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# Regulatory Strategies for Drug Product Registration in North African Countries

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**ABSTRACT**

Regulatory requirements for various countries of world vary from each other. Therefore, it is challenging for the companies to develop a single drug which can simultaneously submitted in all countries for approval. Africa is the second fastest growing pharmaceutical market in the world and is driven by a small number of countries like south-Africa, Nigeria, Ghana, East-Africa, North Africa. During the past decade, the African continent has been home to some of the fastest-growing economies in the world, creating a large window of opportunity for the development of the pharmaceutical sector. Africa's pharmaceutical sector was expected to reach about 30 billion US Dollars by 2016. The main objective of this study is to discuss about the various parameters and requirements for Registration of externally developed pharmaceutical products in North Africa for Approval. Pre-Requisite knowledge of country specific Guidelines and norms is very important to analyse the similarities and differences between the regulatory requirements of different countries. The Pharmaceutical Market in Africa is growing fast at a Compound annual growth rate (CAGR) of 10.6%. The value of Africa's pharmaceutical industry jumped to $20.8 billion in 2013 from just $4.7 billion a decade earlier. That growth is continuing at a rapid pace: the market will be worth $40 billion to $65 billion by 2020. The purpose of this study is to focus on the key assessment parameters required for developing a pharmaceutical product so that it can be simultaneously registered in numerous African countries for approval.



## Introduction[1-2]

Africa's pharmaceutical industry is the fastest growing in the world and is driven by a small number of countries like South African countries, North African countries, East African countries, West African countries and Central Africa. The leading participants in the pharmaceutical field consider South Africa and North African economies to be as important for their businesses as second tire emerging markets. Although sub-Saharan markets are currently awarded the lowest priority, their expected relative increase in importance is the second highest among all of the emerging-market regions, after Southeast Asia.

As growth opportunities continue to move away from the traditional pharmaceutical markets, most multinationals have Africa in the sights for expanding their global footprint. Africa will be significant economic force in the future and the pharmaceutical companies have much to gain. African continent comprises of 54 countries and has total population of just over.

Africa carries around 24% of the global disease and illness burden but its pharmaceutical industry is worth less than 1% of this $857bn global industry. The value of Africa's pharmaceutical industry jumped to $20.8 billion in 2013 from just $4.7 billion a decade earlier. That growth is continuing at a rapid pace: the market will be worth $40 billion to $65 billion by 2020.While the amount that is spent on healthcare in Africa is rising rapidly, access to medicine is often a matter of life and death, and demand is not based on choice but on absolute need. The health and pharmaceutical industries are bound to provoke great emotion, not least because there is a significant difference between the two. Many of the great advances in global public health have been achieved without the benefit of pharmaceuticals, through improved access to clean water and sanitation.

For many years, African medicines regulatory authorities (MRAs) have managed a broad range of responsibilities, often with limited resources. Their focus has generally been on providing their population with access to a wide range of affordable essential medicines, usually multi-source generics, with less emphasis on rapid access to the latest products. As a result, African national MRAs may have experience in managing generics, but many have only limited experience in assessing, approving and registering innovator products, the vast majority of which are for shared 'global' diseases, such as diabetes, hypertension and cancer.

The combination of Africa's long-standing regulatory challenges and new regulatory demands means African MRAs urgently need to be able to assess and make appropriate regulatory decisions regarding new drugs specific to their populations, or to have access to mechanisms to support their assessment and decision-making.

## Objectives

- The main objective of this study is to report various parameters required for the registration of externally developed pharmaceutical products in North African region.

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- Submission of dossier for the registration of drug product in North African countries

**Discussion**

**Table 1. Country profiles in North African Region.**

| Sl.No | Countries | Capital | Official Language | Regulatory Authority |
|---|---|---|---|---|
| 1. | Algeria | Algiers | Arabic | Algerian Ministry of Health |
| 2. | Egypt | Cario | Arabic | Egyptian Drug Authority |
| 3. | Morrocco | Rabat | Arabic | Ministry of Health |
| 4. | Sudan | Khartoum | Arabic & English | National Medicinal Plants Board |

**Table 2.Dossier submission format in North African Region.**

| Sl.No | Country | CTD Format | Country Specific |
|---|---|---|---|
| 1. | Algeria | √ | X |
| 2. | Egypt | X | √ |
| 3. | Morrocco | X | √ |
| 4. | Sudan | √ | X |

**I. ALGERIA[3]**

**Drug Regulatory Agency:** Algerian Ministry of Health

**Language:** English

**Format Followed:** Common Technical Document

**Requirements for Dossier Submission:** Dossier is submitted as per ICH CTD format. It consists of following parts

- Module 1: Administrative Information and Prescribing Information
- Module 2: Common Technical Document
- Module 3: Quality
- Module 4: Non Clinical Study Reports
- Module 5: Clinical Study Reports

**Registration Procedure**

**Step 1**

This involves making of an application by pharmaceutical company seeking to get registration for its pharma products in the prescribed format by regulatory agency.

