth rate	2.45% (2014 est.)
Birth rate	38.83 births/1,000 population (2014 est.)
Death rate	12.34 deaths/1,000 population (2014 est.)
Major cities - population	MAPUTO (capital) 1.15 million; Matola 790,000 (2011)
Infant mortality rate	total: 72.42 deaths/1,000 live births
male	74.53 deaths/1,000 live births
female	70.26 deaths/1,000 live births (2014 est.)
Life expectancy at birth	total population: 52.6 years
Total fertility rate	5.27 children born/woman (2014 est.)
Contraceptive prevalence rate	
HIV/AIDS	adult prevalence rate: 11.1% (2012 est.)
	people living with HIV/AIDS: 1,554,700 (2012 est.)
	deaths 76,800 (2012 est.)
Major infectious diseases	degree of risk: very high, food or waterborne diseases: bacterial and protozoal diarrhea, hepatitis A, and typhoid fever, vector borne diseases: malaria and dengue fever, water contact disease: schistosomiasis, animal contact disease: rabies (2013)
Maternal mortality rate	490 deaths/100,000 live births (2010)
Children under the age of 5 years underweight	15.6% (2011)
Health expenditures	6.6% of GDP (2011)
Physicians density	0.03 physicians/1,000 population (2008)
Hospital bed density	0.7 beds/1,000 population (2011)

6.1 General perspective of National Health System

Ministry of health in Mozambique (MISAU) is responsible for supervising all national health institutions by developing health policies and planning health strategies.
MISAU is also responsible for the creation and adaption to the national law of pharmaceutical legislation, medicines registration, pharmacovigilance and medicine marketing monitoring.

MISAU website has available information on the Minister's Office, the National Directorate of Public Health, the National Directorate of Planning and Cooperation, National Directorate of medical assistance, Directorate of Human Resources of the Ministry of Health of Mozambique among others. There is also information about Mental Health, Malaria, Women and children health, Oral Health, School Health and adolescents, expanded program on immunization, tuberculosis and leprosy.

Information on HIV / AIDS, medicines, and its licensing in Mozambique, health network, laboratories, training, legislation, areas of cooperation, research and investigation services to the MOH citizen, among others is accessible in ministry of health website, which is very important given the prevalence of the disease.

Mozambique health system comprises: public sector (national health system - responsible for around 90% of health services provided), private sector (for-profit and non-profit) and community (such as traditional medicine).[34] National health system, which represents main provider of health services, is organized in the following way:

- Primary level – includes rural and urban health centers, it's more decentralized and is where it is implemented the strategy of primary health care;
- Secondary level – includes general hospitals, either rural or district; it is intended for situations in which the primary health care cannot give an answer, like labour complications or trauma situations;
- Tertiary level – hospital in the provincial capitals – reference for pervious levels; is geared towards more specialized healing actions;
- Quaternary level – Beira, Nampula and Maputo central hospitals; Specialized hospitals) – Similarly to tertiary level, is directed to specialized procedures .[34]

Private for-profit sector has been developing in recent years as a result of growth of household income and the exponential growth of foreign income. As a consequence Private clinics and hospitals have emerged in Maputo .[34] In the north of the country the private sector has also seen developments that resulted from the discovery of mineral and hydrocarbon resources. Will be to predict that the development of this area will include the pharmaceutical industry and others.

Non-profit private sector is mainly constituted by non-governmental organizations (NGO) and some religious entities.[34]

Traditional medicine was recognized officially, in 2007 by government, his paper as health care provider. Traditional medicine institute (IMT) was created.

In what refers to health funding's, and according to World Health Organization, the Mozambican National Health System is financed through two main sources:

•Domestic funds from the state budget

•External funds received from different mechanisms including budget support, the Common Fund, which is a basket fund where partners pool their resources, and various bilateral project support initiatives.[35]

In the last years, there has been a steady increase in funding encompassing a variety of funding mechanisms for health financing in Mozambique. In 2004 health sector attracted significantly more foreign funds than in previous years, but since then the difference between the two funding sources is almost constant. According to WHO information, regional office for Africa, the means for estimating and allocating resources follow the main policy documents, in particular, the Poverty Reduction Action Plan (PARP), the Health Sector Strategic Plan, and the Medium Term Expenditure Framework. Health Sector Strategic Plan was covering the period 2005-12, and a new Plan was designed. These strategic documents all follow the same overall objective of increasing accessibility to health care services while improving quality of care particularly in the area of primary health care[35].

As identified in WHO Global Health Expenditure database, public expenditure on health as a proportion of the total health expenditure is decreasing tendentiously since 2005. In 2004, reached about 14% of government expenditure, and allocations to health have been affected by a

substantial increase in external funds particularly for HIV/AIDS under the President's Emergency Plan for AIDS Relief (PEPFAR). Total health expenditure per capita increased significantly from 1997 to 2010. The Government of Mozambique is the main financial agent managing around 72% of the resources to purchase health care. Other agents purchasing health care include households (around 14%) and Presidential decree nº 191/10, 1st of September – Regulation of pharmaceutical activity. This document aims to set the rules for the exercise of pharmaceutical activity in private and public domains, in all national territory.

sector from the point of view of impeding access to the poor."[35] There is a challenge in health sector of holding increased allocations from the state budget while keeping external funding additional to governmental investments and not replacing it. Simultaneously, the health sector could search for other financing mechanisms such as prepayment schemes and social health insurance.

6.2 Manufacture of Medicines

License to manufacture medicines is granted by Ministry of Health, through the submission of a registration procedure.[36] Request for Manufacturing license is not detailed in specific regulation; however it is required to comply with some conditions, as follows:

- Payment of fee (for application, for renewal and annual retention)
- Existence of appropriate facilities and licensing of those facilities by ministries of health, economy and commerce
- Manufacturing authorisation holder should comply with GMP and allow access to the facility by inspectors
- Should have a Technical Director, specialist in Pharmaceutical Industry and if needed 1 or more professionals to support Technical Director in its duties
- Manufacturers should have a Pharmacist responsible for laboratory of Quality Control.[34]

Validity of Manufacturing authorisation is not set forth in a legal order, however manufacturing license can be suspended by Ministry of Health when the circumstances which led to its concession are not met or it is found that the production does not respect the law.

6.3 Distribution and import of medicines

Distribution of medicines in Mozambique requires license and registration issued by Pharmaceutical Department. Procedure for requesting the authorisation for distribute medicines in Mozambique is not described currently in any regulation or legal document, however there are some conditions that need to be filled for granting the authorization for distributing medicines in Mozambique.

Licensing suppliers request requires the payment of a 9.000 MZN fee and 4.500 MZN to the renewal of the same authorisation. Annually a fee of 500 MZN is paid for the licence. Validity of distribution licences is not currently described in any document. Requests for distribution license made by foreign entities can also be made.

Rules and procedures to import, distribute and export medicines were approved by Dispatch of 23rd of March of 2010. Distributors shall only purchase medicines from entities duly authorized to manufacture or distribute medicines, assure that have enough quantity to supply. Distributors shall also have a qualified person responsible for assuring implementation and maintenance of quality system and technical staff duly trained for handle and store medicines. Training records should be kept updated.

Procedures and records for all distribution operations should be implemented namely in which concerns product reception, storage and monitoring of storage conditions, facilities maintenance and cleanness, stock control, handling during shipment, complaints investigation, etc. Records should be made for all sales and purchase transaction, in order to trace and track any operation of medicinal product as well as products shelf-life.

Appropriate facilities to storage medicines should be available including racks and pallets, temperature and humidity monitoring devices (including the storage of monitored data), cold chain for sensitive drugs and segregated areas for returns, specific categories of drugs or expired medicines.

Falsified or counterfeit medicines when detected should immediately be segregated and competent authorities should be informed. Periodic internal audits should be performed to verify the compliance with standards in which regards medicines storage and distribution.

Distributors can only sell medicines directly to pharmacies or other shopping facilities authorized to sell medicines or directly between distributors. Public and private institutions, as

Health centres or hospitals can acquire medicines directly to manufacturers, importers or wholesalers.

Importing medicines can only be made by entities duly licensed for this operation. Medicines to import need to be registered in Mozambique. Ministry of Health (through Pharmaceutical Department) can authorise a special importation for medicines without registration when, through a clinical justification, these medicines are considered essentials for treatment or diagnosis of some conditions.

Import or use of medicines not registered in Mozambique, needs previous authorization by Pharmaceutical Department. Request to import medicines should be made using an appropriate model along with the following documents:

- Requirement in appropriated model
- MA certificate granted in origin country, with qualitative and quantitative composition
- Copy of SmPC or "Data Sheet"

Special import requires the payment of a 4.000 MZN fee.

Imported medicines, exclusively intended to be used in clinical trials, can also circulate in Mozambique. A request should be formalized to Pharmaceutical department together with the following documents:

- Requirement in appropriated model
- A copy of investigational protocol approval
- Identification of the entity where clinical trial is performed.

Rules and procedures for import medicines are described in Dispatch of 23rd of March of 2010 and includes, among others: quality control of each batch imported, guaranteeing appropriate transport and storage conditions.

6.4 Registration of medicines – Legislation

Pharmaceutical legislation in Mozambique is constituted for several Decrees, Laws and regulations. Hereinafter we reference some of the legislation to be considered for medicines registration in Mozambique:

- Law nº 4/98, of 14th of January – sets a new legal framework for the medicine and the exercise of pharmaceutical profession - Within this new legal framework the Registration

of medicines is compulsory in order that medicines can be introduced and sold within the Country. This document approves Law of medicines and Medicines Council (COMED), intended to rule production, import, marketing and supplying od medicinal products, and also assuring that medicines in Republic of Mozambique are safe, effective and have quality, satisfying the needs of the population;

- Decree nº 21/99, of 4th of May – Approves the regulation of the exercise of pharmaceutical profession;
- Decree nº 22/99, of 4th of May – Defines regulation for the registration of medicines. Defines standards and procedures for medicines manufacture, import, introduction and withdraw from the market, variations and renewals.
- Ministerial order nº 125/2008, of 31st of December – Update the fees regarding the registration of medicines, licensing entities in the pharmaceutical area and it's fees;
- Ministerial order nº 52/2010, of 23rd of March creates Traditional medicine institute (IMT)
- Ministerial order nº 53/2010 of 23rd of March that creates regulation for Pharmacovigilance National System.
- Ministerial order nº 223/2010 of 21st of December – Approves the Handbook drug registration procedure – Document issued by Pharmaceutical department, whose purpose is: to harmonise procedures and activities related to the registration of medicines; clarifying some questions regarding interpretation of Registration Regulation; support professionals in executing daily tasks in a standardized manner; support applicants and MA holders for the compliance with registration procedures. This document is divided in 2 parts: Part 1 – Medicines registration; Part 2 – Post-registration procedures.[37]
- Order of 23rd of March 2010 – Approve procedures for Good import, Distribution and Exportation Practices.

6.5 Marketing Authorisation

Registration of medicines it is mandatory so that they can be introduced and sold in Mozambique. Guide of drug registration procedure issued by Pharmaceutical department of Mozambique describes the existing Marketing Authorisation Procedures, as follows:

Extraordinary registration – simplified process of notifying medicines already existing in the market by licensed operators. This registration is valid for 3 years without being entitled to

renewal or exclusivity. (started in 1999, according Decree 22199 of 4th of May and had a validity of 3 years).

Definitive registration: usual procedure for medicines registration to obtain marketing authorization. Is valid for 5 years, renewable for same periods. With the definitive registration, there are three possible paths Complete registration procedure, abbreviated registration procedure, registration by recognition of a registration already granted by another country.[38] [37]

1. MA Complete Procedures

   Registration of new molecules that have never been marketed in Mozambique, molecules that even being marketed, are being studied, vaccines and biological products. Included in this group are antimalarial, anti-retroviral, anti-leprosy and antituberculosis drugs.

2. MA Abbreviated Procedure

   Registration of known molecules, already marketed, but for which production laboratories are not in the list of countries with which Mozambique established bilateral agreements, specifics for this area.

3. Recognition Procedure of MA granted by another country

   Registration of known molecules, with MA Certificate in other countries that are included in the list of countries for which Mozambique stablished bilateral agreements, specifics for this area.

Table 5 - Reference countries, according to Decree 22/99 of 4th of October in Mozambique

European Union (EU
Germany
Austria
Belgium
Denmark
Spain
Finland
France
Greece
Netherlands
Ireland
Hungry

Italy
Luxemburg
Portugal
United Kingdom
Economic European Space
Iceland
Liechtenstein
Norway
Other countries
United states of America
Brazil
Other countries for which Mozambique stablishes bilateral agreements, specifics on this area

For the submission of a Marketing Authorisation Procedure, each type of registration obeys to an administrative process since submission until final decision by regulator.

The application for registration might only be submitted by a registered company and having registered office in Mozambique. The company may act as representative of foreign companies.[39]
The application should specify:

- Name of medicine;
- Pharmaceutical form;

Dossier submission is made by previous appointment and delivery in person.

Dossier to submit is composed by 4 parts:

- Part I – Summary of procedure and administrative information, including type of procedure, MA Holder and applicant data.
- Part II - Chemical and Pharmaceutical documentation, including information about active substance, finished product, manufacturing process, analytical methods, stability, etc.
- Part III – Documentation about safety, including toxicity data, carcinogenic and mutagenic potential, pharmacodynamics and pharmacokinetics, etc.
- Part IV – Documentation about efficacy, such clinical pharmacology, clinical experience.

