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

CASSS
SHARING SCIENCE SOLUTIONS

BIOASSAYS
SCIENTIFIC APPROACHES AND REGULATORY STRATEGIES 2020
VIRTUAL SYMPOSIUM

April 27-30

dmp
Direction du Médicament et de la Pharmacie

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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 **D**irectorate of **M**edicine and **P**harmacy (**DMP**) is the national regulatory authority in charge of:

  ✓ **Qualité**/ *Quality*,
  ✓ **Sécurité**/ *Safety*,
  ✓ **Efficacité**/*Efficacy*.

  of medicines and health products in Morocco.

- 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:

(http://dmp.sante.gov.ma/textes-legislatifs-et-reglementaires?rlc=853898)

- ✓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 2ed 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

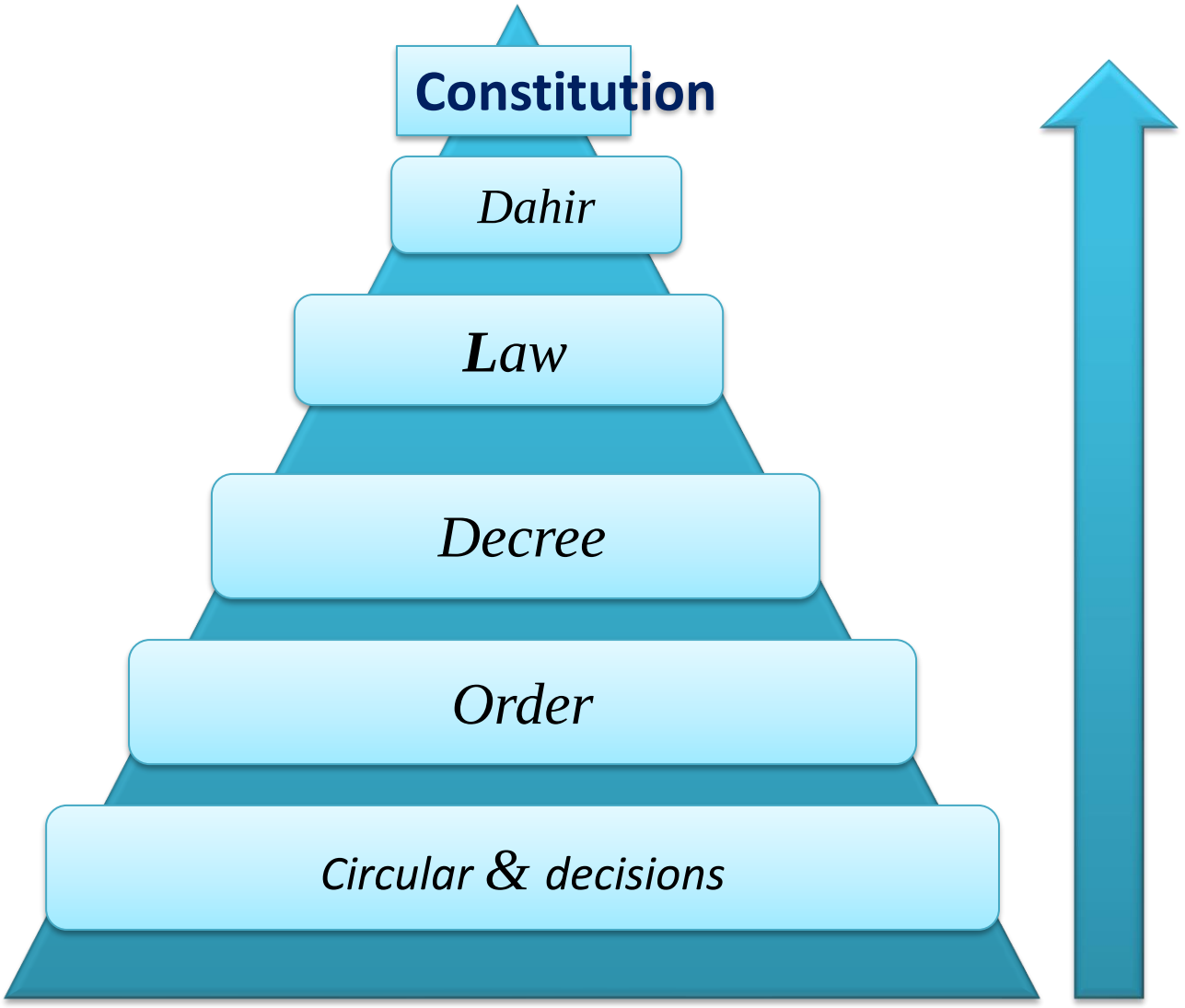
- Order of the Minister of Health of 14 January 1957 for prescribing poisonous substances in Table B

