# The pharmaceutical industry in Tunisia

TUNTWIN Project
«Stakeholders Event»

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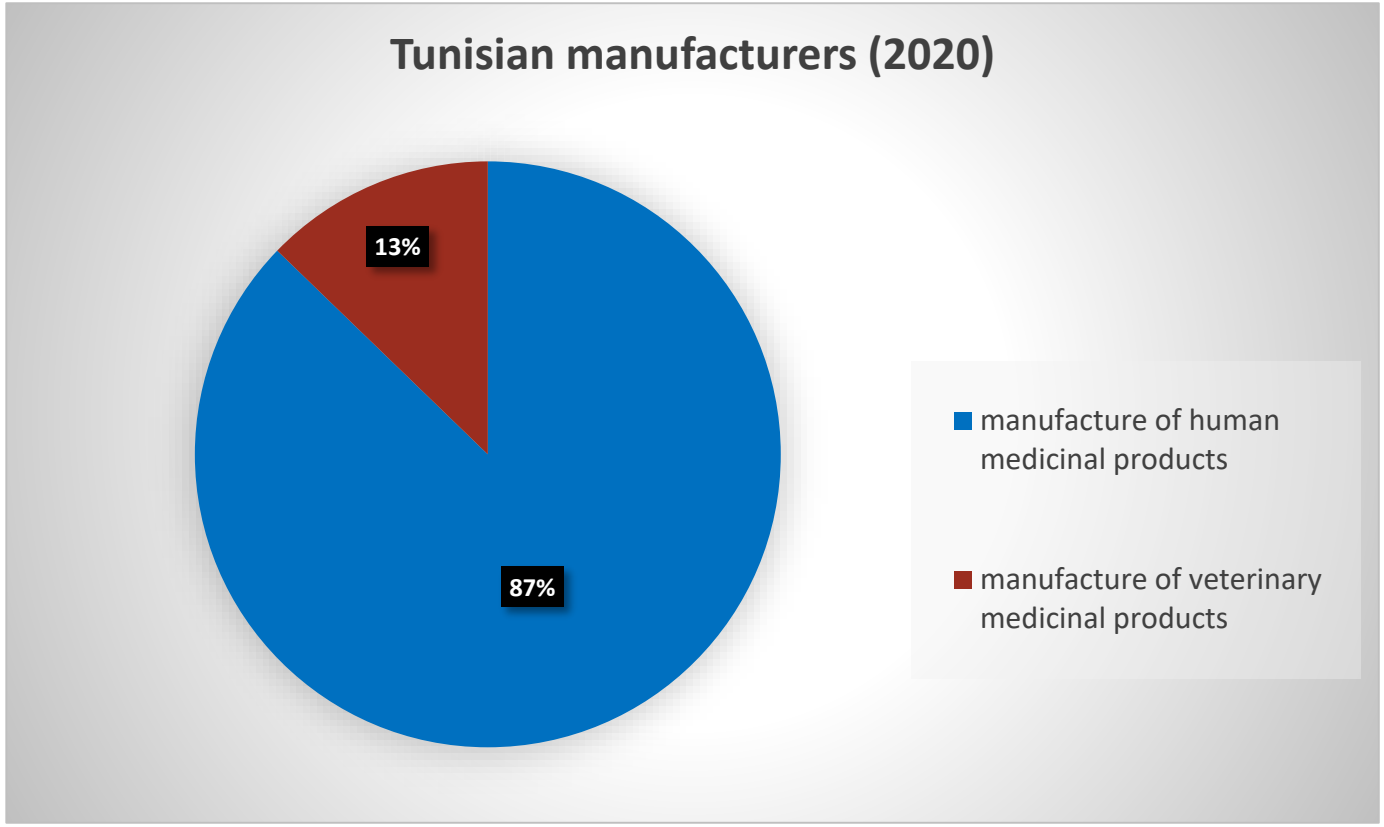
HEAD OF THE SERVICE OF ANALYTICAL CHEMISTRY, LNCM