Part I contains similar documents for all types of procedures. The main difference consists in the content of parts II to IV.

Part I

Management data: Submission of a requirement filled in appropriated model, specifying applicant's name, medicine name, qualitative and quantitative composition of active substances, medicines presentation, pharmaceutical form and manufacturer.
The following documents should also be presented:

- Representative letter
- Manufacturing authorisation
- GMP certificate
- Registration certificate
- Marketing license in origin country (only for imported medicines)
- Certificate of registration in origin country in the WHO terms (CPP)

- Part IA – Application form
- Proof of payment
- Part IB – Product information (Summary of Product Characteristics - SmPC, Package Information Leaflet – PIL and Labelling).
  Additionally to these documents, applicant also needs to present mock-ups in Portuguese language and samples of the medicine intended to register in Mozambique
- Certificates of analysis for finished product

Parts II to IV

Content of parts II to IV is different depending on the type of procedure intended to submit.
For complete registration procedures all documents regarding Parts II to IV, as described above need to be submitted including non-clinical and clinical studies.

For abbreviated procedures, complete documentation is need only for Part II – Chemistry and Pharmaceutical documentation. For Parts III and IV is required the presentation of a Non Clinical Overview (presenting a summary about medicine safety, including at least an updated bibliographic reference on a recognized international publication) and a Clinical Overview (presenting a summary about medicine efficacy, including at least an updated bibliographic reference on a recognized international publication) respectively.

For registration procedure recognition of MA granted by another country, the documentation needed to Parts II to IV is the presentation of Expert report:
Part II – Quality overall Summary – Presentation of Pharmaceutical expert report or Summary about quality information for the medicine, submitted for approval in origin country
Part III – Non-clinical Overview - Presentation of Non-clinical expert report or Summary about safety information for the medicine, submitted for approval in origin Country
Part IV – Clinical Overview – Presentation of Clinical expert report or Summary about efficacy information for the medicine, submitted for approval in origin Country.

We present below a comparative table on the Parts II, III and IV of the registration dossier for the different types of procedures, as is described in the Annex to Ministerial Order No. 223/2010:

Table 6 - Comparative table on Parts II, III and IV of the registration dossier for different types of procedures

	Complete registration procedure	**Abbreviated procedure**	**Recognition Procedure of MA granted by another country**
Part II Composition	Description of the qualitative and quantitative composition, including the proportion of salt / active substance, if appropriate, as well as components of any coatings, capsules, etc.	Description of the qualitative and quantitative composition, including the proportion of salt / active substance, if appropriate, as well as components of any coatings, capsules, etc.	Expert report for Quality (which includes the study of active substances and excipients, manufacturing process, stability).
Primary and secondary packaging description,*	Description of primary and secondary packaging, with respect to the material used, its possible interactions with the drug and control methods.	Description of primary and secondary packaging, with respect to the material used.	
Manufacture	– Batch formula, including number of units of a batch; – - Description of preparation, including manufacturing in process control methods; – Sterilization process validation data, if appropriate	Batch formula, including number of units of a batch.	
Raw materials	– Chemical description of the active substance and excipients (nomenclature, molecular formula, identifying characteristics); – Predictable impurities, specifications and control methods (reference to pharmacopoeia).	– Chemical description of the active substance and excipients (nomenclature, molecular formula, identifying characteristics);	
Finished product	– Global control specifications, – Specifications for controlling active substance, – Data about sterility and pyrogens (if applicable), – Finished product certificate of analyses	– Finished product certificate of analyses, clearly stating limits and specifications. – Data about sterility and pyrogens (if applicable),	Expert report for Quality (which includes the study of active substances and excipients, manufacturing process, stability).

	Complete registration procedure	Abbreviated procedure	Recognition Procedure of MA granted by another country
Stability**	– Length of study; – Study conditions; – Number and size of batches studied; – Tests and limits performed, including any degradation products; – Proposed shelf-life and storage conditions	– Length and conditions of studies, – Proposed shelf-life and storage conditions.	
Other data (if applicable)	– Analytical methods validation, – Manufacturing process validation, – Bioavailability; – Others	Not applicable.	
Part III Toxicity	– Brief description of drug toxicity, including summary of studies performed and bibliographic references, if available	– Summary of studies performed and bibliographic references, if available	Expert report for safety (which includes studies on toxicity, reproductive function and embryo-fetal toxicity and perinatal potential mutagenic and carcinogenic, pharmacodynamics and pharmacokinetics).
Reproductive function and embryo-fetal and perinatal toxicity	– Brief description of the effects of the drug on reproductive function, embryo-fetal and perinatal toxicity, including summary of studies and bibliographic references if available	– Summary of studies performed and bibliographic references, if available	
Mutagenic and carcinogenic potential	Brief description of the effects of the drug on the mutagenic and carcinogenic potential of the drug, including summary of studies and bibliographic references, if available.	Summary of studies performed and bibliographic references, if available.	
Pharmacodynamics and Pharmacokinetics	Brief description of the therapeutic mechanisms of action and pharmacokinetics of the drug, including summary of studies and bibliographic references, if available.	Summary of studies performed and bibliographic references, if available.	
Other safety data	– Local tolerance; – Environmental impact; – Other data.	Not applicable.	

	Complete registration procedure	Abbreviated procedure	Recognition Procedure of MA granted by another country
Part IV Clinical pharmacology Experimental clinic	– Summary description of the therapeutic action of drugs and pharmacokinetics, including summary of studies performed and bibliographic references, if available. – Summary description of clinical trials performed on the medicinal product, as well as of pharmacovigilance data available, including summary of studies conducted, and bibliographic references, if available.	– Summary of studies performed and bibliographic references, if applicable. – Summary of studies performed and bibliographic references, if applicable	Expert report for efficacy (which includes studies on clinical pharmacology and clinical trials)

* When the medicine contains excipients that may cause allergic and other reactions, they shall be discriminated in package leaflet and secondary packaging.

** It is not allowed to be insert in storage conditions the term "ambient temperature, temperature in the room". Should be specified the temperature suitable for storage, for example: store below 25 °C.

Recently, and regarding dossiers submitted by recognition procedure, Pharmaceutical department also asked for:

- Certificates of analysis for active substance
- Certificates of analysis for excipients
- Certificate of suitability (when available)
- Signed updated stability data.

Medicine's name should be included in all documents. In cases where it is not possible, a statement should be issued for clarify the difference.

Dossier is presented to Pharmaceutical department as follows:

- 2 paper copies
- 2 CDs containing all the dossier.

6.6 - Medicines life-cycle – Post Approval activities

Marketing Authorization validity: Council of Medicines will cancel the registration granted if the medicine is not marketed in the first two years after grant of certificate of registration. Are excluded the cases considered of public interest.

Registration certificate is valid for a period of 5 years. Renewal request should be made 180 days before validity ends.

Renewal request is a procedure that occurs at the end of the period of registration granted and aims to re-evaluate the product considering the variations that occurred and new product information during the time of registration. According to Decree nº 22-99 of 4th of May registration granted in Mozambique is valid for a period of five (5) years, which is renewable for equal and successive periods.[39]

Renewal request should be made in appropriate model, in accordance with requirements described in annex 1 of Decree nº 22/99 and in Ministerial Diploma nº223/2010, with at least 180 days in advance regarding the data of registration. Application should be submitted to Pharmaceutical Department, as follows:

- Cover letter
- Application form
- Product information (SmPC, PIL and labelling updated if appropriate)
- Table containing all variations submitted in the last 5 years
- PSUR (periodic safety update report), in a format provided by Pharmaceutical Department

After renewal application submission, there is a validation phase in which benefit-risk ratio is re-evaluated. Request of supplementary information can be made during validation, and should be answered within 20 days. Decision about the renewal request is notified to MA Holder. Positive opinion is accompanied by SmPC, PIL and Labelling texts.

If, until the end of registration validity, no notification is received from Pharmaceutical Department, the renewal request is considered authorised.

Registration is cancelled in case renewal request is not submitted or doesn't comply with the schedule described before.

Renewal application is delivered in the pharmacy department by appointment.

Variations are regulatory activities included in MA maintenance, with the purpose of update the dossier in accordance in current knowledge, either in which concerns the manufacturing process, machines, new analytical methods, or in which regards Product information (SmPC, PIL or labelling) as new safety or efficacy data became available.

Submission of variations to a MA dossier granted in Mozambique is described in Decree nº 22/99[39] and in Ministerial Diploma nº223/2010. The variation application is submitted by filling an appropriated model, in accordance with annex II requirements.

Variations are divided in:

Administrative variations

1- Transfer of marketing authorization for one holder to another

Pharmaceutical variations

1. Changes in Name/Address of Drug product manufacturer
2. Changes in the address of responsible for drug product repackaging
3. Changes in name/address of MA Holder
4. Change to manufacturing authorization terms
5. Change in the medicine's name
6. Changes in active substance name
7. Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)
8. Changes in quantitative or qualitative composition in primary packaging material
9. Change in the batch size of the finished product
10. Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance
11. Widening of shelf-life of finished product
12. Changes on the storage conditions of active substance
13. Changes in analytical procedures of drug product

Clinical variations

1- Changes to SmPC

2- New therapeutic indication to the same therapeutic area

3- New therapeutic indication to a different therapeutic area

Variations requiring a process equivalent to a new registration procedure

1. Introduction of a new strength
2. Change or introduction of a new pharmaceutical form
3. Qualitative or quantitative changes in active substances
4. Introduction of a new administration route

Withdrawal from the market - In case of revocation or registration suspension, withdrawal from the market is a MA Holder responsibility. Local representative should support MA Holder in all activities necessary to execute to accomplish it.

6.7 Fees

Type of Procedure:

MA application registration procedure, per pharmaceutical form, generic drugs – 4.000 MZN (83,09 € (Euros))[32]

Supplementary dosage form for generic drugs – 1.000 MZN (20,77€ (Euros))

MA application registration procedure, per pharmaceutical form, innovative drugs (still patented) – 6.000 MZN (124,63€ (Euros))

Supplementary dosage form for innovative drugs (still patented) – 2.000 MZN (41,54 €(Euros))

MA application registration procedure, per pharmaceutical form, abbreviated procedure – 4.000 MZN (83,09 € (Euros))

Supplementary dosage for abbreviated procedure– 2.000 MZN (41,54 €(Euros))

Granting of license of a MA application registration procedure, per pharmaceutical form, for imported drugs – 16.000 MZN (332,34 €(Euros))

Granting of license of a MA application registration procedure, per pharmaceutical form, for drugs produced in Mozambique – 12.000 MZN (249,26 €(Euros))

Renewal applications for license and registration of imported drugs– 8.000 MZN (166,17 €(Euros))

Renewal applications for license and registration of drugs produced in Mozambique– 6.000 MZN (124,63€ (Euros))

MA application registration procedure, per pharmaceutical form, recognition procedure – 16.000MZN (332,34 €(Euros))

Supplementary dosage form, recognition procedure – 8.000MZN (166,17 €(Euros)).

Variation applications (pharmaceutical variations) – 8.000 MZN (166,17 €(Euros))

Variation applications (clinical variations) – 8.000 MZN(166,17 €(Euros))Variation applications (equivalent to a new registration) – 16.000 MZN

Annual fee for medicines registration retention - 500 MZN (10,39 €(Euros))

Additional presentation, dilution or volumes for drugs to register – 1.000MZN (20,77€ (Euros))

Granting of registration license of an additional presentation, dilution or volumes – 2.500 MZN(51,93€ (Euros))

Request for special importation – 4.000 MZN (83,09€ (Euros))

Issuance of duplicate of registration certificates – 2.000 MZN (41,54€ (Euros))

MA transfer – 1.600 MZN (33,23€ (Euros))

MA application for a medicine, vaccine, biological products or other products by expedite procedure – 10.000 MZN (207,71€ (Euros))

Ministerial order also describes, among others:

- Fees for authorizing the use of medicines not authorized in Mozambique for research purposes.
- Fees for licensing private operators in pharmaceutical area (e.g. Industries licencing – 12.500 MZN (259,64€ (Euros))) and fees for its renewal (e.g. renewal of industries licences – 6.250 MZN (129,82€ (Euros)).
- Annual retention charges of an operating license (e.g. annual retention of industries licences – 750 MZN (15,58€ (Euros))

The complete and detailed information regarding fees is described in the ministerial order No. 125/2008, as described above.

6.8 Clinical investigation

Clinical trials in Mozambique are conducted only after approval of investigation protocol by Ministry of Health. Also, according to Law nº 4/98 of 14th of January, medicines intended to be used in investigation and clinical trials may enter the territory without the existence of a registration procedure, through a special import request (described in article 22).

Currently there are no additional national specific requirements, and Good Clinical practices and internationals guidelines for clinical investigation should be followed and applied. Despite no authorisation procedure for conduction of clinical trials, clinical trial protocol should be submitted to Mozambique Ministry of Health. Evaluation of this document is made by Pharmaceutical Department and Technical and Scientific Committee which belongs to National Health System. Both entities shall issue an opinion about Clinical Protocol in a period of approximately 30 days.

In case of positive opinion, Bioethics National Committee for Health should analyse and give an opinion about ethical concerns and GCPs.