- 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

PROCESS DEVELOPING REGULATORY TEXT

Direction du Médicament et de la Pharmacie

Step 1	• Elaboration and consultation internally
Step 2	• Consultation with the Regulatory and Litigation departement • 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 stakholders
Step 6	• Parliament (law)
Step 7	• Government (law decree)
Step 8	• Publication in official bulletin.

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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.**

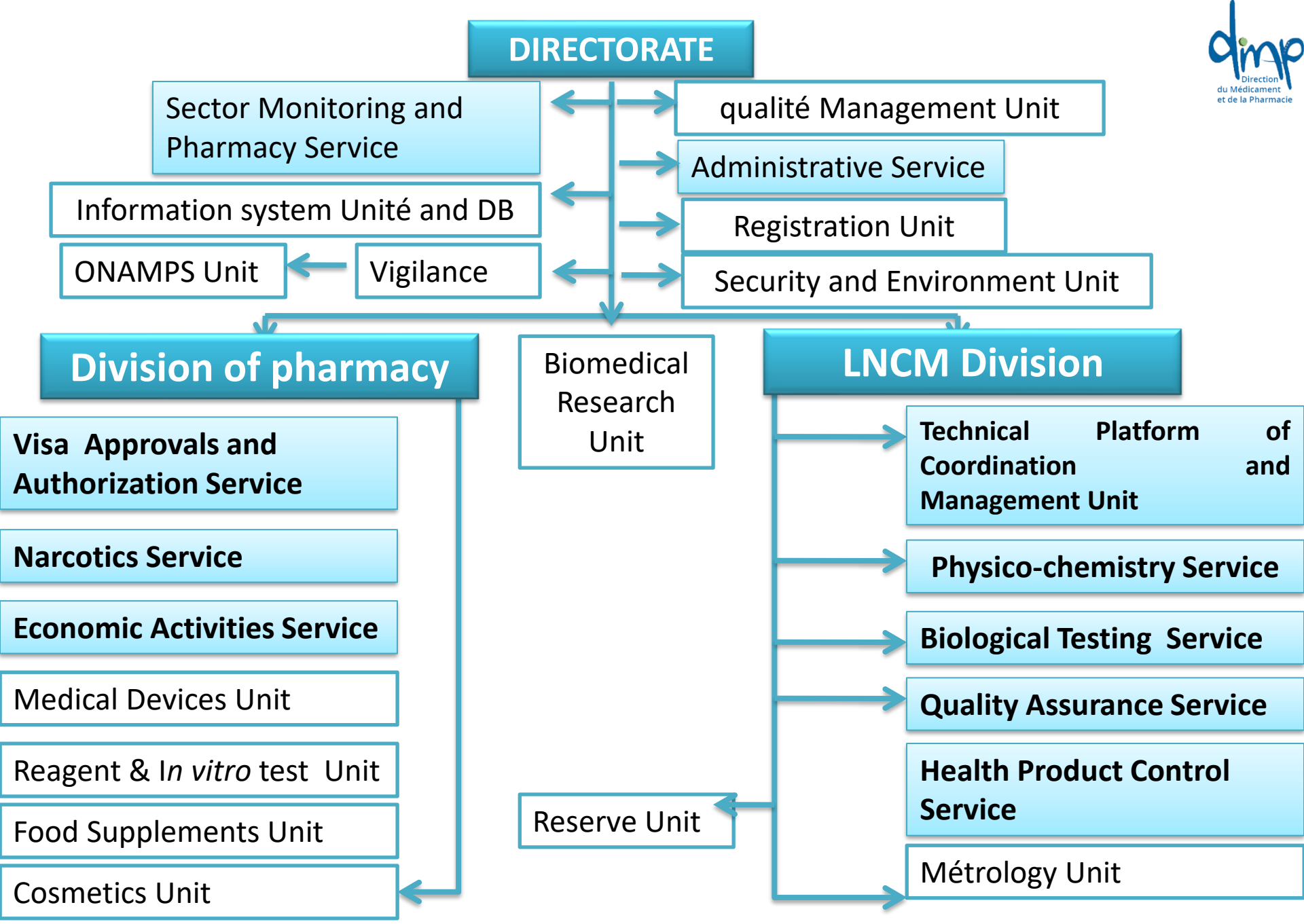
-Missions 1/2-

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;

