MOROCCAN GOOD REGULATORY PRACTICES:
Regulatory and technical requirements for the registration of medicines for human use in Morocco

April 27-30

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30 April 2020
Disclosure Statement

- I am employed by a regulatory authority and have nothing to disclose.

- The views expressed in this presentation are my personal opinions and do not necessarily reflect the official opinions of the DMP.
Agenda

- INTRODUCTION
- REGULATORY SYSTEM
- TEXT PYRAMID OF REGULATION IN MOROCCO
- DIRECTORATE OF MEDICINES AND PHARMACY (DMP)
- STEPS IN DRUG REGISTRATION BY DMP
- LAW 17-04 & DECREE n°2-14-841 du 5 AUGUST 2015
- BIOSIMILARS IN MOROCCO
- QUALITY RISK MANAGEMENT
INTRODUCTION

• The **Directorate of Medicine and Pharmacy (DMP)** is the national regulatory authority in charge of:

  ✓ *Qualité/ Quality*, of medicines and health products in Morocco.
  ✓ *Sécurité/Safety*,
  ✓ *Efficacité/Efficacy*.

• In order to protect and promote health and safety of the public is based on laws, regulations, national and international guidelines and also on pharmacopeias.
LEGISLATION / REGULATION

Highly regulated pharmaceutical sector:

✓ More than 20 law
✓ More than 14ene Decrees
✓ More than 25 Order
✓ More than 30 circulars and ministerial decisions
REGULATED ACTIVITIES

- Medicine Policy & Legislation
- Marketing Authorization (M) & Registration certificate (HP)
- Licensing of Establishments Medicines (M) & health products (HP)
- Set prices of drugs and medical devices
- Quality Control / Laboratory Testing
- Information Sharing / Recall & withdrawal
- Vigilances / counterfeit medicines
REGULATORY SYSTEM

- Dahir of 2nd December 1922 regulates the import and trade in and possession of poisonous substances

- Dahir/ Law n° 17-04 with Drug and Pharmacy Code

- Dahir/ Law n° 84-12 concerning medical devices

- Dahir/ Law n° 11-08 concerning In Vitro Diagnostic Reagents

- Dahir/Law n° 28-13 concerning protection of persons involved in biomedical research.
REGULATORY SYSTEM

- Decree of 3th October 1977 establishing a national commission on narcotic drugs
- Decree of 21th November 1994 on the powers, duties and organisation of the Ministry of Health
- Decree of 13 November 2003 instituting remuneration for services rendered by the Ministry of Health
- Decree of 9 July 2008 on the exercise of pharmacy in the establishment and opening of pharmacies and pharmaceutical establishments
- Decree no. 2-13-852 of 18 December 2013 on the terms and conditions for fixing the public price for the sale of medicines manufactured locally or imported
- Decree of 5 August 2015 on the marketing authorization of medicinal products for human use
- Etc.
REGULATORY SYSTEM

- Order of the Minister of Health of 14 January 1957 for prescribing poisonous substances in Table B

- Joint Order of the Minister of Health and the Minister of Finance and Privatization of 24 April 2006 fixing the rates for services rendered by the Directorate for Medicine and Pharmacy,

- Order of the Minister of Health April 2014 on the revision of public prices for the sale of medicines

- Order of 14 January 2016 procedures for fixing the public sales price and the invoice price of Class III DMs

- Etc.
TEXT PYRAMID OF REGULATION IN MOROCCO

Regulatory system

- Constitution
- Dahir
- Law
- Decree
- Order
- Circular & decisions
PROCESS DEVELOPING REGULATORY TEXT

Step 1
• Elaboration and consultation internally

Step 2
• Consultation with the Regulatory and Litigation department
  • Stakeholder consultation

Step 3
• Transmission to General Secretariat of the Government (SGG)

Step 4
• Presentation and consultation session with SGG

Step 5
• Publication on SGG site for consultation: public and stakeholders

Step 6
• Parliament (law)

Step 7
• Government (law decree)

Step 8
• Publication in official bulletin.
Directorate of Medicines and Pharmacy

« Direction du Médicament et de la Pharmacie »

Takes care of organizational, legislative, control and inspection aspects of the pharmaceutical sector.

- **Before 1994**
  - Central Pharmacy Service
  - National Laboratory for Drug Control (LNCM) created in 1974

- **After 1994**
  - Creation of the DMP by decree in December 1994
  - Pharmacy Division + LNCM Division

- **April 1996**: Effective birth by the Appointment of the 1st Director.