In clinical trials conducted or under the responsibility of CNBS – *Comité Nacional de Bioética para a Saúde* (National Health Institute, Bioethics Institutional Committee for Health) belonging to CIBS-INS – *Comité Institucional de Bioética para a Saúde do Instituto Nacional de Saúde* (National Institute of Health), is the entity that gives an opinion about ethical concerns and GCPs.

6.9 Pharmacovigilance

Pharmacovigilance in Mozambique is ruled by Ministerial Order nº 53/2010 of 23rd of March that approves National Pharmacovigilance System regulation. This system is responsible for detecting, assessing and registering adverse reactions to medicines occurring in Mozambique. Pharmaceutical Department is the entity responsible for National Pharmacovigilance System.

All companies in the possession of medicines registered in Mozambique need to present Periodic Safety Update Reports at time intervals detailed in the law.

Any MA Holder of a medicine for human use, should have, in a permanent way, a person, properly qualified, responsible for Pharmacovigilance issues. This person is responsible for implementing a Pharmacovigilance System which should monitored and record all adverse reactions, informing the MA Holder, which will assess the adverse reaction, and provide answer to any information requested to Pharmaceutical Department or by Health care professionals.

The responsible person should also search in literature for any adverse reactions including active substances of the products registered in Mozambique. In the document mentioned above is also set the frequency for the submission of Periodic safety update reports, after MA granting and in Annex 1 is constituted Nacional Commission for Pharmacovigilance and its competences.

Chapter 7 - Mozambique - Practical approach:

Drug registration in Mozambique is made by following rules and procedures described in Mozambique law and following instructions elaborated by Pharmaceutical Department. As already described, the definitive registration comprises two modalities: Complete and Simplified Registration:

- SIMPLIFIED - regards the application for registration by acknowledgement of one registration granted in a country of reference;
- COMPLETE - corresponds to the submission of all technical documentation required for registration when the Simplified Registration is not possible.

Since Portugal is considered a reference country, in accordance with Decree nº 22/99, of 4th of May, the submission procedure in Mozambique for products already approved in Portugal is made by Recognition of a registration already granted by another country.

This is as simplified submission, in which the evaluation of dossier is based on expert reports about Chemistry and Pharmaceutical documentation, safety documentation and efficacy documentation.

After an initial approach about the required documentation for the submission of a registration by recognition procedure, there are additional documents requested by authority:

- Approved Stability studies updated or presentation of new stability data if the authority considers that the data provided already have many years (number of years not specified).
- In case the dossier documents don't include the product's name approved in the origin country, then a statement should be filled by MA Holder regarding the name currently approved.
- In case a medicinal product is approved in several countries, a copy of a MA certificate in each country is required; the same is applicable for PIL. In case of being difficult to present all approved leaflets, it's enough to present PIL in English, French, Spanish and Portuguese language.

Recently module 3.2.R – Certificate of Suitability was also requested as part of initial dossier.

National authority in Mozambique, for the purpose of registration procedure by recognition of a registration already granted by another country allows the submission of dossier, in NTA

(notice to applicants) format. Recently CTD (Common technical document) format also started to be accepted.

In which concerns the dossiers submission, it is allowed to submit a maximum of 10 files per month. Recent orientations from the Pharmaceutical Department changed the possibility of appointment for a monthly appointment.

Another remark is made to Manufacturing Authorisations and Good Manufacturing Practices certificates, whose originals are required by authority. Is also acceptable to present authenticated copies for these documents, however an authenticated copy per submission is required.

After granting of MA certificate, begins the medicine life-cycle, including the submission of variations and renewals. In which concerns renewals, MA is valid for a period of 5 years after approval. The renewal application needs to be submitted 180 days before.

The variations submitted in origin country should be submitted also in Mozambique, in order to keep the dossier updated. Regardless the classification made in country of origin, variations classification in Mozambique should follow the type of variations presented above. According to the information currently available, the variation can only be submitted in Mozambique after it has been approved in Portugal.

As an example, is presented a possible structure of folders and files for the dossier to be submitted in authority:

Figure 8 - Folder containing Dossier for registration

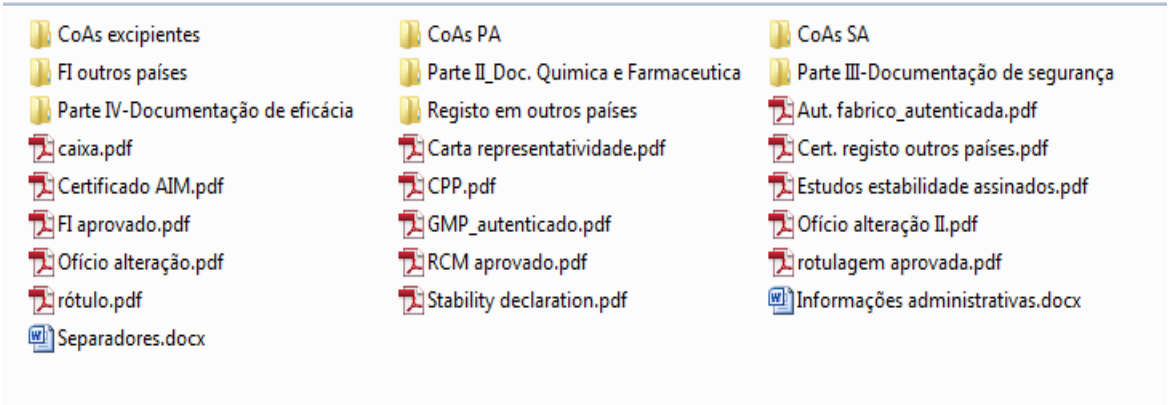


Figure 9 - Files organization for each medicine

Chapter 8 - Discussion

Medicinal products main purpose is to save lives, reduce suffering and improve health and this can only be achieved if they are of good quality, safe, efficacious, available, properly prescribed and well used by patients. The production, marketing and use of substandards/spurious/falsely-labelled/falsified/counterfeit medicinal products can result in therapeutic failure, resistance to medicines and ultimately death. Therefore, quality and safety of medical products require government intervention in the pharmaceutical sector through regulation including promulgation of laws, monitoring of law enforcement and delegation of authority to ensure that the manufacture, marketing and use of medicinal products are effectively regulated. Strong regulatory measures should be in place and be effectively implemented, especially in countries of the African Region that are increasingly exposed to the threats of SSFFC - Substandard/spurious/falsely-labelled/falsified/counterfeit medical products medical products.

Each country should define and stablish the implementation of procedures and appropriate regulation regarding medicinal products, as well as detailing the responsibilities and the different functions and related activities with the purpose of guaranteeing that patients have access to safe and quality medicines, effective in combating the disease that they are suffering. Scope and methods of operation may vary from country to country.

Regulatory authorities in most developing countries, particularly in Africa, lack resources to evaluate the safety, efficacy and quality of new medicines, and usually rely on registration by stringent regulatory authorities in developed countries. On the other hand, more demanding regulatory authorities lack knowledge of medicines intended to NTDs - neglected tropical diseases, which only affect very small numbers of people in their territories, to make the appropriate risk-benefit assessment with regard to populations most affected. Lack of registration capacity in developing countries represents, for the reason exposed, an obstacle to access to NTD drugs in developing countries.

The WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property adopted by the World Health Assembly in May 2008 required stakeholders to “develop and/or strengthen the capacity of national regulatory authorities to monitor the quality, safety and efficacy of health products while sustaining ethical review standards” and “to initiate

programmed actions on regional and sub-regional levels with the ultimate goal of harmonization of processes employed by the regulatory authorities for drug marketing approvals"[40].

Differences in the structure and requirements of regulatory dossiers between countries can also present hurdles. Most Western regulators follow the Common Technical Document (CTD) structure set out by the 2003 International Conference on Harmonisation (ICH), which was agreed by the MRAs of Europe, Japan and the US and the research-based industry. Many African MRAs structure their dossier requirements along WHO guidelines which, while very close to the CTD format, are according to African regulators better adapted to developing country needs. African regulators are also gradually starting to implement CTD in their national settings as part of the African harmonisation initiative, making it easier for an African MRA to leverage a prior external decision.

Despite all constraints and difficulties regarding the registration of medicinal products and any instability recently seen in some African markets, we consider that is a good opportunity for pharmaceutical companies to invest in this geographical area. When selecting target markets, a consideration for economic strength, the adequacy of the healthcare environment, demographic transitions towards a larger population of working age and therapy potential are crucial points.

Most African markets have emergent market access capabilities. Despite Africa represents just 3% of the global economy and Sub-Saharan Africa (excluding South Africa) makes up less than half of the continent's GDP (gross domestic product), this group of countries is growing faster than anywhere else in the world and Investors are waking up to the enormous potential.

A recent survey of core types of investors, institutional investors into Africa, was carried out across a number of multinational companies operating in Africa or looking at operating in Africa. The results found that Africa held the greatest overall investment potential for all frontier markets going globally, and this is also an area where investors plan to increase their asset allocation in the long term.

Pharmaceutical companies that wish to invest in African countries must understand market particularities, so is beneficial and profitable to work with local partners not only to fulfil legal requirements of the country but also to have information on product consumption and market demands in order to make strategic choices on location, operations and portfolio.

Up to date, three types of pharmaceutical industry players have a track record of success, defined as sustainable revenue-generating business operation: innovative multinational companies (MNCs), Indian and Chinese pharmaceutical companies and local manufacturers in Northern and South Africa. This last one is limited to some African countries, like South Africa or Algeria due to high costs of active pharmaceutical ingredients (APIs) in Africa and implementation of good manufacturing practices (GMP) ensuring quality production.

Major multinational companies that have entered in African continent, predominantly focused on branded innovative and generics drugs to the private sector in urban areas and have targeted therapeutic areas such as anti-infectives and vaccines.[5] French companies, for example Sanofi, have typically performed best in predominantly Francophone North and West Africa, while companies from the UK and former British colonies see the healthiest revenues in predominantly Anglophone East and Southern Africa.

The forecasted pharmaceutical market growth in African countries has already generated interest both among companies with existing African operations and those that plan future presence. From MNCs to Indian and Chinese generics manufacturers, pharmaceutical companies from all over the world are attracted by increasing African economic strength and the potential of its emerging middle class. These factors are triggering a rising demand for healthcare services and medicines, offering a strong growth opportunity for the companies with the right sustainable business model.

Focusing particularly in the Countries chosen, there has been an effort, in recent years, to improve the training of personnel, creation of regulatory authorities who oversee the evaluation of medicinal products for human consumption. They have been quite important partnerships established with other regulatory agencies, or other African countries, whether European, highlighting the important role played by Infarmed, or other agencies with greater degree of expertise and development such as ANVISA – National Agency of Sanitary Vigilance (Agência Nacional de Vigilância Sanitária), a member country of the FARMED, which share information and training staff, helping to provide the technical knowledge to these agencies. It is frequent the development of collaboration agreements between these agencies.

Critical analysis of existing health systems: difficulties and opportunities

Cape-Verde SWOT Analysis

Strengths	**Weaknesses**
- Regulation organized and simple to access; - Website well-structured and easy to search; - Available legislation and adequate templates for the registration procedures; - Right to health universal e tending to be unpaid; - Recognition Procedure of MA granted by another country	- Distribution and import is made exclusively by two entities; - Only one manufacturer currently approved in the country; - Low number of inhabitants and geography may lead to is not considered as a priority country to invest, - Lack of qualified human resources; - Chinese manufacturers have gained market share but have poor reputation for medicines quality;
Opportunities	**Threats**
- Empowerment of the pharmacovigilance system; - Increase of robustness of ARFA and increasing of their expertise; - Reduction of mortality rates; - Infrastructure development, including power generation, water development management, rail and air transport, and telecommunication; - Achieve GMP standards; - Increase of patient awareness;	- Lack of specific legislation in specific fields such as clinical investigation and pharmacovigilance, - Scarce financial resources, - Medicines availability, - HIV/AIDS epidemic and its impact on the availability and productivity of labour, - Inexistence of a system to manage human resources, - Lack of medicines;

Angola – SWOT analysis:

Strengths	Weaknesses
- Oil and Minerals resources; - Growing and stable relationship with foreign partners; - Country with a lot of population, in development, with growth potential; - Fastest growing in pharmaceutical sector; - High concentration of pharmaceutical spending in big cities like Luanda; - Strong pharmaceutical sales growth is expected in line with rapid growth in GDP;	- Angola's oil dependent economy - Geographic distribution and operation costs - Lack of human resources and qualified personnel; - Non-transparent tendering and procurement processes; - Weaknesses in administration and legal systems; - Lack of legislation for medicines circuit; - Difficult control of stocks in the distributors and pharmacies; - No control over informal imports; - Chronic stock-outs of essential drugs
Opportunities	**Threats**
- Implementation of a registration process and pricing & reimbursement system; - Publication of specific legislation regarding medicines regulation; - Achieving GMP standards - Fulfil pharmaceutical opportunity potential, taking into account market needs; - Increase of patient awareness; - Investment in the public health sector - Partnerships with Portuguese hospitals and doctors; - Private Market Health growth (Girassol Clinic); - Increase of health care offer in provinces; - Improve access to medication.	- Economy too reliant on oil and diamonds - Economic boom does not directly affect the population - Lack of medicines control; - Risk of existence of substandard and counterfeit medicines; - Pharmacovigilance most of data not centralized or examined at the national level;

Mozambique – SWOT analysis:

Strengths	Weaknesses
- Mozambican government's efforts to achieve universal health coverage through its 2014-2019 Health Sector Strategic Plan - Population density - Strong pharmaceutical sales growth is expected in line with rapid growth in GDP; - Recognition Procedure of MA granted by another country	- Access and use of health services, - Poor regulatory environment - Scarcity of economic and health human resources qualified and duly trained - Structure of dossiers not harmonized with international conventions (CTD format) - Indian and Chinese manufacturers have gained market share primarily through competitive prices and simultaneously targeting different markets in the generics space;
Opportunities	**Threats**
- Economic development, particularly in northern country, which may lead to an improvement in provision of health care; - Strengthening health systems and ensuring increasing equitable access to health services; - Fulfil pharmaceutical opportunity potential, taking into account market needs; - Increase of patient awareness; - Achieving GMP standards	- Existence of counterfeit medicines in the market; - Lack of access to innovative drugs - Lack of medicines control; - Scarcity of health care human resources qualified and duly trained;

In Mozambique, similarly to other African countries, private specialist hospitals have been established by African Medical Investments giving an answer to the "demand for quality, international standard healthcare from emerging middle classes, overseas investors, governments and health insurers." These trends are compounded by concerns around the quality and source of local brands and generics from India and China and the larger issue of counterfeit and substandard drugs.[5]

In Mozambique, the recognition Procedure of MA granted by another country, allowed the introduction in the market through a registration procedure, in simplified manner, of

medicines already evaluated and approved by other countries, with which Mozambique established bilateral agreements. Regulatory agencies of these countries have experience in the evaluation of medicinal products.