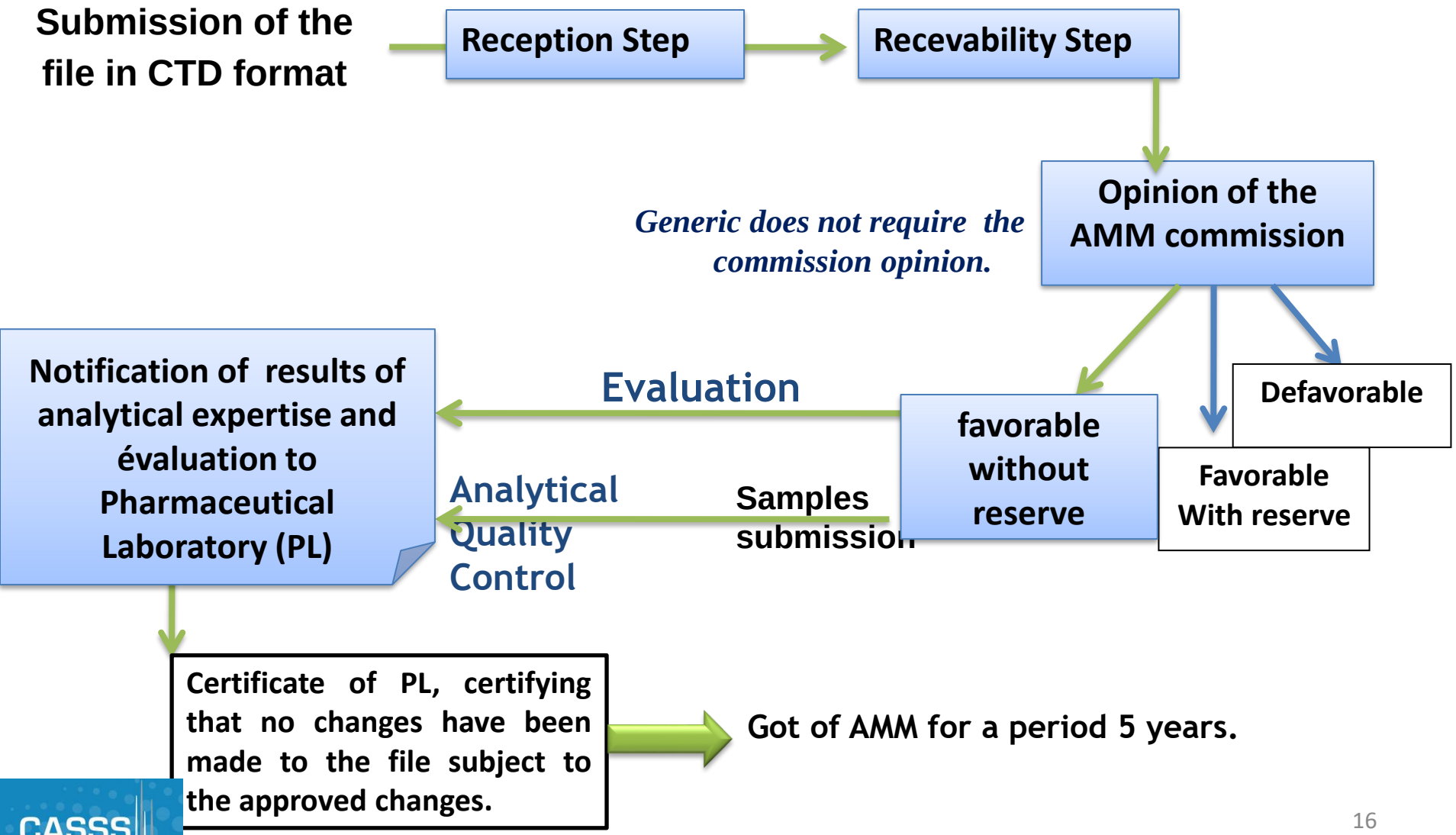
-Missions 2/2-

- 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 of Medicines and Pharmacy Fonctional organizational chart

STEPS IN DRUG REGISTRATION BY DMP



AMM: Marketing Authorization

Loi 17-04

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.

LAW 17-04

1/5

«Code of the drug and the pharmacy»

Code du médicament et de la pharmacie

- 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.

LAW 17-04

2/5

«Code of the drug and the pharmacy»

Code du médicament et de la pharmacie

Direction du Médicament et de la Pharmacie

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**

CASSS SHARING SCIENCE SOLUTIONS

LAW 17-04
3/5

Direction du Médicament et de la Pharmacie

1. Adjusted the rules contained in the Dahir of 1960

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, ..**

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LAW 17-04
4/5

Medication registration procedures and marketing authorization procedure

Chapter II: Provisions relating to medicinal products
Section I: **Marketing authorization**

Article7: 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..

LAW 17-04
5/5

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**.

DECREE n° 2-14-841 of 5 August 2015 1/2

"The marketing authorization of medicinal products for human use"

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