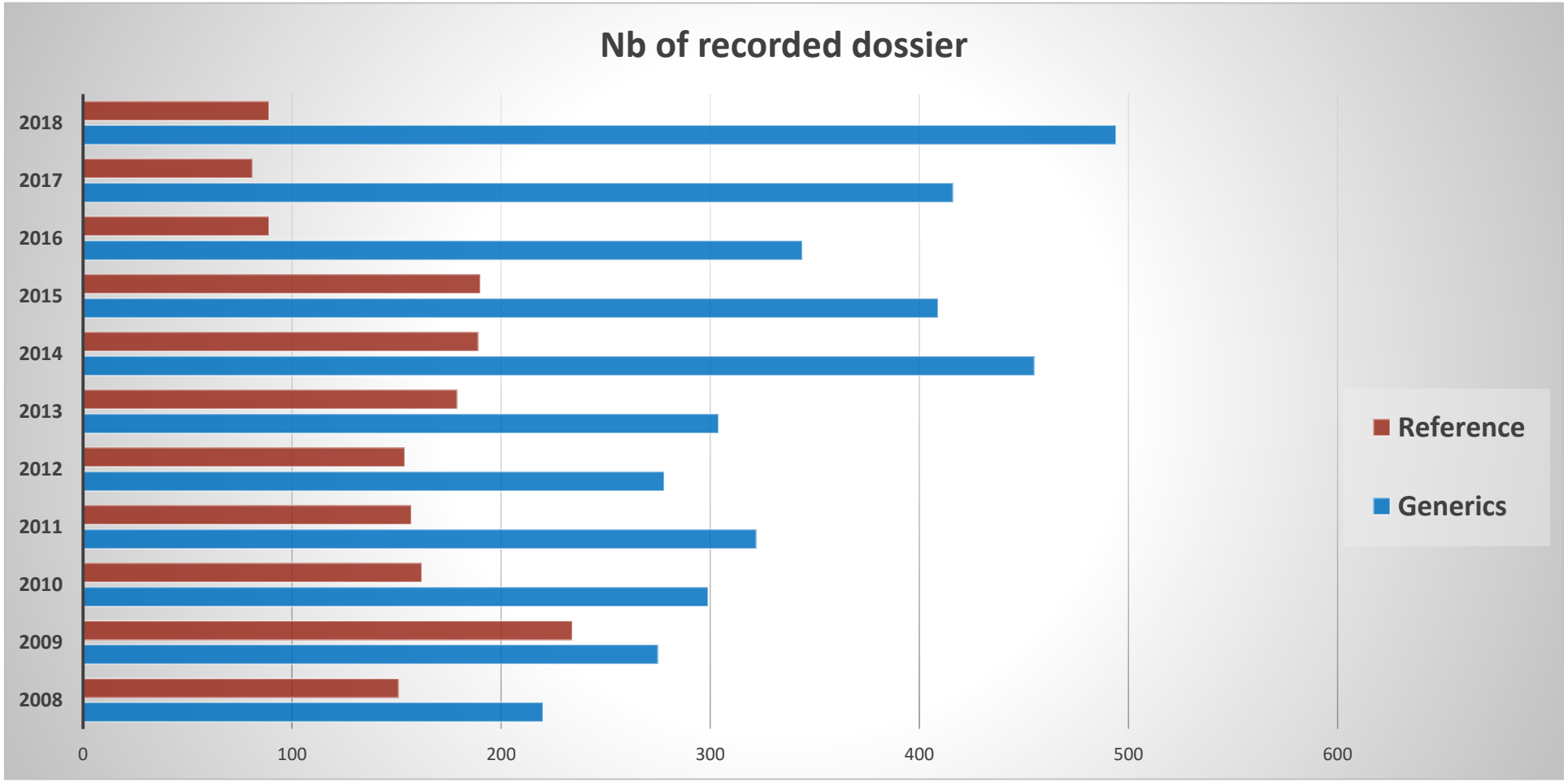
Monday, November 15, 2021

# Drug Tunisian