In Angola, its city Luanda plays an important role in terms of pharmaceutical opportunity. Luanda accounts for 26% of Angola's GDP will probably remain the focal point of growth in this country From a strategic and financial point of view, a pharmaceutical company intending to go into Angola, needs to give particular relevance to Luanda and possibly Huambo and Lobito. IMS white paper states the following: " The importance of African cities has been more recently emphasized in research conducted by the Economist Intelligence Unit on the 25 top African cities, finding that companies across most sectors are late in harnessing the potential of urban centers across the continent.[5] Strong pharmaceutical sales growth is expected in line with rapid growth in GDP, however is necessary to be aware, particularly in Angola, that fluctuation in oil prices impacting heavily on growth indicators and consequently affect the perspective economic growth of the country. In the last year this trend was observed.

Cape Verde has an authority with a more robust system with regard to medicines registration, the placing on the market and surveillance and control.
But its geography and population may be factors that limit the interest in introducing medicines and other health products in this country.
Additionally, import and distribution of medicinal products either in public or in private in the country is in charge of two entities, which may also limit the entry of the pharmaceutical industry.

In all the focused countries significant improvements are necessary in the number of qualified health professionals in various areas, in order to allow a greater number of patients to have access to health care will need, to have personnel in sufficient number to evaluate and control medicines that enter in the market, allowing to detected substandard or counterfeit medicines, and adequate staff to report any side effects due to medicines use.
All these points will improve quality of health services provided to patients, and will reduce adverse reactions to medicines, including potential hospitalizations, additional spending on treatments and eventually death.

<u>Future:</u>

As already described, strategic partnerships with locally-trusted stakeholders can help companies navigate non-transparent elements of the market access process. In doing so, they allow companies to leverage proven channels to enter the market and reach target patient groups to optimize the go-to-market strategy. Collaboration with public sector payers such as the government, partnerships with non-governmental organizations (NGOs) and patient groups can help determine tender requirements and/or opportunities to shape them, as well as identify clinical key opinion leaders (KOLs) who influence guideline development and care for particular patients. Among private payers, distributors and community health workers can support assessments of relevant payer channels and patient preferences to define tactics for building brand loyalty.

FARMED can also play a very important role in the development of procedures and common strategies between Portuguese speaking countries. Some countries like Cape Verde and Mozambique recognize the evaluation performed by Portuguese authorities, becoming more streamlined the registration procedure in these countries. Maybe in the future a similar procedure can be adopted by other partners, recognizing the evaluation already made. For this purpose partnerships should be consolidated.

In which concerns the registration procedure in Portugal and comparing it with the procedures being applied in Cape Verde and Mozambique, we found that instructions and applications for submissions are available for MA holders and the procedure is clear and harmonized with other European countries.

In which concerns Republic of Angola, registration procedures are still waiting for publication of regulation; the same applies to pharmacovigilance and clinical investigation.

Although there are some particularities that apply at national level, these are primarily to meet specific requirements of each country.

In Europe, where most of the legislation, requirements, templates, etc. are similar between countries, most differences are observed in the administrative section. This similitude between European agencies requirements and the recognition of the evaluation made between authorities (for Mutual recognition and Decentralised procedures) is an advantage in terms of regulatory submission.

It is desirable that the evolution of regulation in emerging countries can evolve in order to reduce the unexpected component (ex.: unexpected requests), which in turn results from the lack of clear and complete instructions by the appropriate bodies.

Chapter 9 - Conclusions

Regulation of medicinal products is an extremely important process that allows to place in the market medicines that are subject to previous assessment and approval, trying to minimise use of drugs with low quality, ineffective or counterfeit. In the research performed, and namely for developing countries, it was perceived that National Medicines Regulatory Authority struggles with limited funding and lack of human resources, either in number and adequately trained.

Simultaneously, due to several changes in recent years, these authorities face the challenge of evaluating drugs that have not been subject to prior assessment by more experienced authorities. In addition, due to economic growth in African countries, these markets are currently seen as potential targets and it is expectable that NMRAs are to be requested to evaluate more medicines.

It has been clear that significant efforts have been made in recent years by National Medicines Regulatory Authority, and further changes are foreseen in the near future, leading to an improvement of procedures and the strengthening of awareness of the regulatory authorities in African countries studied, by human resources training. We have also observed that some countries (e.g.: Cape Verde) have adopted European legislation and templates, harmonising the information regarding the registration procedure. Cape Verde and Mozambique have also implemented registration procedure for recognition of a registration already granted by another country.

However it must be emphasized that there is still a lot to do in some national authorities that need to make changes and implement systems that are currently inexistent.

The analysis on the current state of the health sector, particularly in medicines registration area in the countries referred, was very enlightening insofar as allowed us to learn more about country reality, improvement opportunities and points to be strengthened.

Certainly, analysis of all countries that are part of PALOP would be enriching, but we consider that the selected countries provide a good starting point and represent the majority of markets in which there has been clear interest from different stakeholders to register medicines either by its economic growth, either by the population or by the health sector developments, that facilitate the drug registration process and all the inherent activities.

We hopefully expect that the analysis carried out can be a contribution to other health care professionals who wish to know more about the registration process and the medicines circuit in these countries.

The ultimate goal should be focused on patient and provision of quality medicines in a global context of better delivery of health care.

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Attachment 1 – Check list issued by Cape Verde Pharmaceutical department for Registration by recognition procedure

arfa	LISTA DE VERIFICAÇÃO DO PROCEDIMENTO DE RECONHECIMENTO DA AIM CONCEDIDA POR OUTROS ESTADOS	MOD.DRF.019.00

DADOS GERAIS DO MEDICAMENTO

Nome do medicamento	
Data de Entrada	
Substância activa	
Forma farmacêutica	
Dosagem	
Embalagem	
Requerente	
N. de Processo	
Contacto	

Nota: Assinalar na coluna da direita com **V** ou **X** consoante o item está, ou não, em conformidade. Assinalar **N.A.** se o item não for aplicável.

MEDICAMENTO GENÉRICO? SIM ☐ NÃO ☐

1. LISTA NACIONAL DE MEDICAMENTOS E Nº DE MEDICAMENTOS REGISTADOS

1.1 Medicamento Pertence à lista nacional de medicamentos de Cabo Verde	
1.2 Não existem mais de dois medicamentos registados para a mesma DCI + forma farmacêutica + dosagem.	

2. DOCUMENTAÇÃO ENTREGUE

2.1 Requerimento e formulário em suporte de papel (exceptuando os anexos do formulário) com assinatura original	
2.2 Dossier completo em suporte digital	
2.3 Verificação da conformidade da estrutura electrónica	

3. PAGAMENTO DA(S) TAXA(S) APLICÁVEL(EIS)

3.1Apresenta o Comprovativo e o Resumo de Pagamento segundo o modelo	
3.2 Taxas pagas estão conforme a Lei	
3.3 Ok do DFGR	

4. Tabela de Conteúdos

4.1 Apresenta Tabela de Conteúdos Conforme o Modelo	

5. REQUERIMENTO

5.1 Redigido em língua portuguesa	
5.2 Dirigido ao Presidente do Conselho Administração da Arfa	
5.3 Nome ou firma do requerente	
5.4 Domicílio ou sede do requerente	
5.5 Número de Identificação Fiscal	
5.6 Nome do Diretor Técnico	

5.7 Enquadramento regulamentar **(AIM por Reconhecimento de AIM concedida por outros Estados)**	
5.8 Nome proposto para o medicamento	
5.9 Dosagem	
5.10 Forma Farmacêutica	
5.11 Via de administração	
5.12 Composição qualitativa e quantitativa em substância ativa e excipientes	
5.13 Indicações Terapêuticas	
5.14 Posologia	
5.15 Documentação que constitui o processo	
5.16 Assinatura original do requerente	
5.17 Assinatura do Director Técnico	

6. FORMULÁRIO DO PEDIDO

6.1 Declaração e assinatura

6.1.1 Nome do medicamento	
6.1.2 Dosagem	
6.1.3 Forma farmacêutica	
6.1.4 Substância(s) activa(s)	
6.1.5 Dados do Requerente	
6.1.6 Pessoa autorizada para contacto em representação do requerente	
6.1.7 Anexo 4.3 Autorização para contato em representação do requerente/titular proposto conforme o modelo	
6.1.8 Assinatura original do requerente	

6.2 Tipo de Pedido

6.2.1 Assinalado o tipo de pedido "Um Procedimento De Reconhecimento de AIM concedida por outros estados"	
6.2.2 Estado de Referência	
6.2.3 Data de autorização	
6.2.4 Número de Autorização de Introdução no Mercado	
6.2.5 Anexo 4.10 Cópia de Autorização Inicial no Estado de Referência	
6.2.6 Anexo 4.4 Autorização para troca de informação confidencial entre a ARFA e a entidade de referência	
6.2.7 O nome do medicamento de referência, se for um medicamento genérico	
6.2.8 O Titular de Introdução no Mercado do medicamento de referência, se for um medicamento genérico	
6.2.9 A data da autorização do medicamento de referência, se for um medicamento genérico	
6.2.10 O número da AIM do medicamento de referência, se for um medicamento genérico	
6.2.11 País de autorização do medicamento de referência, se este não estiver autorizado em Cabo Verde, se for um medicamento genérico	

6.3 Caracterização do pedido de AIM

6.3.1 Nome proposto para o medicamento	
6.3.2 Anexo 4.12 A Lista de Nomes fantasia nos diferentes estados em que o medicamento se encontra autorizado	
6.3.3 Nome da(s) substância(s) activa(s)	
6.3.4 Código ATC	
6.3.5 Classificação farmacoterapêutica (CFT)	
6.3.6 Forma farmacêutica	
6.3.7 Dosagem(ns)	

6.3.8 Via de administração	
6.3.9 Acondicionamento primário	
6.3.10 Material do acondicionamento primário	
6.3.11 Fecho do Acondicionamento Primário	
6.3.12 Dispositivos de administração	
6.3.13 Dimensão da(s) embalagem(ns)	
6.3.14 Prazo de validade proposto	
6.3.15 Prazo de validade proposto após abertura do acondicionamento primário	
6.3.16 Prazo de validade proposto após reconstituição/diluição	
6.3.17 Condições de conservação propostas	
6.3.18 Condições de conservação propostas após abertura do acondicionamento primário	
6.3.19 Anexo 4.11 Projetos de embalagem planificados/exemplares	
6.3.20 Dados (Pessoa de contato, Morada, código postal, país, telefone. Fax. E-mail) do Fabricante de dispositivo médico, se aplicável	
6.3.21 Nome do dispositivo médico, se aplicável	
6.3.22 Número de série do dispositivo médico, se aplicável	

6.4 Titular da AIM proposto

6.4.1 Titular da AIM proposto / pessoa legalmente responsável pela colocação do medicamento no mercado (Nome, Morada, Código Postal, País, Telefone, Fax e E-mail)	
6.4.2 Anexo - comprovativo de registo notarial do requerente/titular de AIM no país onde se encontra sediado (Anexo 4.2)	
6.4.3 Pessoa/Empresa autorizada pelo requerente para contacto durante a avaliação do processo (Nome e título da pessoa, Empresa, Morada, Código Postal, País, Telefone, Fax e E-mail)	
6.4.4 Anexo 4.3 Carta de Autorização	
6.4.5 Pessoa/Empresa autorizada pelo requerente para contacto entre o Titular de AIM e as Autoridades Competentes, após autorização para assuntos regulamentares, farmacovigilância, defeitos de qualidade, alertas de segurança e alertas de qualidade	
6.4.6 Anexo 4.3 Carta de Autorização	