DECREE n° 2-14-841 of 5 August 2015 2/2

Direction du Médicament et de la Pharmacie

"The marketing authorization of medicinal products for human use"

Some highlights

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

ART. 7. Lorsque la demande porte sur un médicament biologique similaire à un médicament biologique de référence, la matière première, les procédés de fabrication dudit médicament et les essais précliniques et cliniques doivent satisfaire aux essais de comparabilité selon les directives de l'Organisation Mondiale de la Santé et de « la Conférence Internationale sur l'harmonisation » concernant les biosimilaires.

- Clarification of **deadlines** for the Ministry of Health and for pharmaceutical Laboratories

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Circular N°041 DMP/2016 of 26 April 2016

"Specific requirements for the registration of biosimilar medicinal products"

❖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. "

Circular N°041 DMP/2016 of 26 April 2016

"Specific requirements for the registration of biosimilar medicinal products"

2/3

❖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''**

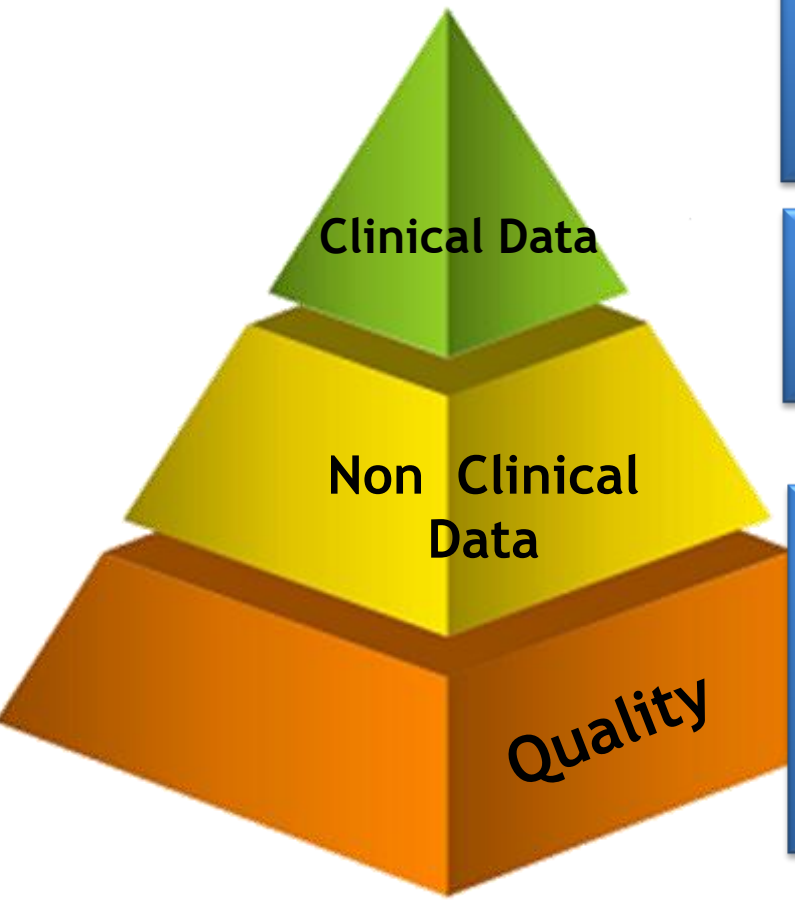
For the regulatory authority, biosimilars are by definition not generics, which is why the procedure in force for generics is not appropriate for biosimilar.