Manufacturers

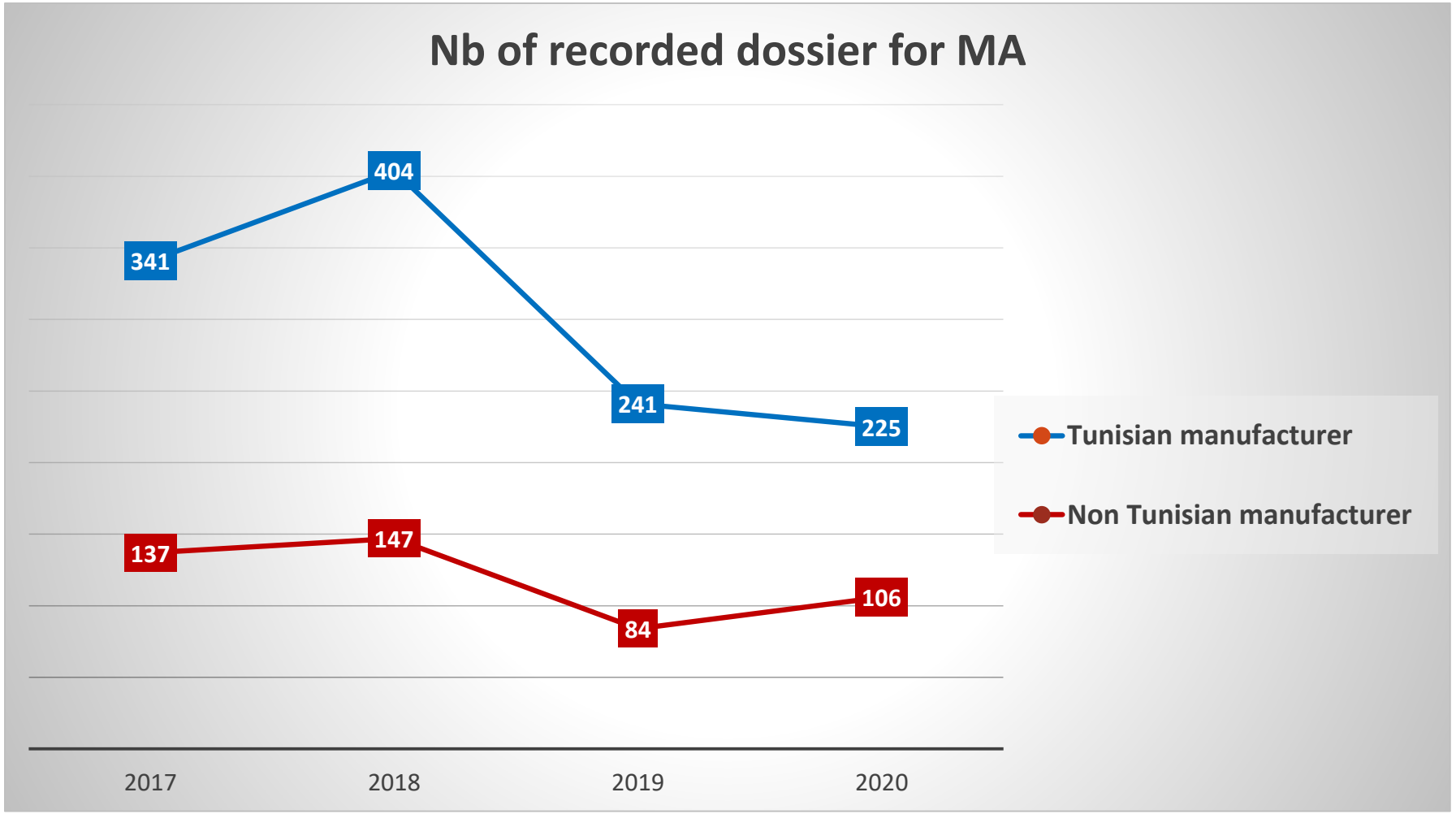
**47**
**pharmaceutical industries**