- **Future Evolution**: Medicines and Health Products Safety Agency.
It’s Charged:

- Establishing manufacturing **standards**, packaging, transport, sales and storage of medicines and health products;

- **Pricing** of medicines and pharmaceutical products,

- Performing **analytical testing of medicines** by National Laboratory for Medicines Control (LNCM),

- Establishing and updating the **list of essential medicines** and ensure quality control;
-Missions 2/2-

▪ Performing the **inspection** of pharmacies, pharmaceutical manufacturers and pharmaceutical distributors;

▪ Granting **marketing authorizations and certificates** for pharmaceutical products;

▪ Managing a technical and economic **data bank on medicines**

▪ **Monitoring** medicines use and health product use following their approval;

▪ Contributing to medical and pharmaceutical **education**.
DIRECTORATE

Sector Monitoring and Pharmacy Service
Information system Unité and DB
ONAMPS Unit
Vigilance

quality Management Unit
Administrative Service
Registration Unit
Security and Environment Unit

Biomedical Research Unit

Division of pharmacy

Visa Approvals and Authorization Service
Narcotics Service
Economic Activities Service
Medical Devices Unit
Reagent & In vitro test Unit
Food Supplements Unit
Cosmetics Unit

Biomedical Research Unit

LNCM Division

Technical Platform of Coordination and Management Unit
Physico-chemistry Service
Biological Testing Service
Quality Assurance Service
Health Product Control Service
Métrology Unit

Reserve Unit

Directorate of Medicines and Pharmacy Functional organizational chart
Submit the file in CTD format. 

Reception Step \rightarrow Recevability Step 

Opinion of the AMM commission 

Samples submission 

Evaluation 

Evaluation of the AMM commission 

Favorable without reserve 

Got of AMM for a period 5 years. 

Certificate of PL, certifying that no changes have been made to the file subject to the approved changes.

Generic does not require the commission opinion.
On December 07, 2006 was promulgated the law n°17-04 carrying the code of the drug and the pharmacy in Morocco, repealing the reference text, the Dahir of February 19, 1960 which governed the pharmaceutical profession with its various components (pharmacy, industry, wholesaler distribution) and the drug, for almost half a century.
The drug and pharmacy code is made up of 159 articles dealing with the drug as a whole.

This law revolves around four titles covering the two main axes:
- Drug and non-drug pharmaceuticals
- Pharmacy exercise or practice.

Defines the drug and the conditions of:
- Production,
- Marketing,
- Distribution,
- and dispensation.

Governs access to the profession of pharmacist and its exercise.
1. Adjusted the rules contained in the Dahir of 1960

- Requirement of the national doctorate degree in pharmacy
- Definition of categories of pharmaceutical establishments.
- Modification of the rules concerning the authorization scheme.
- Definition of generic drug.
- Establishment of the legal definition of the drug, pharmaceutical specialty, marketing authorization.
- Liberalization of pharmaceutical capital
2. Introduction of new pharmacy practice rules

- Extension of the pharmaceutical monopoly to non-pharmaceutical pharmaceutical products.
- Definition of the status and attributions of the pharmacy responsible for a pharmaceutical establishment.
- Drug donation provisions.
- Definition of the pharmacy as a place of dispensation (sale).
- Installation of standards and rules of good practice.
- Organization of drug promotion and medical information, ..
**Article 7:** Any drug **manufactured industrially, imported or exported**, even in samples forme, must be the subject, before its marketing or distribution free of charge or against payment, wholesale or retail, of an **authorization** issued by the administration in the following forms:

- either in the form of a **marketing authorization**, the number of which must be shown on the secondary packaging of any medicinal product intended for sale;
- either in the form of a **specific authorization** in the case of samples for the registration of products, for clinical trials, or in the case of drugs prescribed and not registered in Morocco, or in the case of the temporary use of certain medicines intended to treat serious or rare diseases when there is no suitable treatment in

- Morocco.
Chapter II: Provisions relating to medicinal products
Section I: Marketing authorization

Article 8: The marketing authorization can only be issued if the drug has previously met an appropriate experiment aimed at:
1. highlight the effectiveness of the drug;
2. guarantee its safety under normal conditions of use;
3. demonstrate its therapeutic value;
4. establish bioequivalence when it is a generic drug

In addition, the manufacturer or importer must justify:
- That he had carried out a qualitative and quantitative analysis of the drug;
- That it actually has a manufacturing method and control procedures that guarantee the quality of the product at the industrial manufacturing stage.
In a few words

✓ 6 chapters
✓ 40 articles
✓ One annex: Conditions relating to the application for Marketing Authorization

❖ Chapter premier: Definitions
❖ Chapter II: The marketing authorization request
❖ Chapter III: Renewal of the marketing authorization
❖ Chapter IV: Transfer of the marketing authorization
❖ Chapter V: The suspension and withdrawal of the marketing authorization
❖ Chapter VI: The national commission for the marketing authorization of medicines
Some highlights

- Submission of the file in CTD format (commun Technical document)
- Admissibility study (recevabilité)
- Biosimilar

Clarification of deadlines for the Ministry of Health and for pharmaceutical Laboratories
What is a biosimilar?