6.5 Fabricantes

6.5.1 Fabricante(s) autorizado(s) (ou importador(es)) responsável(eis) pela libertação dos lotes *(Nome, Morada, código Postal, País, Telefone, Fax, E-mail, número da autorização de fabrico*	
6.5.2 Anexo 4.5 Autorização(ões) de fabrico (documento na língua original e respectiva tradução para Português ou Inglês se aplicável)	
6.5.3 Anexo 4.7 Certificado de GMP (inspecção ocorrida há menos de 3 anos) (documento na língua original e respectiva tradução para Português ou Inglês se aplicável) ou Anexo – Certificado Modelo OMS com cadeia de fabrico	
6.5.4 Local/ locais no(s) qual(quais) o controlo/análise dos lotes é realizado (Nome da empresa, Morada, Código postal, País, Telefone, Fax e E-mail)	
6.5.5 Descrição dos testes de controlo realizados	
6.5.6 Anexo 4.5 cópia da(s) Autorização(ções) de Fabrico ou outra prova de cumprimento das GMP	
6.5.7 Fabricante(s) autorizado(s) para produto a granel *(Nome da Empresa, Morada, Código Postal, País, Telefone, Fax e E-mail)*	
6.5.8 Anexo 4.6 Fluxograma indicando a sequência dos diferentes locais de fabrico e dos ensaios	
6.5.9 Anexo 4.5 Autorização(ões) de fabrico (documento na língua original e respectiva tradução para Português ou Inglês se aplicável)	
6.5.10 Anexo 4.7 Último certificado GMP ou certificado OMS	

6.5.11 Fabricante(s) autorizado(s) para acondicionamento primário *(Nome da Empresa, Morada, Código Postal, País, Telefone, Fax e E-mail)*	
6.5.12 Anexo 4.5 Autorização(ões) de fabrico (documento na língua original e respectiva tradução para Português ou Inglês se aplicável)	
6.5.13 Anexo 4.7 Último certificado GMP ou certificado OMS	
6.4.14 Fabricante(s) autorizado(s) para acondicionamento secundário *(Nome da Empresa, Morada, Código Postal, País, Telefone, Fax e E-mail)*	
6.5.15 Anexo 4.5 Autorização(ões) de fabrico (documento na língua original e respectiva tradução para Português ou Inglês se aplicável)	
6.5.16 Anexo 4.7 Último certificado GMP ou certificado OMS	
6.5.17 Fabricante do solvente/ fabricante de fase intermédia *(Nome da Empresa, Morada, Código Postal, País, Telefone, Fax e E-mail)*	
6.5.18 Anexo 4.5 Autorização(ões) de fabrico (documento na língua original e respectiva tradução para Português ou Inglês se aplicável)	
6.5.19 Anexo 4.7 Último certificado GMP ou certificado OMS	
6.5.20 Fabricante(s) da(s) substância(s) activa(s) Substância ativa *(Nome da empresa, Morada, Código postal, País, Telefone, Fax e E-mail)*	
6.5.21 Descrição dos passos de fabrico realizados no local	
6.5.22 Anexo fluxograma indicando a sequência e as atividades realizadas nos diferentes locais envolvidos no processo de fabrico, incluindo os locais de controlo analítico dos lotes	
6.5.23 Se o local foi inspeccionado para BPF/GMP verificar o anexo 4.7 resumo da inspecção, certificado GMP ou declaração da entidade que inspecionou.	
6.5.24 Titular de CEP (Susbtância ativa, Nome da Empresa, número de CEP, Data da última actualização)	
6.5.25 Anexo 4.13 Cópia do CEP	
6.**5.26 Titular de ASMF** (Susbtância ativa, Nome da empresa, número da versão, data de actualização)	
6.5.27 Anexo 4.14 Carta de Autorização de acesso ao ASMF	
6.5.28 Titular de VAMF (Substância ativa, Nome da Empresa; Número do certificado ou referência do pedido, data de submissão ou data de aprovação)	
6.5.29 Anexo 4.15 Cópa do pedido ou do Certificado	
6.5.30 Empresas Contratadas para Ensaios Clínicos de BD/BE (Título do estudo, código do protocolo, Número de registo do ensaio, Nome da Empresa, Morada, Código Postal, País, Telefone, Fax e E-mail)	
6.5.31 Obrigações cumpridas de acordo com o contrato	

6.6 Composição qualitativa e quantitativa

6.6.1 Composição qualitativa e quantitativa em relação à(s) substância(s) ativa(s) e ao(s) excipiente(s)	
6.6.2 Verificar validade da Substância Ativa (DCI, Farmacopeia, etc)	
6.6.3 Lista de matérias de origem animal e/ou de origem humana contidos ou utilizados no processo de fabrico do medicamento	
6.6.4 Anexo- Certificado de Conformidade da Farmacopeia Europeia, se aplicável (Anexo 4.8)	
6.6.5 Anexo cópia de qualquer (quaisquer) consentimento(s) escrito(s) das autoridades competentes para a libertação deliberada de OGMs para o ambiente para fins de pesquisa e desenvolvimento, onde necessário, se aplicável (Anexo 4.9)	

6.7 Outros pedidos de AIM

6.7.1 Autorização de Introdução de mercado em pelo menos um estado (País, data de Autorização, Nome fantasia, Número de autorização)	
6.7.2 Anexo – cópia(s) da(s) Autorização(ões) de Introdução no Mercado (Anexo 4.10)	

6.7.3 Se o mesmo medicamento foi indeferido/suspenso/revogado pela Autoridade Competente, tem um pedido pendente, ou foi retirado de mercado pelo titular ou pela autoridade competente, noutro(s) Estado(s), verificar se os dados foram preenchidos, e as devidas justificativas foram descritas, quando aplicável.	

7. INFORMAÇÃO SOBRE O MEDICAMENTO (RCM, ROTULAGEM E FI)

7.1 RCM

7.1.1 Último RCM aprovado	
7.1.2 Nome do medicamento *Denominação do medicamento, dosagem, forma farmacêutica*	
7.1.3 Composição qualitativa e quantitativa	
7.1.4 Forma farmacêutica	
7.1.5 Informações clínicas	
7.1.6 Indicações terapêuticas	
7.1.7 Posologia e modo de administração	
7.1.8 Contra-indicações *Hipersensibilidade à(s) substância(s) activa(s) ou a qualquer um dos excipientes*	
7.1.9 Advertências e precauções especiais de utilização	
7.1.10 Interacções medicamentosas e outras formas de interacção	
7.1.11 Gravidez e aleitamento	
7.1.12 Efeitos sobre a capacidade de conduzir e utilizar máquinas	
7.1.13 Efeitos indesejáveis	
7.1.14 Sobredosagem	
7.1.15 Propriedades farmacológicas	
7.1.16 Propriedades farmacodinâmicas	
7.1.17 *Classificação Farmacoterapêutica (completa),*	
7.1.18 *Código ATC*	
7.1.19 Propriedades farmacocinéticas	
7.1.20 Dados de segurança pré-clínica	
7.1.21 Informações farmacêuticas	
7.1.22 Lista dos excipientes	
7.1.23 Incompatibilidades	
7.1.24 Prazo de validade	
7.1.25 Precauções especiais de conservação	
7.1.26 Natureza e conteúdo do recipiente	
7.1.27 Precauções especiais de eliminação	
7.1.28 Titular da Autorização de Introdução no Mercado	
7.1.29 Número(s) da Autorização de Introdução no Mercado	
7.1.30 Data da primeira autorização/renovação da Autorização de Introdução no Mercado	
7.1.31 Data da revisão do texto	

7.2 Folheto Informativo

7.2.1 Último Folheto Informativo Aprovado (Anexo 4.14 do Formulário)	
7.2.2 Nota introdutória	
7.2.3 DCI	
7.2.4 Composição qualitativa e quantitativa das substâncias ativas por unidade de toma	
7.2.5 Forma farmacêutica	
7.2.6 Dosagem	

7.2.7 Modo e via de administração	
7.2.8 Duração média do tratamento	
7.2.9 Instruções sobre a atitude a tomar quando for omitida a administração de uma ou mais doses	
7.2.10 Indicação de como parar o tratamento sem causar efeitos de privação	
7.2.11 Precauções particulares de conservação	
7.2.12 Advertência ao utente para comunicar ao médico os efeitos adversos que não constam do folheto	
7.2.13 Advertência ao utente para verificar o prazo de validade	
7.2.14 Data de revisão do FI	

7.3 Rotulagem

7.3.1 Embalagem Secundária ou (na sua ausência) na embalagem primária

7.3.1.1 DCI	
7.3.1.2 Composição qualitativa e quantitativa das substâncias activas por unidade de administração, volume ou peso	
7.3.1.3 Forma Farmacêutica	
7.3.1.4 Dosagem	
7.3.1.5 Apresentação e conteúdo em peso, volume ou número de unidades	
7.3.1.6 Modo e via de administração	
7.3.1.7 Lista de excipientes de declaração obrigatória	
7.3.1.8 Nº de Lote	
7.3.1.9 Expressão *"Manter fora do alcance e da vista das crianças"*	
7.3.1.10 Expressão *"Só pode aplicar-se mediante vigilância clínica"*	
7.3.1.11 Expressão *"Uso Externo" em fundo vermelho, aplicável*	
7.3.1.12 Classificação do medicamento relativamente à dispensa ao público	
7.3.1.13 Prazo de validade, inclusive mês e ano	
7.3.1.14 Prazo de utilização após reconstituição ou primeira abertura do acondicionamento primário, se aplicável	
7.3.1.15 Precauções particulares de conservação, se aplicável	
7.3.1.16 Precauções especiais para a eliminação dos medicamentos não utilizados ou dos resíduos ou detritos deles provenientes	
7.3.1.17 Nome ou firma e domicílio ou sede do Titular da AIM	

7.3.2 Embalagem Primária de Ampolas

7.3.2.1 Nome do medicamento	
7.3.2.2 A dosagem	
7.3.2.3 O modo e a via de administração;	
7.3.2.4 Prazo de validade	
7.3.2.5 O número de lote de fabrico.	

7.3.3 Embalagem primária contendo uma dose unitária deve ter pelo menos

7.3.3.1 O nome do medicamento	
7.3.3.2 A dosagem	
7.3.3.3 O prazo de validade	

8. DECLARAÇÕES/LISTAGENS

8.1 Declaração do requerente atestando que as informações contidas no dossier são idênticas às contidas no dossier no país cuja AIM se pede reconhecimento, conforme Modelo	

8.2 Declaração "Lista de alterações aos termos da AIM", conforme modelo	
8.3 Declaração sobre a retirada do medicamento noutro Estado, conforme modelo	
8.4 Certificado OMS emitido pela autoridade competente do país cuja AIM se pede reconhecimento	
8.5 Declaração de existência de dados de comercialização emitida pela entidade competente do país cuja AIM se pede reconhecimento	
8.6 Declaração de inexistência de alteração do balanço risco/benefício emitida pela entidade competente do país cuja AIM se pede o reconhecimento	
8.7 Listagem de alertas de segurança em relação ao medicamento, emitida pela entidade competente do país cuja AIM se pede reconhecimento	
8.8 Métodos Analíticos e Especificações	

RESUMO DE PEDIDOS DE ELEMENTOS/ESCLARECIMENTOS

N.	Descrição	Status	Data	Data da Resposta

Parecer Positivo ☐

Parecer Negativo ☐

OBSERVAÇÕES:

Data:

Assinatura:

Attachment 2 – Check list issued by Mozambique Pharmaceutical department for Registration procedures

ANEXO I

PROTOCOLO DE RECEPÇÃO E VALIDAÇÃO DE UM PROCESSO DE REGISTO COMPLETO

Nota: O Director Técnico deve estar presente

		Validação
Nome do medicamento		
Substância activa		
Forma Farmacêutica		
Dosagem		
Apresentação		
Data de entrada		
N.º de processo		
Requerente		
Contacto do requerente	**Rua/bairro/Avenida -** **Tel.** **Fax**	

	Sim	Não	Validação
Pagamento da taxa			

***DOSSIER* DE GESTÃO**

PARTE 0

ÍNDICE GERAL	**Sim**	**Não**	**Validação**
REQUERIMENTO			
Entregue pelo requerente			
"O requerente deve ser empresa registada e com sede em Moçambique" (art.º18,Dec. 22/99, de 04/05)			
Entregue pelo seu Representante Legal *"O requerente deve apresentar documentação comprovativa de que actua como representante legal da empresa estrangeira" (art.º 17,Dec. 22/99 de 04/05)"*			
Conteúdo do requerimento (modelo do Dec. 22/99 de 04/05)			
Papel Timbrado do requerente			
Dirigido ao Ministro da Saúde			
Nome e sede do requerente			
Nome proposto para o medicamento *(vide art.º 11 e 12 Dec. 22/99, de 04/05)*			
Forma farmacêutica			
Apresentação			
Composição quantitativa e qualitativa em substância(s) activa(s)			
Fabricante do produto acabado			
Se a documentação científica for comum para formas farmacêuticas diferentes e/ou dosagem diferentes, referência no requerimento			
N.º de volumes que constitui o processo			

O pedido de registo deverá apresentar os seguintes certificados:
(art.º19 Dec. 22/99 de 04/05)