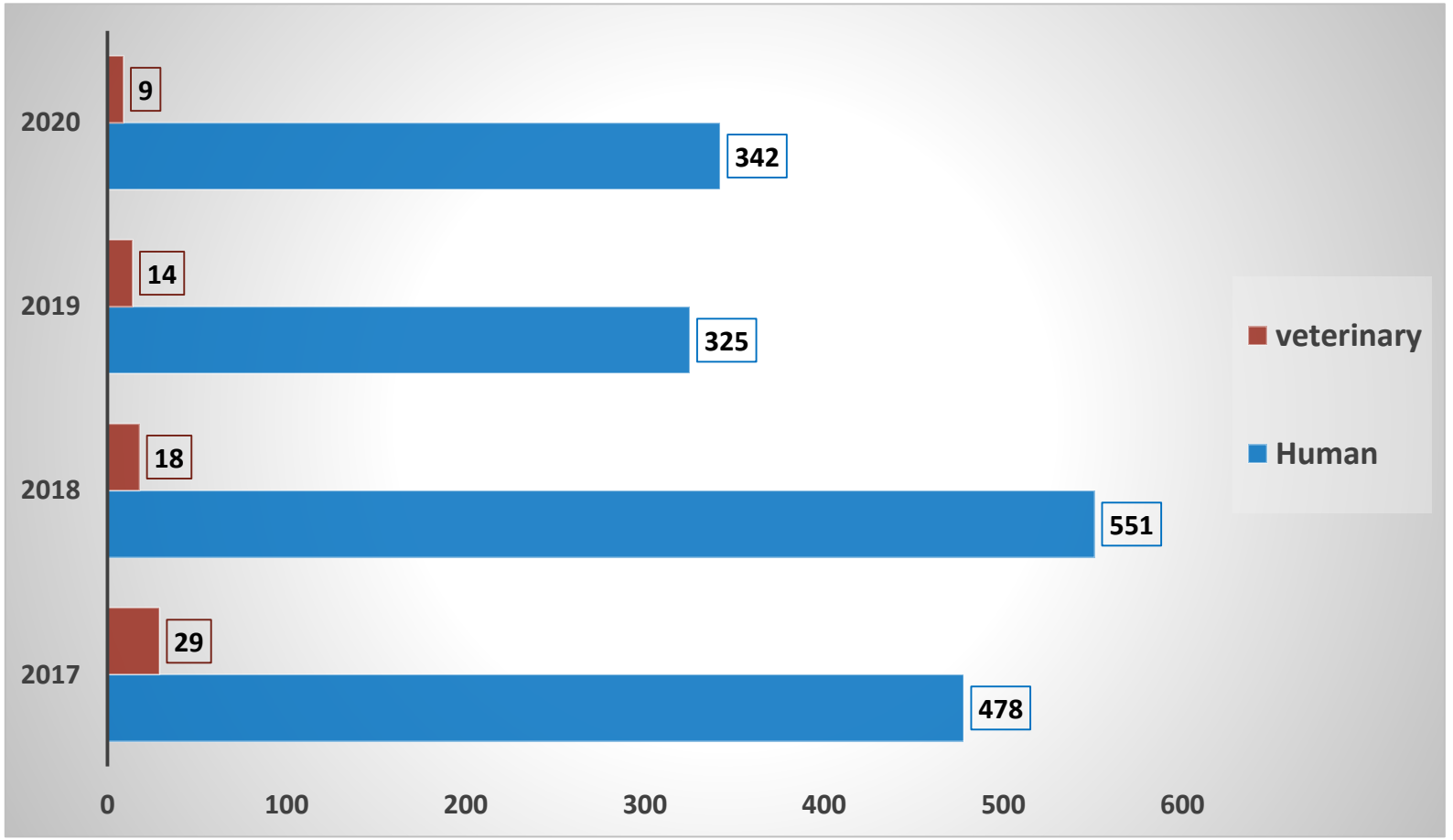
# Generic versus reference medicinal product