Circular N°041 DMP/2016 of 26 April 2016

"Specific requirements for the registration of biosimilar medicinal products"

3/3

❖Comparability data?



- ✓ PK/PD Studies
- ✓Eefficiency-safety studies ►► Immunogenicity data
- ✓Conditions for indications Extrapolation

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

- ✓Physico-chemical properties
- ✓Immunochemical properties
- ✓Biological activity and potency
- ✓Purity, impurities and content of the SA.
- ✓Specifications
- ✓Stability.

Guidelines on evaluation of similar biotherapeutic products (SBPs). *WHO Expert Committee on Biological Standardization. Sixtieth report;* WHO 2013 (Technical Report Series No. 977), Annex2

BIOSIMILARS IN MOROCCO

- **57 biosimilar drugs on the National market**

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

- **Infliximab is the first biosimilar monoclonal antibody (for REMICADE) approved in Europe on 2013, In Marocco on 2015; under the name of REMSIMA**

BIOSIMILARS IN MOROCCO

- **21 products declaring themselves to be biosimilars are being assessed at the DMP for a marketing authorization.**

Biosimilars under registration at the DMP*

	INN	Nbre lettres	Présence d'un autre bio similaire	Présence de la spécialité de Référence	Recevabilité
2018	TRASTUZUMAB	6	Yes	Yes	Yes
	INSULINE GLARGINE	1	Yes	Yes	Yes
	BEVACIZUMAB	2	Yes	Yes	No
	INTERFERON BETA-1A	1	No	Yes	No
	ERYTHRPOIETINE Hum Rec	2	Yes	Yes	Yes
	ADALIMUMAB	2	No	Yes	Yes
2019	TRASTUZUMAB	2	Yes	Yes	Yes
	EPOETINE ALFA	4	Yes	Yes	No
	PEGFILGRASTIM	1	Yes	No	Yes
	TOTAL	21			

*data until March 2020.Source: DMP

BIOLOGY & BIOTECHNOLOGY LABORATORY

Part 1: New biology laboratory

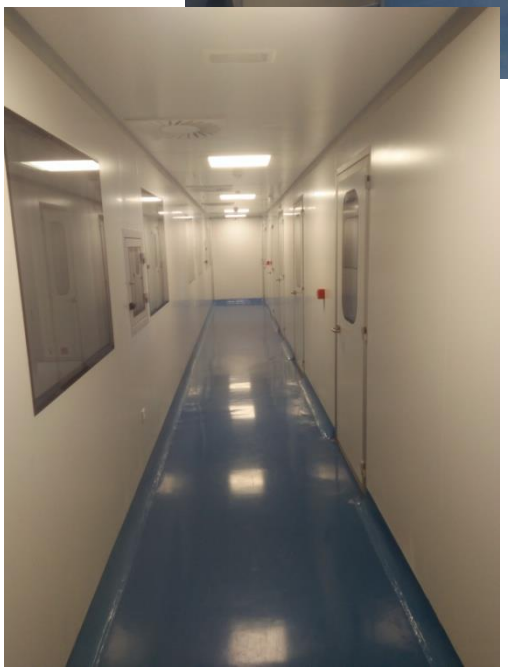
- Area 150 m^2
- Air conditioning & Air treatment are completed
- The equipment is being validated and qualified

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



QUALITY MANAGEMENT SYSTEM 1/3

Our department:

- Implemented the process approach
- Identified the processes
- Established process mapping including the inputs, activities and outputs of any process.