	Sim	Não	Validação
Requerimento autenticado emitido pelo Ministério da Saúde do País de origem comprovando que o produtor é um fabricante licenciado para a produção do medicamento, para o qual está a solicitar o registo Autorização de fabrico/Licença de fabrico			
No caso de medicamentos importados, Certificado de Registo no País de origem (CPP), nos termos estabelecidos pela Organização Mundial de Saúde, conforme o *Sistema de Certificação de Qualidade dos Produtos Farmacêuticos no Mercado Internacional.*			
No caso de medicamentos importados: Licença de comercialização no País de origem, nos termos estabelecidos pela Organização Mundial de Saúde, conforme o *Sistema de Qualidade dos Produtos Farmacêuticos no Mercado Internacional.*			
Certificado de Boas Práticas de Fabrico (GMP)			
Certificado de pré-qualificação da OMS ou outra entidade reconhecida ou uma carta comprovativa			

PARTE I

PARTE I-A: INFORMAÇÕES ADMINISTRATIVAS

(verificar se toda a informação foi traduzida para português)	Sim	Não	Validação
Tipo de processo			
Nome proposto para o medicamento (nome fantasia/marca)			
Composição quantitativa e qualitativa relativa à(s) subs. activa (s) e aos excipiente (s)			
Classificação fármaco – terapêutica de acordo com o Formulário Nacional de Medicamentos (art.º10 Dec. 22/99, de 04/05)			
Forma Farmacêutica e dosagem			
Apresentação			
Prazo de validade/Condições de armazenamento			
Classificação quanto ao modo de dispensa (art.º 9º Dec. 22/99, de 04/05)			
Nome e morada do requerente			
Fabricante do produto acabado			

PARTE I-B1: CARACTERÍSTICAS DO MEDICAMENTO

1 – Resumo das Características do Medicamento (verificar se toda a informação foi traduzida para português)	Sim	Não	Validação
Nome do medicamento			
Composição qualitativa/quantitativa em substâncias activas			
Forma farmacêutica e respectivo conteúdo em peso, volume ou número de unidades			
Validade/ Condições de armazenamento			
Indicações terapêuticas			
Posologia e modo de administração			
Contra indicações			
Interacções medicamentosas			
Utilização em caso de gravidez e de lactação			
Efeitos sobre a capacidade de condução e utilização de máquinas			
Efeitos indesejáveis			
Nome do titular de registo do medicamento em Moçambique			

PARTE I-B2: RÓTULO

2 – Rótulo e Cartonagem	Sim	Não	Validação
Nome do medicamento			
Composição qualitativa e quantitativa das substâncias activas por unidade			
Número de lote			
Data de fabrico			
Prazo de validade			
Número de registo			
Nome do titular do registo			
Classificação quanto ao modo de dispensa			
Nome do fabricante			
Precauções particulares de conservação, quanto for o caso disso			
A expressão "Uso externo" impressa em fundo vermelho, quando for o caso			

Folheto Informativo	Sim	Não	Validação
Nome do medicamento			
Nome DCI			
Composição			
Forma farmacêutica e respectivo conteúdo em volume/massa			
Indicação terapêutica			
Contra-indicação			
Efeitos indesejáveis			
Interacções medicamentosas e outras			
Precauções especiais de utilização			
Efeitos na gravidez e lactação			
Efeito em pediatria			
Efeito em geriatria e doentes com patologias especiais			
Efeitos na capacidade de condução e utilização de máquinas			

Folheto Informativo	Sim	Não	Validação
Posologia			
Modo e via de administração			
Indicação do momento mais favorável à administração do medicamento			
Atitude a tomar em caso de omissão de uma ou mais doses			
Sobredosagem, sintomas, medidas de urgência e antídotos			
Precauções especiais de conservação			
Deve conter a expressão: *Em caso de observação de efeitos secundárias não mencionados neste folheto, aconselha-se a sua comunicação ao médico ou profissional de saúde.*			
Data da última revisão deste folheto			
Fabricante			
Titular de registo no País de origem			

DOSSIER TÉCNICO

	Sim	Não	Validação
Três cópias com informação completa			

ou

Uma cópia em papel e dois "CD"	Sim	Não	Validação

PARTE I

	Sim	Não	Validação
Toda documentação do Dossier de Gestão			

PARTE II

DOCUMENTAÇÃO QUÍMICA E FARMACÊUTICA

PARTE II – A. Documentação Completa

A-1. Composição	Sim	Não	Validação
Descrição da composição qualitativa e quantitativa, incluindo a proporção sal/ /substância activa, se for o caso assim como os componentes de eventuais revestimentos, cápsulas, etc.			
Descrição da embalagem primária e secundária, no que diz respeito ao(s) material(is) utilizado(s), suas possíveis interacções com o medicamento e métodos de controle.			
Função dos constituintes não activos.			
A-2. Fabrico			
Fórmula de fabrico, incluindo número de unidades de lote.			
Descrição da preparação, incluindo métodos de controlo em processo de fabrico			
Dados de validação de processos de esterilização			

A-3. Matérias-Primas	Sim	Não	Validação
Descrição química da substância activa e excipientes (nomenclatura, fórmula molecular, características identificativas)			
Impurezas previsíveis, especificações e métodos de controlo (Referência as Farmacopeias usada)			
Identificação do fabricante e boletim analítico da responsabilidade do mesmo ou do requerente			
A-4. Produto acabado			
Especificações de controlo globais			
Especificações de controle da(s) substância(s) activa(s)			
Dados sobre esterilidade e pirogéneos (se aplicável)			
Boletim analítico do produto acabado			
A-5. Estabilidade			
Duração dos estudos			
Condições dos estudos			
Número e dimensão dos lotes estudados			
Ensaios efectuados e limites, incluindo eventuais produtos de degradação			
Conclusão do estudo			
Quando o estudo não esta completo, uma carta onde a empresa se compromete a enviar a parte do estudo em falta para a Autoridade Reguladora.			
A-6. Outros dados (se aplicável)			
Validação de métodos analíticos			
Validação de processos de fabrico			
Biodisponibilidade			
Outros			

PARTE III

DOCUMENTAÇÃO SOBRE SEGURANÇA

PARTE III– A. Documentação Completa

	Sim	Não	Validação
A-1. Toxicidade			
Descrição sumária da toxicidade do medicamento, incluindo resumo de estudos efectuados e referências bibliográficas, se disponíveis.			
A-2. Função Reprodutora e toxicidade embrio-fetal e perinatal			
Descrição sumária dos efeitos do medicamento sobre a função reprodutora, toxicidade embrio-fetal e perinatal, incluindo resumo de estudos efectuados e referências bibliográficas, se disponível.			
A-3. Potencial mutagénico e carcinogénico			
Descrição sumária dos dados existentes sobre o potencial mutagénico e carcinogénico do medicamento, incluindo resumo de estudos efectuados e referências bibliográficas, se disponíveis.			
A-4. Farmacodinamia e Farmacocinética			
Descrição sumária dos mecanismos de acção e da farmaconética do medicamento, incluindo resumo de estudos efectuados e referências bibliográficas, se disponíveis.			
A-5. Outros dados sobre segurança			
Tolerância local			
Impacto ambiental			
Outros dados			

PARTE IV

DOCUMENTAÇÃO SOBRE A EFICÁCIA

PARTE IV– A. Documentação Completa

	Sim	Não	Validação
A-1. Farmacologia Clínica Descrição sumária dos mecanismos de acção terapêutica e da farmacocinetica do medicamento, incluindo resumo de estudos efectuados, e referências bibliográficas, se disponíveis. **A-2. Experiência Clínica** Descrição sumária dos ensaios clínicos efectuados sobre o medicamento, assim como dos dados de farmacovigilância disponíveis, incluindo resumo de estudos efectuados e referências bibliográficas, se disponíveis.			

PROTOCOLO DE RECEPÇÃO E VALIDAÇÃO DE UM PROCESSO DE REGISTO ABREVIADO

Nome do medicamento		
Substância activa		
Forma Farmacêutica		
Dosagem		
Apresentação		
Data de entrada		
N.º de processo		
Requerente		
Contacto do requerente	**Rua/bairro/Avenida -** **Tel.** **Fax**	

A-3. Matérias Primas	Sim	Não	Validação
Pagamento da taxa			

DOSSIER DE GESTÃO

PARTE 0

	Sim	Não	Validação
ÍNDICE GERAL			
REQUERIMENTO			
Entregue pelo requerente *"O requerente deve ser empresa registada e com sede em Moçambique"* *(art.º18, Dec. 22/99, de 04/05)*			
Entregue pelo seu Representante Legal *"O requerente deve apresentar documentação comprovativa de que actua como representante legal da empresa estrangeira"* *(art.º 17,Dec. 22/99, de 04/05)"*			
Conteúdo do requerimento (modelo do Dec. 22/99, de 04/05)			
Papel Timbrado do requerente			
Dirigido ao Ministro da Saúde			
Nome e sede do requerente			
Nome proposto para o medicamento *(vide art.º 11º e 12º Dec. 22/99, de 04/05)*			
Forma farmacêutica			
Apresentação			
Composição quantitativa e qualitativa em substância(s) activa(s)			
Fabricante do produto acabado			
Se a documentação científica for comum para formas farmacêuticas diferentes e/ou dosagem diferentes, referência no requerimento			
N.º de volumes que constitui o processo			

O pedido de registo deverá apresentar os seguintes certificados:
(art.º 19 Dec.22/99, de 04/05)

	Sim	Não	Validação
Requerimento autenticado emitido pelo Ministério da Saúde do País de origem comprovando que o produtor é um fabricante licenciado para a produção do medicamento, para o qual está a solicitar o registo Autorização/Licença de fabrico			
No caso de medicamentos importados, Certificado de Registo no país de origem/ /Certificado do Produto Farmacêutico (CPP), nos termos estabelecidos pela Organização Mundial de Saúde, conforme o *Sistema de Certificação de Qualidade dos Produtos Farmacêuticos no Mercado Internacional.*			
No caso de medicamentos importados, Licença de comercialização no País de origem, nos termos estabelecidos pela Organização Mundial de Saúde, conforme o *Sistema de Qualidade dos Produtos Farmacêuticos no Mercado Internacional.* Certificado de Boas Práticas de Fabrico (GMP), nos termos estabelecidos pela Organização Mundial de Saúde, conforme o *Sistema de Qualidade dos Produtos Farmacêuticos no Mercado Internacional*			

(art.º 20 Dec. 22/99 de 04/05 e Apêndice 2)

	Sim	Não	Validação
Rotulagem e resumo das características do medicamento, na versão aprovada no País de origem			

PARTE I-A: INFORMAÇÕES ADMINISTRATIVAS

(verificar se toda a informação foi traduzida para português)	Sim	Não	Validação
Tipo de processo ABREVIADO			
Nome proposto para o medicamento (nome fantasia/marca)			
Composição quantitativa e qualitativa relativa à(s) subs. activa(s) e dos excipiente(s)			
Classificação fármaco – terapêutica de acordo com o Formulário Nacional de Medicamentos (art.º 10 Dec. 22/99 de 04/05)			
Forma Farmacêutica e dosagem			
Apresentação			
Prazo de validade/Condições de armazenamento			
Classificação quanto ao modo de dispensa (art.º 9º Dec.22/99, de 04/05)			
Nome e Morada do requerente			
Fabricante do produto acabado			

PARTE I-B1: CARACTERISTICAS DO MEDICAMENTO

1 - Resumo das Características do Medicamento (verificar se toda a informação foi traduzida para português)	Sim	Não	Validação
Nome do medicamento			
Composição qualitativa/quantitativa em substância activas			
Forma farmacêutica e respectivo conteúdo em peso, volume ou número de unidades			
Validade/Condições de armazenamento			
Indicações terapêuticas			
Posologia e modo de administração			
Contra-indicações			
Interacções medicamentosas			
Utilização em caso de gravidez e de lactação			
Efeitos sobre a capacidade de condução e utilização de máquinas			
Efeitos indesejáveis			
Nome do titular de registo do medicamento			

PARTE I-B2: RÓTULO

2 – Rótulo (prestar atenção: a informação do rotulo em *word* tem que ser igual a da proposta de rotulo)	Sim	Não	Validação
Nome do medicamento			
Composição qualitativa e quantitativa das substâncias activas por unidade			
Número de lote			
Data de fabrico			
Prazo de validade			
Número de registo			
Nome do titular do registo			
Classificação quanto ao modo de dispensa			
Nome do fabricante			
Precauções particulares de conservação, quanto for o caso disso			
A expressão "Uso externo" impressa em fundo vermelho, quando for o caso			

Folheto Informativo	Sim	Não	Validação
Nome do medicamento			
Nome DCI			
Composição			
Forma farmacêutica e respectivo conteúdo em volume/massa			
Indicação terapêutica			
Contra-indicação			
Efeitos indesejáveis			
Interacções medicamentosas e outras			
Precauções especiais de utilização			
Efeitos/utilização na gravidez e lactação			
Efeito em pediatria			
Efeito em geriatria e doentes com patologias especiais			
Efeitos na capacidade de condução e utilização de máquinas			
Posologia			
Modo e via de administração			
Indicação do momento mais favorável à administração do medicamento			
Atitude a tomar em caso de omissão de uma ou mais doses			
Sobredosagem, sintomas, medidas de urgência e antídotos			
Precauções especiais de conservação			
Deve constar a expressão: *Em caso de observação de efeitos secundárias não mencionados neste folheto, aconselha-se a sua comunicação ao médico ou profissional de saúde.*			
Data da última revisão deste folheto			
Fabricante			
Titular de registo no País de origem			

DOSSIER TÉCNICO

	Sim	Não	Validação
Três cópias com informação abreviada			

ou

Uma cópia em papel e dois "CD"			

PARTE I

	Sim	Não	Validação
Toda documentação do Dossier de Gestão			

PARTE II

DOCUMENTAÇÃO QUÍMICA E FARMACÊUTICA

PARTE II – A. Documentação Abreviada

A-1. Composição	Sim	Não	Validação
Descrição da composição qualitativa e quantitativa, incluindo a proporção sal/ /substância activa, se for o caso assim como os componentes de eventuais revestimentos, cápsulas, etc. Descrição da embalagem primária e secundária, no que diz respeito ao(s) material(is) utilizado(s).			