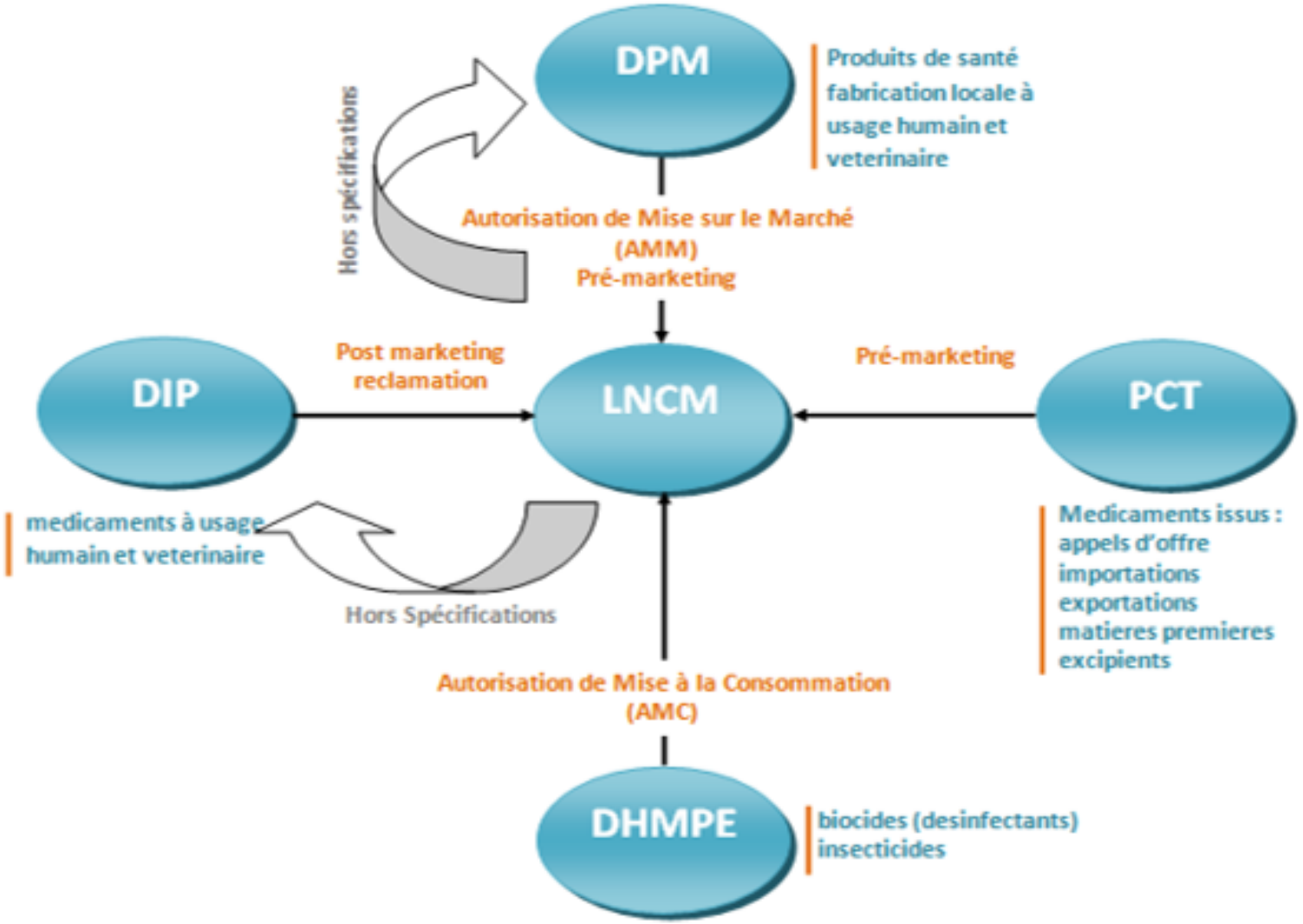
# Marketing Authorization



# Marketing Authorization



# Regulatory structures : Organization



# Missions and goals

- Ensure adequate and reliable supply of safe effective and quality-controlled drugs, and promote its rational use
- Enhance the governance of the health system and improve the quality and the cost-effectiveness of health care services

# Missions and goals

- Support the Local Industry while maintaining and continuously upgrading its standards to meet the International requirement.
- Enable it to increase, its local Market Share and expand to Export Countries.

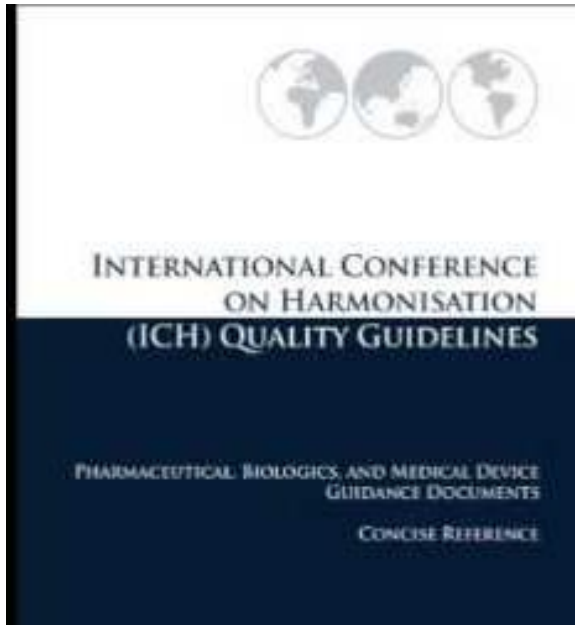
# Missions and goals

- Quality control for medicines appliying for marketing authorization (AMM) during registration process, variations or renewal.
- Quality control for medicines for human and veterinary use in addition to raw materials and insecticides.