It requires

- General Information
- Information regarding how the medicine is going to improve health situation in Algeria, and market price in the country origin and the prices in three other countries.
- After the submission of application, the health ministry would ascertain whether the particular medicinal product is required in this country and decide if the detailed dossiers for registration of this medicine should be accepted or not.
- The medicine to be registered should generally be listed in the Nomenclature.
- However, if a particular medicine is not listed in this Nomenclature, then another application as per the format of Formulaire d 'Information Therapeutique en vue de I "Enregistrement as Algerie (a remplir par le demandeur) should also be filed in, which seeks more detailed information regarding characteristics, mode of administration, pharmacological properties, efficiency, evaluation of therapeutic risks, etc. of the medicine.

***Step 2:*** Once the request is accepted, the concerned pharmaceutical company is required to make a detailed application in the form of a dossier as per detailed instructions contained in Procedures d' Expertise analytiques analytics pharmacologie et cliniques appliques aux products pharmaceuticals.

- The dossier is required to be sent in triplicate – One containing all original documentsand two dossiers containing copies, along with two samples for each for each dosage form submitted for registration
- The samples must accompany analysis of the

i. Basic raw material
ii. Intermediate Products
iii. Finished Products

- The proforma price list of the samples and the certificate to the effect that the 'products being sent are for sample purposes only' should also be dispatched along with the samples.
- Technical information regarding international and commercial names of the product, quantity, lot manufacturer and expiry dates of the product provided as per Echantillons Medicaux Gratuits form would secure assistance form the Ministry of Health to expedite customs clearance in Algiers

**Stability Conditions**

**General Requirements**

**Table 3. Stability Requirements in Algeria.**

| Storage Temperature $^{o}$C | Relative Humidity % | Minimum time period covered (months) |
|---|---|---|
| Accelerated: 40±2 | 75±5 | 6 |
| Long term: 25±2 | 60±5 | 12 |

**Bioequivalence Requirements:** Not Mentioned

**Timelines:** Generally a period of 3months or more is taken for evaluation. A Provisional registration is valid for one year.

**Sample Requirements:** Requires 30 ampoule units for drugs of 5ml/mg or above, and 50 ampoule units for drugs of 1 to 1.5ml.

**II. EGYPT[4]**

**Drug Regulatory Agency:** Egyptian Drug Authority

**Language Used:** English

**Format Followed:** Common Technical Document

**Registration Requirements**

- Covering letter indicating the documents contained in the file
- An application form for registration/ dully filled in and signed
- Certificate or origin and free sale issued from the ministry of health in the country origin, legalised by Egyptian Embassy or consulate in that country.
- Five copies of complete formula, quantitative, qualitative of active and inactive ingredients, colouring matter, etc
- Five copies or method of analysis and assay of active ingredients in the finished product in detail, in English.
- Seven to ten original samples of analysis
- Certificate of Analysis in two copies
- In case of Antibiotics another Certificate of Analysis
- Five original outer labels, inner labels and pamphlets
- List of the countries where the product is registered and marketed
- Agency agreement of Authorization for Registration
- A governmental postal order for the fee of five Egyptian pounds

**Stability Conditions**

**General Requirements**

**Table 4.Stability Requirements in Egypt.**

| Storage Temperature $^{o}$C | Relative Humidity % | Minimum time period covered (months) |
|---|---|---|
| Accelerated: 40±2 | 75±5 | 6 |
| Long term: 30±2 | 65±5 | 12 |

**Registration Procedure in Egypt:** The registration process starts by receiving the registration submission request via e-mail as described in following guidelines:

- Applicant sends an appointment request to appd@eda.mohp.gov.eg
- CAPA will send back an email to inform the applicant with the date and time for application submission within 3 working days.
- Maximum number of applications could be submitted by one company is four applications per month at four different meetings. Import and toll companies could submit only two applications per month at two different meetings. Exception to these constraints is request to register different concentrations of same dosage form. In this case, they might be submitted at the same meeting.
- CAPA will receive a maximum 10 applications per day, four days per week
- The application may be refused for reasons other than "the box is closed at that present time"
- If a company representative was late 15 minutes after the predetermined appointment, the meeting will be cancelled and the company will have to ask for another appointment.
- Accepting the application doesn't guarantee a marketing authorization only when the company receives the final authorization.
- Application file may be rejected at any stage and the reason of rejection will be given to the applicant.
- Make sure that your company profile had been received by CAPA before submitting the application.

**Bioequivalence Requirements**

**Clinical Research Organisation**

Must be audited and inspected by Egyptian Drug Authority.

**Choice of Reference Product**

The reference product must be registered in Egypt.