- "A drug containing an active substance made using recombinant DNA technology ..."

- "A similar biological medicinal product is a biological medicinal product with the same qualitative and quantitative composition as an active substance and in the same pharmaceutical form as a reference biological medicinal product, but which cannot be considered as a generic because of differences linked in particular to the variability raw material or manufacturing processes and requiring the additional preclinical and clinical data."
Demonstration of biosimilarity?

- The concept of biosimilarity is based on the essential principle of the direct comparison of two biotherapeutic drugs (from biotechnology, one is the reference drug, the other being the drug declared "biosimilar" to the reference drug in the areas of Quality, Safety and Efficacy,

- Biosimilar does not mean “biogeneric”

For the regulatory authority, biosimilars are by definition not generics, which is why the procedure in force for generics is not appropriate for biosimilar.
Comparability data?

- **In vitro tests**: Establish the comparability between the activity and the PD.
- **In vivo tests**: PK/PD and multi-dose toxicity study

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BIOSIMILARS IN MOROCCO

- 57 biosimilar drugs on the National market

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Biosimilars (Nbre of medicines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth factors</td>
<td>h.r.-Erythropoétine (16) Filgrastim (5) Pegfilgrastim (1) Lenograstim (1)</td>
</tr>
<tr>
<td>Hormones</td>
<td>Humaine Insuline and Insuline glargine (21) Somatotropine (Growth Hormone) (1)</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Interférent alpha (3)</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Infliximab (1) Trastuzumab (4) Bevacizumab (2) Rituximab (2)</td>
</tr>
</tbody>
</table>

- **Infliximab** is the first biosimilar monoclonal antibody (for REMICADE) approved in Europe on 2013, In Marocco on 2015; under the name of REMSIMA
21 products declaring themselves to be biosimilars are being assessed at the DMP for a marketing authorization.

### Biosimilars under registration at the DMP*

<table>
<thead>
<tr>
<th>INN</th>
<th>Nbre lettres</th>
<th>Présence d’un autre biosimilaire</th>
<th>Présence de la spécialité de Référence</th>
<th>Recevabilité</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2018</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRASTUZUMAB</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>INSULINE GLARGINE</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BEVACIZUMAB</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>INTERFERON BETA-1A</td>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ERYTHRPOIETINE Hum Rec</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ADALIMUMAB</td>
<td>2</td>
<td>No</td>
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<td>Yes</td>
</tr>
<tr>
<td><strong>2019</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRASTUZUMAB</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>EPOETINE ALFA</td>
<td>4</td>
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<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PEGFILGRASTIM</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
<td>21</td>
</tr>
</tbody>
</table>

*data until March 2020. Source: DMP
Part 1: New biology laboratory

- Area 150 m²
- Air conditioning & Air treatment are completed
- The equipment is being validated and qualified

Part 2: Bioassay lab. In progress

- Layout of the old biology building
- The most of the equipment is available, the rest being purchased:
  - Hotte microbiologique (PSM)
  - Microscope optique inverse
  - Electrophorese capillaire
  - IEF system
Our department:

- Implemented the process approach
- Identified the processes
- Established process mapping including the inputs, activities and outputs of any process.
Our department plan periodically:

To maintain the ISO 9001: 2015:
All the department of DMP (registration, pricing, evaluation, analytical testing, ..)

Certified Quality System Standard
The laboratory was accredited by EDQM ISO 17025 in 2007

Renewal of accreditation by EDQM
- August 2011
- December 2014
- August 2019

WHO prequalified in 2007

Renewal WHO prequalified in
- 2012
- 2014
- 2018
• Integrating quality risk management into quality Management systems

➢ Documentation/ Documentation
➢ Training/ Formation en continue
➢ Periodic Direction Review / Revue direction périodique
➢ Internal and external audit / Audit interne et externe

Continuous improvement / Amélioration continue
Our department adopt policies that promote regulatory convergence and harmonization (directives of WHO, ICH, EMA...)

Cooperation:
- EDQM in the context of European Official Medicines Control Laboratory (OMCL) Network (LNCM is member of OMCLs)
- USP associate member
- EP observer member

Morocco adopted the European and American pharmacopoeias by Order (arrêté n° 1372612 du 30 avril 2019).
CONCLUSION

▪ The evolution of Moroccan regulations:

➢ Allows better use of resources and repositories

➢ Increase mutual trust with the pharmaceutical industry

"Risk is inversely proportional to knowledge"
http://dmp.sante.gov.ma/