# Missions and goals

- Quality control for all medicines marketed in Tunisia before commercialization in collaboration with the central pharmacy of Tunisia PCT (Pre-marketing)
- Quality control during inspection operations especially in case of complaints and post-marketing

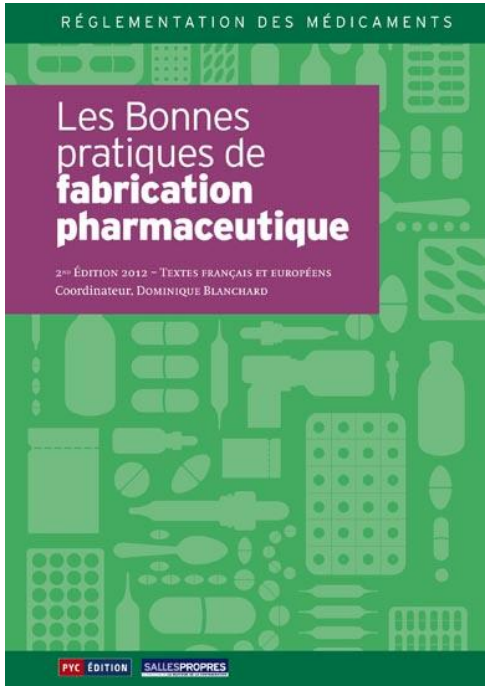
# Guidelines



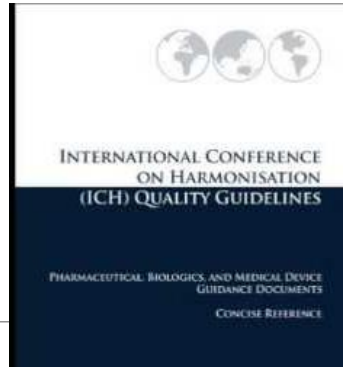

Organisation mondiale de la Santé

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA
Food and Drug Administration



# Guidelines




## Guidelines ICH

- ICH : ***International Conference on Harmonisation*** *of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*

**Quality** Guidelines (Q ) : ICH Q1 ➔ Q12.

**Safety** guidelines ( S) : ICH E1 ➔ ICH E18


**Efficacy** guidelines ( E) : ICH E1 ➔ ICH E18

**Multidisciplinary** guidelines (M) : ICH M1 ➔ ICH M8

# Guidelines

## Guidelines EMA

- *Decentralized agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.*

- *Networking organization whose activities involve thousands of experts from across Europe.*

# Guidelines

## Guidelines OMS

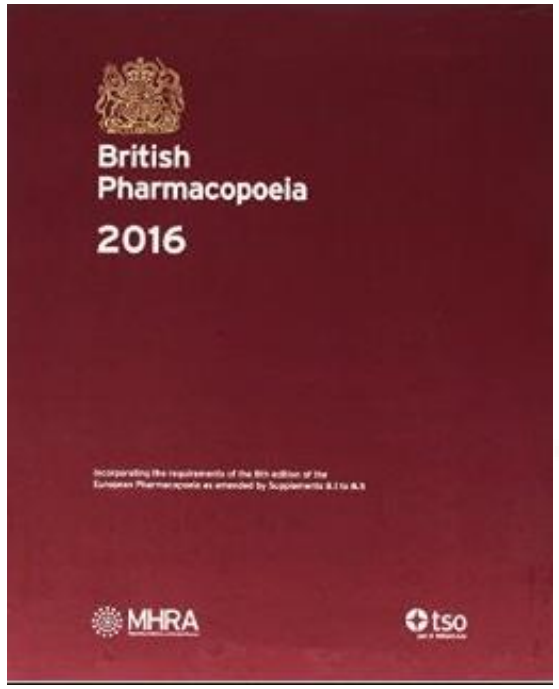
- *Lead and coordinate global health within the United Nations system.*
- *Set standards and criteria, promote and monitor their implementation*