**Fee Requirements:** The registration fee for New Chemical Entity (NCE) and for generic pharmaceutical product is US$ 1,625.21

**Timelines:** The time limit imposed for the assessment of all Marketing Authorization application is 12 months.

**III. MOROCCO[5]**

**Drug Regulatory Authority:** Ministry of Health

**Language:** English

**Format Followed:** Country Specific

**Regulatory Requirements for Dossier Submission:**

- Module 1: Administrative and Prescribing Information
- Module 2: Experts file
- Module 3: Technical file
- Module 4: Efficacy
- Module 5: Safety

**CPP:** Packaging project: leaflet- carton box –label

**Regulatory Guidelines for Price Regulation:**

PFHT=prix fabricant hors taxes (wholesaler price without VAT)

If the molecule exists and is marketed in Morocco, the PFHT will be the price of the following table:

| Reference Price PHFT | % of reduction compared to the reference price |
|---|---|
| X<15 | 0% |
| 15<X<30 | 15% |
| 30<X<70 | 30% |
| 70<X<150 | 35% |
| 150<X<300 | 40% |
| X>300 | 50% |

If the molecule is not marketed in Morocco, then the PFHT will be the lowest price from the bench mark price of the six countries such as Spain, France, Italy, Belgium, Portugal, Turkey and Saudi Arabia

***Reimbursement price:*** Reference price of the benchmark (lowest price)

**Stability Conditions**

**General Requirements**

**Table 5. Stability conditions in Morocco.**

| Storage Temperature $^{o}$C | Relative Humidity % | Minimum time period covered (months) |
|---|---|---|
| Accelerated: 40±2 | 75±5 | 6 |
| Long Term: 25±2 | 60±5 | 12 |

**Bioequivalence Requirements**

**CRO:** Not Mentioned

**Choice of Reference**

- The reference marketed in Morocco
- If not marketed originator reference product can be used
- First product approved through submission clinical studies and marketed in Morocco

**IV. SUDAN[6]**

**Drug Regulatory Authority:** National Medicines and Poisons Board (NMPB)

**Language:** English and Arabic

**Format Followed:** Common Technical Document (CTD)

**Who may apply for registration?**

The applicant should be

- Holder of a valid wholesales pharmaceutical license and an agency agreement with the manufacturer.
- A public sector establishment authorized by the Pharmacy and Poisons Act to deal with pharmaceutical products

**Drug Registration**

According to Pharmacy and Poisons Act it is an offence to manufacture, import, sell, offer for sale any pharmaceutical unless registered under the provisions of the Act, and regulations directives issued under the Act. So all applicants for registration of pharmaceutical products should be familiar with all such provisions and requirements issued by Federal Board of Pharmacy. Directorate General of Pharmacy in the Federal Ministry of Health, the executive arm of the Board.

Pharmaceutical products submitted for registration should be manufactured in a registered plant. The criteria for registration of a pharmaceutical product are:

- Need (Health or market need
- Efficacy
- Safety
- Quality
- Advantage over similar registered products
- Price

**Stability Conditions**

**General Requirements**

**Table 6. Stability Requirements in Sudan.**

| Storage Temperature $^{o}$C | Relative Humidity (%) | Minimum time period covered (months) |
|---|---|---|
| Accelerated: 40±2 | 75±5 | 6 |
| Long Term: 30±2 | 65±5 | 12 |

**Bioequivalence Requirements**

**CRO:** Not Mentioned

**Choice of Reference:** Not Mentioned

**Sample Requirements:** Minimum 10 samples for each of the dosage form

**Timelines:** Not Mentioned

**Summary and Conclusion**

As the regulatory requirements of various countries vary from each other, it is challenging for pharmaceutical companies to develop a drug formulation which can be simultaneously submitted in numerous countries for approval at the same time. Therefore continuous process of harmonization is taking place all around the world; still we see a huge challenge, which is yet to be overcome by the pharmaceutical industry in case of generic drug development and filing as it involves strategic planning.

To formulate a drug product, it is a prerequisite requirement that the formulator must have a detailed knowledge about the country specific regulatory guidelines and norms. The format followed for dossier submission in most of the North African countries such as Algeria and Sudan follows CTD format and the countries such as Egypt and Morrocco follows country specific format. The following parameters are of prime concern which should always be considered when a product is being developed, so that it can be simultaneously registered in key North African countries:

1. We must have the stability studies report for the following conditions
- 30±2$^{o}$C 65±5% RH
- 30±2$^{o}$C 75±5% RH
- 25±2$^{o}$C 65±5% RH

2. The bioequivalence centres should be audited and inspected by the respective regulatory authorities.
3. The reference standard product should either be a first registered product in the respective country or it should be from ICH associated countries or from a WHO list of international comparator products.
4. Following documents are the utmost important for the product registration:
- Process Validation Report
- Analytical method validation report
- Bioequivalence study report
- Comparative Dissolution Profile

5. Legal documents such as GMP Certificate, Manufacturing licence, Product licence, Certificate of Pharmaceutical Product, Free sale Certificate, Trade mark certificate and NQCL Certificate should be available as per the countries requirement.
6. All the documents must be submitted in English language and the patient information leaflet should be in English, and Arabic.
7. Results of not less than 3 batch analysis must be presented
8. The labelling instruction such as
- List of excipients known to be a safe concern for some patients Eg: Lactose, Gluten, Parabens etc.
- Expression “External use” in Red print, etc.

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