QUALITY MANAGEMENT SYSTEM 1/3

Direction du Médicament et de la Pharmacie

EXIGENCES DU MINISTERE DE TUTELLE, DES CLIENTS, DES INSTITUTIONS ET DES PARTENAIRES

SATISFACTION DU MINISTERE DE TUTELLE, DES CLIENTS, DES INSTITUTIONS ET DES PARTENAIRES

PS CI : Communication

PS PS :Pilotage stratégique

PS AM :Amélioration

PS PR : Etude et fixation des prix

PS ER : Enregistrement

PS EV : Evaluation et édition des visas, homologations , autorisations et certificats

PS VI : Vigilances

PS LB : Réalisation des contrôles techniques

Laboratoire

- Essais biologiques et microbiologiques
- Essais physico-chimiques
- Essais mécaniques
- Essais galéniques

PS OB : Observatoire des approvisionnements et consommations en médicaments et produits de santé

PS IS : Inspection et suivi du secteur

PS GS : Suivi et Contrôle de la Gestion des stupéfiants, psychotropes et précurseurs chimiques

PS SI : Gestion du SI

PS RH : Gestion RH

PS GB : Gestion des budgets et Dépenses

PS NR : Veille réglementaire et normative

PS MT : Métrologie

PS SE : Sécurité & environnement

QUALITY MANAGEMENT SYSTEM 2/3

Our department plan periodically:

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

Certified Quality System Standard

ISO 9001: 2015.

POLYCERT

CERTIFICAT

N° QM/ 2017/99114

DIRECTION DU MEDICAMENT ET DE LA PHARMACIE

Rue Lamfadal Gharkaoui
6206 RABAT
Maroc

ENREGISTREMENT DES MEDICAMENTS ET PRODUITS DE SANTE, REGULATION DU SECTEUR PHARMACEUTIQUE ; CONTROLE QUALITE ET INSPECTION
REGISTRATION OF MEDICINAL PRODUCTS AND HEALTH PRODUCTS, REGULATION OF THE PHARMACEUTICAL SECTOR;QUALITY CONTROL AND INSPECTION

Polycert certifie que pour les sites et activités référencés ci-dessus, toutes les dispositions ont été mises en œuvre pour répondre aux exigences requises. Elles ont été vérifiées et jugées conformes aux normes :

Polycert certifies that all the arrangements covering the above-mentioned activities and location established to meet the requirements. It has been examined and declared conform of the international standards:

ISO 9001 : 2015

Date de délivrance / *Liberation date:* 29/11/2017

Date de validité: / *Valid date:* 28/11/2020

Yvan GERARDIN

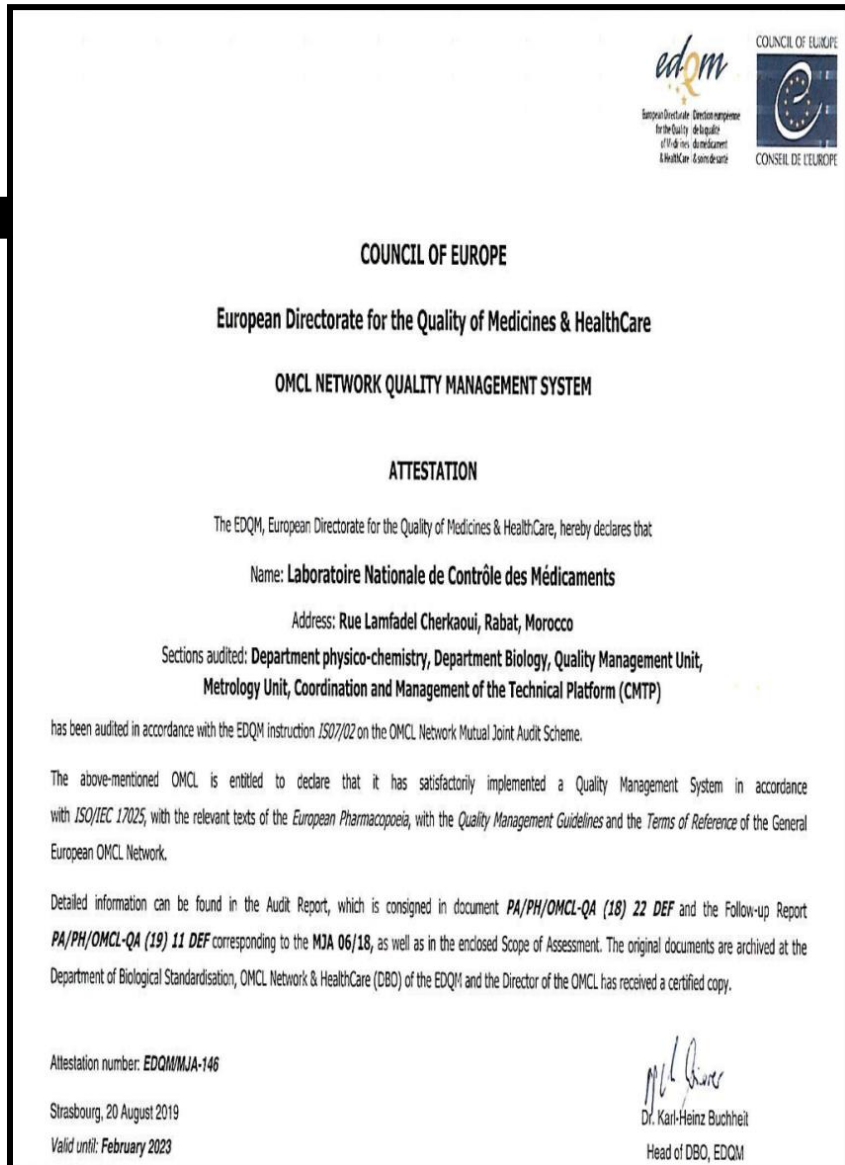
Yvan GERARDIN
Représentant de Polycert

Dr. BOUAZZA Omar
Représentant de l'Entreprise

S.A.R.L POLYCERT au Capital de 10 000 € - RCS EVRY 491 968 293 - SIRET N° 491 968 293 00028 – Code APE 8299 Z
9 rue du Poitou 91220 BRETIGNY SUR ORGE France

QUALITY MANAGEMENT SYSTEM 3/3

- **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**



COUNCIL OF EUROPE

European Directorate for the Quality of Medicines & HealthCare

OMCL NETWORK QUALITY MANAGEMENT SYSTEM

ATTESTATION

The EDQM, European Directorate for the Quality of Medicines & HealthCare, hereby declares that

Name: **Laboratoire Nationale de Contrôle des Médicaments**

Address: **Rue Lamfadel Cherkaoui, Rabat, Morocco**

Sections audited: **Department physico-chemistry, Department Biology, Quality Management Unit, Metrology Unit, Coordination and Management of the Technical Platform (CMTP)**

has been audited in accordance with the EDQM instruction *ISO7/02* on the OMCL Network Mutual Joint Audit Scheme.

The above-mentioned OMCL is entitled to declare that it has satisfactorily implemented a Quality Management System in accordance with *ISO/IEC 17025*, with the relevant texts of the *European Pharmacopoeia*, with the *Quality Management Guidelines* and the *Terms of Reference* of the General European OMCL Network.

Detailed information can be found in the Audit Report, which is consigned in document ***PA/PH/OMCL-QA (18) 22 DEF*** and the Follow-up Report ***PA/PH/OMCL-QA (19) 11 DEF*** corresponding to the **MJA 06/18,** as well as in the enclosed Scope of Assessment. The original documents are archived at the Department of Biological Standardisation, OMCL Network & HealthCare (DBO) of the EDQM and the Director of the OMCL has received a certified copy.

Attestation number: ***EDQM/MJA-146***

Strasbourg, 20 August 2019

Valid until: ***February 2023***

Dr. Karl-Heinz Buchheit

Head of DBO, EDQM

QUALITY RISK MANAGEMENT

- 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*

INTERNATIONAL REGULATORY COOPERATION

▪**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/