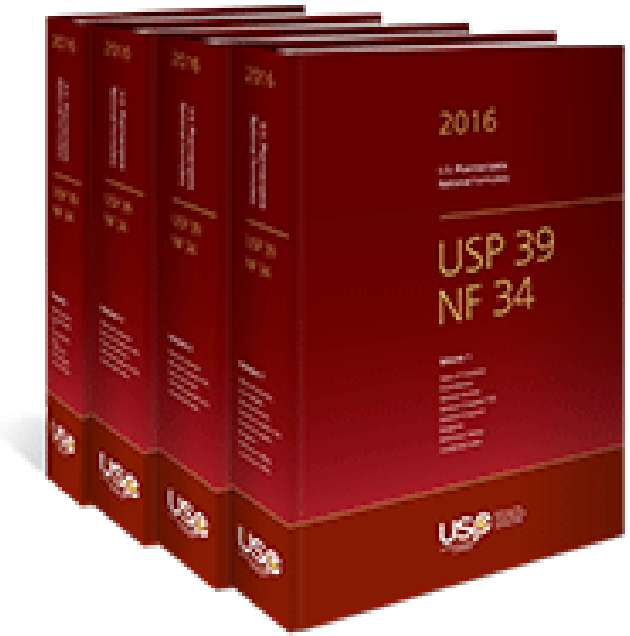
## Guidelines FDA

- *The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.*

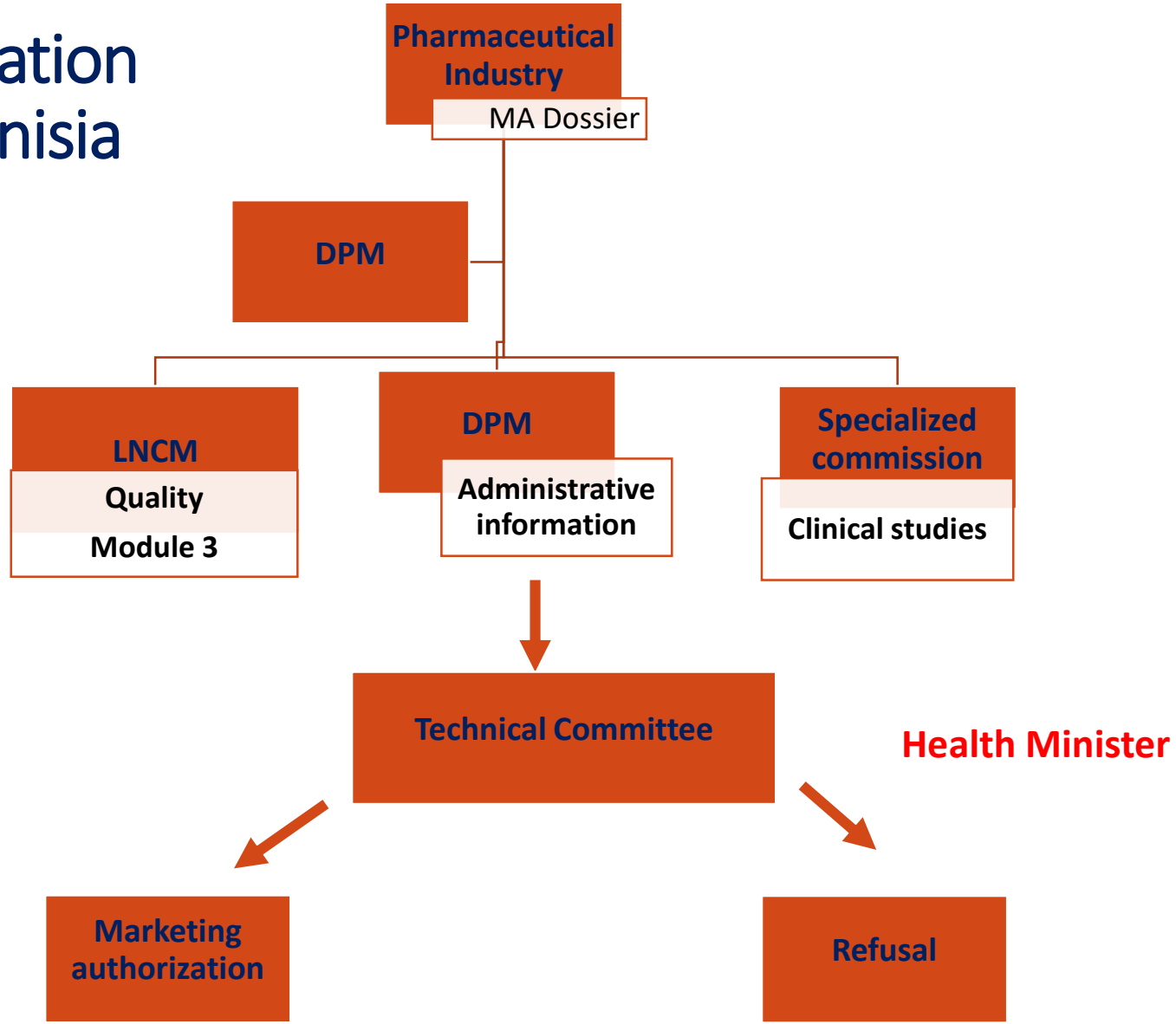
# Guidelines


Pharmacopée
Européenne
8.0
tome I
01/2014


British
Pharmacopoeia
2016
MHRA
tso


2016
USP 39
NF 34