A-1. Composição	Sim	Não	Validação
A-2. Fabrico			
Fórmula e processo de fabrico, incluindo número de unidades de lote.			
A-3. Matérias-primas			
Descrição química da substância activa e excipientes (nomenclatura, fórmula molecular, características identificativas)			
A-4. Produto acabado			
Boletim analítico do produto acabado indicando claramente especificações e limites			
A-5. Estabilidade			
Duração e condições dos estudos			
Prazo de validade proposto e condições de conservação			

PARTE III

DOCUMENTAÇÃO SOBRE SEGURANÇA

PARTE III– A. Documentação Abreviada

	Sim	Não	Validação
Apresentação de um resumo sobre a segurança do produto, incluindo pelo menos uma referência bibliográfica em publicação de reconhecida credibilidade internacional			

PARTE IV

DOCUMENTAÇÃO SOBRE A EFICÁCIA

PARTE III– A. Documentação Abreviada

	Sim	Não	Validação
Apresentação de um resumo sobre a eficácia do produto, incluindo pelo menos uma referência bibliográfica em publicação de reconhecida credibilidade internacional			

PROTOCOLO DE RECEPÇÃO E VALIDAÇÃO DE UM PROCESSO DE REGISTO POR RECONHECIMENTO DO REGISTO EM OUTRO PAÍS

		Validação
Nome		
Número de processo		
Substância activa		
Forma farmacêutica		
Apresentação		
Dosagem		
Data de entrada		
Requerente		
Contacto do requerente		

	Sim	Não	Validação
REQUERIMENTO			
Papel timbrado			
Dirigido ao Ministro da Saúde			
Nome e sede do requerente			
Nome proposto para o medicamento			
Forma farmacêutica			
Apresentação			
Composição qualitativa e quantitativa relativa a substâncias activas			
Fabricante do produto acabado			
Se a documentação for comum para formas farmacêuticas diferentes e ou dosagens diferentes, referência no requerimento			

	Sim	Não	Validação
DOCUMENTAÇÃO			
Carta de Representatividade			
Certificado de Fabrico			
Certificado de Boas Práticas de Fabrico			
Certificado de Registo do Medicamento			
Licença de Comercialização no País de Origem			

	Sim	Não	Validação
PARTE I-A: RESUMO DO PROCESSO - INFORMAÇÕES ADMINISTRATIVAS			
• Tipo de processo (Completo/Abreviado/Por Reconhecimento)			
• Nome proposto para o medicamento			
• Composição qualitativa e quantitativa relativa à(s) substância(s) activa(s)			
• Classificação farmacoterapêutica de acordo com o Formulário Nacional de Medicamentos			
• Forma Farmacêutica e dosagem			
• Apresentação			
• Prazo de validade/Condições de armazenamento			
• Classificação quanto ao modo de dispensa			
• Nome e morada do requerente			
• Fabricante do produto acabado			

PARTE IV : DOCUMENTAÇÃO SOBRE EFICÁCIA	Sim	Não	Validação
PARTE I-B: CARACTERÍSTICAS DO MEDICAMENTO 1. RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO (RCM) • Nome do medicamento			
• Composição qualitativa/quantitativa em substâncias activas			
• Forma farmacêutica e respectivo conteúdo em peso, volume ou número de unidades			
• Validade/Condições de armazenamento			
• Indicações terapêuticas			
• Posologia e modo de administração			
• Contra-indicações			
• Interacções medicamentosas			
• Utilização em caso de gravidez e de lactação			
• Efeitos sobre a capacidade de condução e utilização de máquinas			
• Efeitos indesejáveis			
2. RÓTULO			
• Nome do medicamento			
• Composição qualitativa/quantitativa das substâncias activas por unidade de toma, volume ou peso			
• Forma farmacêutica e respectivo conteúdo em peso, volume ou número de unidades			
• Prazo de validade			
• Número de registo			
• Nome do titular do registo			
• Classificação quanto ao modo de dispensa			
• Precauções particulares de conservação, quando for caso disso			

	Sim	Não	Validação
PARTE II : DOCUMENTAÇÃO QUÍMICA E FARMACÊUTICA			
• Apresentação de Relatório do Perito Farmacêutico ou resumo da informação sobre a qualidade do medicamento submetida para aprovação do registo no País de origem			

PARTE III : DOCUMENTAÇÃO SOBRE SEGURANÇA	Sim	Não	Validação
• Apresentação de Relatório do Perito Toxicológico ou resumo da informação sobre a segurança do medicamento submetida para aprovação do registo no País de origem			

PARTE IV : DOCUMENTAÇÃO SOBRE EFICÁCIA	Sim	Não	Validação
•Apresentação de Relatório do Perito Clínico ou resumo da informação sobre a eficácia do medicamento submetida para aprovação do registo no País de origem			

Attachment 3 – Inquiry for Identification and Pre-Qualification of Pharmaceutical Products of Suppliers in Angola

REPÚBLICA DE ANGOLA
MINISTERIO DA SAUDE
DIRECÇÃO NACIONAL DE MEDICAMENTOS E EQUIPAMENTOS

IDENTIFICAÇÃO E PREQUALIFICAÇÃO DOS FORNECEDORES DE PRODUTOS FARMACÊUTICOS EM ANGOLA

Luanda Agosto 2012

1

SUMÁRIO

1 INTRODUÇÃO

O presente questionário destina-se à identificação e qualificação como fornecedor de medicamentos e dispositivos médicos (fabricantes/laboratórios, seus representantes e os importadores), e à recolha de informação precisa e completa, relativa à qualidade e a fiabilidade do serviço prestado, ou a prestar.

Este questionário refere-se às especificações técnicas da OMS relativas às preparações farmacêuticas, tais como, definidas nos «Relatórios Técnicos» Nº.823 e 863.

Este questionário é o elemento chave de um dossier administrativo e técnico de avaliação dos fornecedores do ramo farmacêutico em Angola.

A avaliação dará lugar a um Certificado de Acreditação emitido pela Direcção Nacional de Medicamentos e Equipamentos (DNME), em termos de aceitação do fornecedor com vista ao licenciamento.

O Certificado terá uma validade de 3 anos a partir da data da aprovação, se, se mantiverem as condições avaliadas no âmbito do presente inquérito.

Em caso de qualquer alteração, mudança ou modificação das condições actuais, avaliadas no âmbito do actual inquérito, o fornecedor devera informar a DNME para a actualização do processo.

O questionário apresenta-se segundo o plano seguinte:

Informações gerais

Dirigidas a todos os Agentes económicos, que actuem em Angola, quer sejam Fabricantes titulares de AIM, Titulares de AIM, Representantes ou Entidades importadoras de produtos farmacêuticos.

Informações farmacêuticas

Subdivididas em três partes, respeitantes a cada uma das actividades específicas dos Agentes económicos:

a) A primeira parte diz respeito aos **Fabricantes de medicamentos, titulares de AIM e seus Representantes**;

b) A segunda parte diz respeito aos **Fabricantes de dispositivos médicos, de material médico e de meios de diagnóstico**;

c) A terceira parte diz respeito às **Entidades importadoras de produtos farmacêuticos** (fornecedores não fabricantes: importadores e centrais de compra).

Todos os fornecedores devem comprometer-se pelas declarações assumidas, sob pena de rejeição do pedido. O inquérito **deve ser assinado obrigatoriamente pelos representantes legais dos acima referidos fornecedores.**

Os fabricantes devem a este título, completar as Informações Farmacêuticas relativas à parte do «Fabricante», em função dos produtos fabricados.

Os fabricantes que, para além da sua própria produção, comercializem produtos farmacêuticos não fabricados por eles serão considerados, para esta gama complementar, como **Representantes/importadores**. Eles devem a este título completar igualmente a parte relativa às entidades importadoras e, conformarem-se com as disposições relativas a estas entidades.

Os fornecedores que rotulem os produtos que comercializam só com o seu nome serão considerados, do ponto de vista da sua responsabilidade farmacêutica, como fabricantes. Devem a este título completar as «Informações Farmacêuticas» da parte relativa ao «Fabricante».

Para ser aceite, o presente questionário deve ser preenchido na íntegra. As informações fornecidas serão tratadas confidencialmente.

Devem ser anexadas ao questionário as cópias autenticadas dos originais, e as traduções em português reconhecidas pelos serviços consulares de Angola, dos seguintes documentos essenciais emitidos no País de origem, pelas Autoridades competentes:

1- Autorização de Fabrico indicando os locais de produção, de acondicionamento e de libertação do lote;
2- Certidão comprovativa da Titularidade de Autorização do fabrico do medicamento num país terceiro;
3- Declaração relativa ao estatuto de Autorização de Introdução no Mercado do país exportador;
4- Autorização de fabrico para exportação;
5- Certificado de Pré-qualificação em casos de produtos usados para as grandes endemias (HIV/SIDA, tuberculose, malária, …) e para os produtos usados na saúde reprodutiva e vacinas.
5- Certificado de Inspecção dos últimos dois anos;
6- Autorização do Exercício de Actividade;
7- Parecer científico sobre a avaliação de medicamentos destinados exclusivamente à exportação, emitido pela Autoridade Reguladora Farmacêutica;
8- Autorização de Exportação.

Reserva-se ao Serviço o direito de solicitar toda a informação ou documento complementar, que julgar útil para a apreciação do questionário.

A documentação deve ser organizada de acordo com a estrutura divulgada no presente questionário e apresentada:

a) Em suporte de papel, em pasta de arquivo rotulada na lombarda com o nome e endereço da Entidade;
b) Em suporte electrónico (CD R) igualmente identificado.

Todas as páginas do dossier em suporte de papel devem ser numeradas, rubricadas e carimbadas com o carimbo em uso nos serviços da entidade inquerida.

A análise do questionário far-se-á tendo em conta o conjunto das respostas fornecidas e, dará lugar a uma avaliação inicial.

A ausência de documentos considerados como essenciais, ou uma resposta não satisfatória a certas questões, consideradas como fundamentais, dará lugar a uma rejeição do dossier após audiência do interessado.

INFORMAÇÕES GERAIS

1.1 Identificação do Fornecedor

Nome: ……

Direcção completa: ……

…… ……

Tel. : ……

Fax. : ……

E-mail : ……

Nº de Identificação Fiscal: ……

Nº. Registo Comercial : ……

(anexar uma cópia autenticada da Escritura da empresa e do Registo Comercial)

Actividade principal definida no Registo Comercial: ……

……

…… ……

1.2 Campos de Actividades e Autorização de Exercício Farmacêutico

Assinale com **x** ou negrito os casos correspondentes

☐ Fabricante /	☐ Entidade importadora
☐ Titular de AIM	
☐ Representante	
☐ De especialidades farmacêuticas	☐ De especialidades farmacêuticas
☐ De medicamentos genéricos	☐ De medicamentos genéricos
☐ De outros artigos médicos	☐ De outros artigos médicos
Listar em anexo…… ……	Listar em anexo……
……	……
……	……
…../……	…../……
☐ Para o mercado nacional (país exportador)	☐ Para o mercado nacional
☐ Para a exportação	
Nº. da Autorização de exercício: ……..	Nº. da Autorização de exercício: ……..

Anexar, uma cópia das autorizações de exercício como Fabricante e/ou como Entidade importadora de produtos farmacêuticos passados pela Autoridade Reguladora Nacional e do País de origem.

1.3 Inspecção pelas Autoridades Nacionais Competentes

A vossa empresa foi objecto de inspecção nestes três últimos anos pela autoridade nacional?

☐ **Sim** ☐ **Não**

Se sim, anexar a cópia do relatório da inspecção feita nos últimos dois anos.

1.4 Inspecção por Organismos Internacionais

A vossa sociedade foi objecto de inspecção nestes três últimos anos por autoridades ou organismos internacionais?

☐ **Sim** ☐ **Não**

Se sim, anexar a cópia do relatório da última inspecção.

1.5 Quadro do Pessoal

NB: dentro e/ou fora do país

Pessoal total: .....

Pessoal administrativo: .....

Pessoal técnico: .....

Número de farmacêuticos: .....

O pessoal encontra-se inscrito no Instituto Nacional de Segurança Social? ☐ **Sim** ☐ **Não**

Nome das pessoas que ocupam um posto chave, precisar as qualificações e funções.

Director: .....

Outras pessoas habilitadas a representarem ou a responsabilizarem-se pela sociedade: .....

.....

.....

Farmacêutico responsável: .....

.....

Farmacêuticos adjuntos e funções: .....

.....

.....

.....

.....

Nome do responsável pela exportação: .....

Tel.: .....

E-mail: .....

1.6 Relações Comerciais

Citar no mínimo 5 clientes actuais representativos no mercado nacional (organismos estatais ou privados, ONG…)

Nome do cliente	Tipologia do cliente
1-	
2-	
3-	
4-	
5-	
…/..	

1.7 Estado dos Stocks

a. Mantém um stock permanente de todos os vossos produtos? ☐ **Sim** ☐ **Não**

b. Mantém um stock permanente de uma parte dos vossos produtos? ☐ **Sim** ☐ **Não**

Se sim, qual a percentagem do stock permanente:

Stocks	Superfície %	Volume %
Todos os produtos		
Parte dos produtos		

1.8 Estatuto e Ligações da Sociedade

a. Se a sociedade é uma filial, indicar o nome e a localização da sociedade mãe:

……

……

……

b. Se a sociedade possui filiais, indicar num quadro os nomes e localizações e anexar ao questionário.

Filial	Localização
1.	
2.	
3…./…	

c. Indicar as sociedades com as quais a vossa sociedade estabeleceu acordos tipo joint-venture, assim como o objecto desses acordos:

Sociedade	Localização
1.	
2.	
3…./…	

d. Indicar num quadro as sociedades com as quais a vossa empresa estabeleceu acordos permanentes de prestação de serviço para, certas operações de fabricação, e anexar ao questionário com as seguintes especificações:

Sociedade	Produto	Desde quando
1.		
2.		
3…./…		

1.9 Organização das Expedições

a. Habitualmente, quais são as vossas condições de envio:

☐ CIF
☐ FOB
☐ DDP

b. As vossas remessas são feitas a partir de que porto de embarque:

☐ Aeroporto/ África
☐ Aeroporto/ China
☐ Aeroporto/ Europa
☐ Aeroporto/ Índia
☐ Porto Marítimo/ África
☐ Porto Marítimo/ China
☐ Porto Marítimo/ Europa
☐ Porto Marítimo/ Índia
☐ Porto Rodoviário Norte
☐ Porto Rodoviário Sul
☐ Porto Rodoviário Leste
☐ Porto Ferroviário

c. Indicar o nome do transitário do transporte aéreo habitual:
Sociedade:……

Endereço: ……

Pessoa de contacto: ……

Fax. ……

E-mail: ……

d. Indicar o nome do transitário do transporte marítimo habitual:

Sociedade: ……,,

Endereço: ……

Pessoa de contacto: ……

Fax. ……

E-mail:……

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e. Indicar o nome do despachante oficial local:

Entidade :

.....

Endereço: .....

Tel: .....

Pessoa de contacto: .....

Fax. : .....

E-mail: .....

f. Indicar o nome da Entidade de Seguros cujos serviços utiliza habitualmente:

.....

.....

g. Qual a Entidade que realiza a vistoria da mercadoria no ponto de embarque?

.....

.....

A referida Entidade tem representação em Angola? ☐ **Sim** ☐ **Não**

Nome da Entidade: .....

Direcção: .....

Tel.: .....

Fax: .....

E-mail: .....

INFORMAÇÔES FARMACÊUTICAS

FABRICANTE DE MEDICAMENTOS / TITULARES DE AIM / REPRESENTANTES

GAMA DE PRODUÇÃO E DOCUMENTOS OFICIAIS

1.10. Gama de Produção

Assinalar, na lista abaixo, os casos correspondentes à vossa gama de produção e indicar em relação a cada forma do produto a vossa capacidade de produção (em número de unidades por ano).

Formas orais:

☐ Comprimidos
☐ Drageias
☐ Cápsulas/Gélulas
☐ Soluções bebíveis
☐ Xaropes
☐ Pós para suspensão oral
☐ Outras: listar em anexo ao questionário

Formas injectáveis:

☐ Formas líquidas (ampolas ou vials)
☐ Pós para preparações injectáveis
☐ Soluções para perfusão
☐ Outras: listar em anexo ao questionário

Outras formas medicamentosas:

☐ Cremes e unguentos
☐ Supositórios
☐ Óvulos
☐ Preparações oftálmicas
☐ Preparações ópticas
☐ Soluções nasais
☐ Soluções e emulsões de uso externo
☐ Outras: listar em anexo ao questionário

1.11 Sistema OMS de Certificação da Qualidade dos Produtos que Entram no Mercado Internacional

Pode fornecer as cópias autenticadas dos Certificados do Sistema OMS de Certificação da Qualidade dos Produtos Farmacêuticos que entram no Comercio Internacional: i) Certificado de Produto Farmacêutico, ii) **Declaração relativa ao Estatuto de Autorização de Introdução no mercado de produtos farmacêuticos**, iii) Certificado de Lote. (Modelos definidos no «Relatório Técnico» OMS Nº 823 e 863)?

☐ **Sim** ☐ **Não**

10

1.12 Registo dos Produtos no País do Fabricante

Os produtos estão registados no País do fabricante?

☐ **Sim** ☐ **Não**

Anexar: a «**Declaração relativo ao Estatuto de Autorização de Introdução no Mercado de produtos farmacêuticos** », conforme o modelo previsto pelo Sistema OMS de Certificação da Qualidade dos produtos farmacêuticos que entram no mercado Internacional (Relatórios Técnicos OMS nº.823 e 863), documento autenticado bem como a respectiva tradução em língua portuguesa.

Produto	Forma farmacêutica	Princípio Activo		Autorização de Introdução no Mercado (AIM)	
		Designação	Quantidade /dose unitária	Número	Data
.../...					

Anexar ao questionário, a lista dos vossos produtos **registados para a exportação**.

1.13. Certificado de Boas Práticas de Fabrico (BPF)

Anexar, para cada local de fabrico, as cópias dos Certificados de Boas Práticas de Fabrico (BPF) autenticadas, bem como a tradução em língua portuguesa.

1.14 Produção

1. Nome e Qualificação do Responsável da Produção

Nome: .....

Qualificação: ☐ Farmacêutico
☐ Outro: precise.....

2. Linhas de Produção por local de fabrico

Fazer uma breve descrição das vossas linhas de produção interna por local de fabrico:
.....
.....
.....
.....

3. Subcontratação

Recorre à subcontratação de toda ou parte das operações de fabrico? ☐ **Sim** ☐ **Não**

Se sim, indicar num quadro o nome da ou das entidades, os locais e os motivos da subcontratação e anexar ao questionário:

Nome da sociedade subcontratada	Local
.../...	

11

Quais são as operações subcontratadas: (se for o caso)

☐ Fabricação da forma Farmacêutica — precisar as operações

....
....
....

☐ Acondicionamento da forma farmacêutica acabada
☐ Rotulagem da forma farmacêutica acabada
☐ Libertação do lote

Os produtos acabados, fabricados em regime de subcontratação, são fisicamente recepcionados nos vossos locais antes da sua distribuição? ☐ **Sim** ☐ **Não**

Os produtos acabados, fabricados em regime de subcontratação são controlados por vós antes da distribuição?

☐ **Sim** ☐ **Não**

Explicar o protocolo aplicado: .....
.....
.....
.....
.....
.....
.....
.....

1.15 Garantia de Qualidade

1. Nome e Qualificação do Responsável pela Libertação dos Lotes

Nome: .....

Qualificação: ☐ Farmacêutico
☐ Outro: precise.....

2. Nome e Qualificação do Responsável pela Garantia de Qualidade

Nome: .....

Qualificação: ☐ Farmacêutico
☐ Outro: precise.....

3. Nome e Qualificação do Responsável do Controle de Qualidade (**Laboratório**)

Nome: .....

Qualificação: ☐ Farmacêutico
☐ Outro: precise.....

4. Operações de Controlo de Qualidade

Efectua controlo de qualidade sobre: (indicar se for o caso)

☐ As matérias primas activas
☐ As matérias primas não activas (excipientes)
☐ Os artigos de acondicionamento
☐ Os produtos intermediários
☐ Os produtos farmacêuticos a granel
☐ Os produtos acabados
☐ Os produtos fabricados e/ou acondicionados em regime de subcontratação.

5. Subcontratação do Controle de Qualidade

Recorre à subcontratação de toda ou parte das operações de controlo da qualidade?

☐ **Sim** ☐ **Não**

Se sim, indicar o nome da ou das entidades às quais recorre, quais as operações subcontratadas e os motivos da subcontratação. Juntar ao questionário um mapa com as especificações abaixo indicadas.

Nome e endereço da subcontratada	Testes subcontratados
.../...	

6. Aprovação das Matérias-primas

1. Possuis um Certificado Europeu de Conformidade do Produto (CEP) ou um Drug Master File (DMF) para as matérias-primas utilizadas?

☐ **Sim** ☐ **Não**

Anexar ao questionário, a lista das respectivas matérias-primas, com as referências CEP ou DMF.

2. Pode disponibilizar aos vossos clientes, a título confidencial, as vossas fontes de aprovisionamento em matérias-primas?

☐ **Sim** ☐ **Não**

Se não, explicar a razão:

.....
.....
.....
.....

3. É feito o controlo de matéria-prima activa (princípio activo)?

Explicar o vosso procedimento de amostragem:

☐ **Sim** ☐ **Não**

.....
.....
.....

4. É feito o controlo da matéria-prima não activa (excipientes)?

☐ **Sim** ☐ **Não**

Explicar o vosso procedimento de amostragem:

.....
.....
.....

13

7. Dossier de Lote

É conservado um dossier de fabricação para cada lote de produto? ☐ **Sim** ☐ **Não**

Se sim, assinalar os elementos constitutivos do referido dossier:

☐ Os números de lote das matérias-primas utilizadas
☐ Os resultados das análises das matérias-primas
☐ Etapas e datas de fabricação
☐ O nome dos responsáveis das referidas etapas
☐ A identificação do material utilizado durante a fabricação
☐ Os resultados dos controlos intermediários efectuados no decorrer da produção
☐ Os resultados dos controlos do ambiente
☐ Os comentários sobre os incidentes de produção
☐ Os comentários sobre o não seguimento da fórmula padrão de fabricação
☐ O balanço comparativo da produção
☐ O número de lote dos artigos de acondicionamento
☐ Os resultados do controlo da qualidade dos produtos a granel
☐ Os resultados do controlo da qualidade dos produtos acabados

8. Procedimento de Libertação dos Lotes

Explicar o vosso processo de libertação dos lotes:

1.Em caso de produção interna (sem nenhuma subcontratação):

.....
.....
.....
.....
.....
.....

2.Em caso de subcontratação de toda ou parte da fabricação:

.....
.....
.....
.....
.....

9. Determinação do Prazo de Validade e da Data de Caducidade dos Produtos Fabricados

Como procede à determinação do prazo de validade e da data de caducidade/ de expiração dos produtos produzidos? São tidas em conta as condições **tropicais**?

☐ **Sim** ☐ **Não**

Descrever sucintamente o método utilizado (**tempo, temperatura e humidade relativa**):

.....
.....
.....
.....
.....

10. Determinação da Biodisponibilidade (**Genéricos**)

Como demonstra a equivalência terapêutica dos produtos?

1. Por estudos de bioequivalência? ☐ **Sim** ☐ **Não**

Se sim, para que tipos de produtos, com que produto de Referência, em que países e o número de voluntários?

Anexar, ao questionário, um mapa com as especificações abaixo indicadas.

Tipo de Produto	Produto de Referência	País	Número de Voluntários
…			

2. Por testes de dissolução comparados "in vitro"? ☐ **Sim** ☐ **Não**

Se sim, para que tipos de produtos, e com que produto de Referência?

Anexar, ao questionário, um mapa com as especificações abaixo indicadas.

Tipo de Produto	Produto de Referência

3. Na falta de um dos métodos acima citados, como demonstra a biodisponibilidade dos produtos:

……
……
……
……
……
……
……

11. Conservação de Amostras

Conserva as amostras de cada lote fabricado? ☐ **Sim** ☐ **Não**

Se sim, em que condições?

Qual a temperatura? ……

Durante quanto tempo? ……

Qual o acondicionamento (de venda, outro: precise)? ……

……
……
……

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12. Procedimento de Amostragem

Como se processa a amostragem? Explique resumidamente:

.....
.....
.....
.....
.....

13. Acompanhamento dos Lotes

1. Assegura um seguimento de todos os lotes que entrega aos seus clientes? ☐ **Sim** ☐ **Não**
Explique:

.....
.....
.....
.....
.....

2. Está em condições de organizar rapidamente um procedimento de recolha de lotes, em caso de problema?

☐ **Sim** ☐ **Não**

Descreva resumidamente, o procedimento:

.....
.....
.....
.....
.....
.....
.....
.....
.....

DECLARAÇÃO DE COMPROMISSO

Nós abaixo assinados,

Sr. /Sra.…… ……., Director Geral

Sr. /Sra. ……., Farmacêutico Responsável

Sr. /Sra. ……., Responsável pela libertação dos lotes

Sr. /Sra. ……., Responsável pela Garantia de Qualidade

Certificamos que as informações fornecidas neste questionário são exactas.

Feito em, …… *ao*……

Assinatura do Director Geral: …….....

Assinatura do Farmacêutico Responsável: …….....

Assinatura do Responsável pela libertação dos lotes: …….....

Assinatura do Responsável pela Garantia de Qualidade: …….....

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