# Medicine registration procedure in Tunisia



# Medicine registration procedure in Tunisia

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

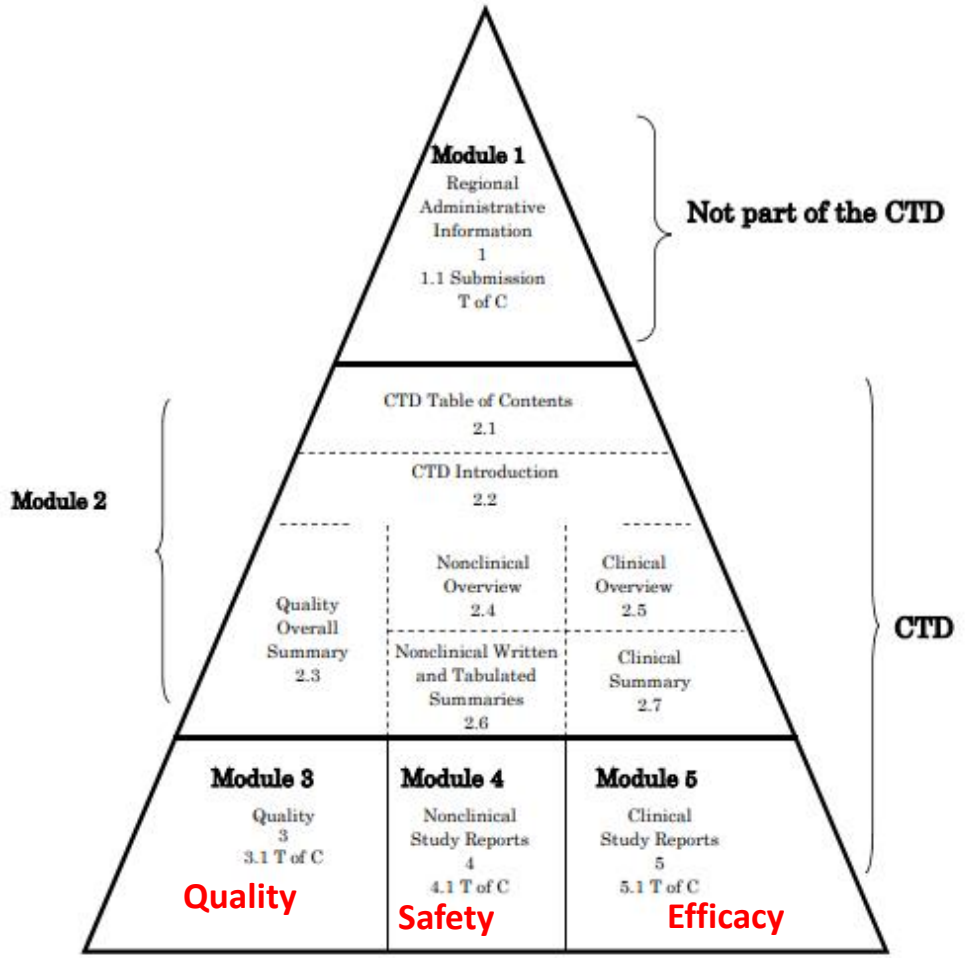
**ICH HARMONISED GUIDELINE**

**ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE**
**M4**

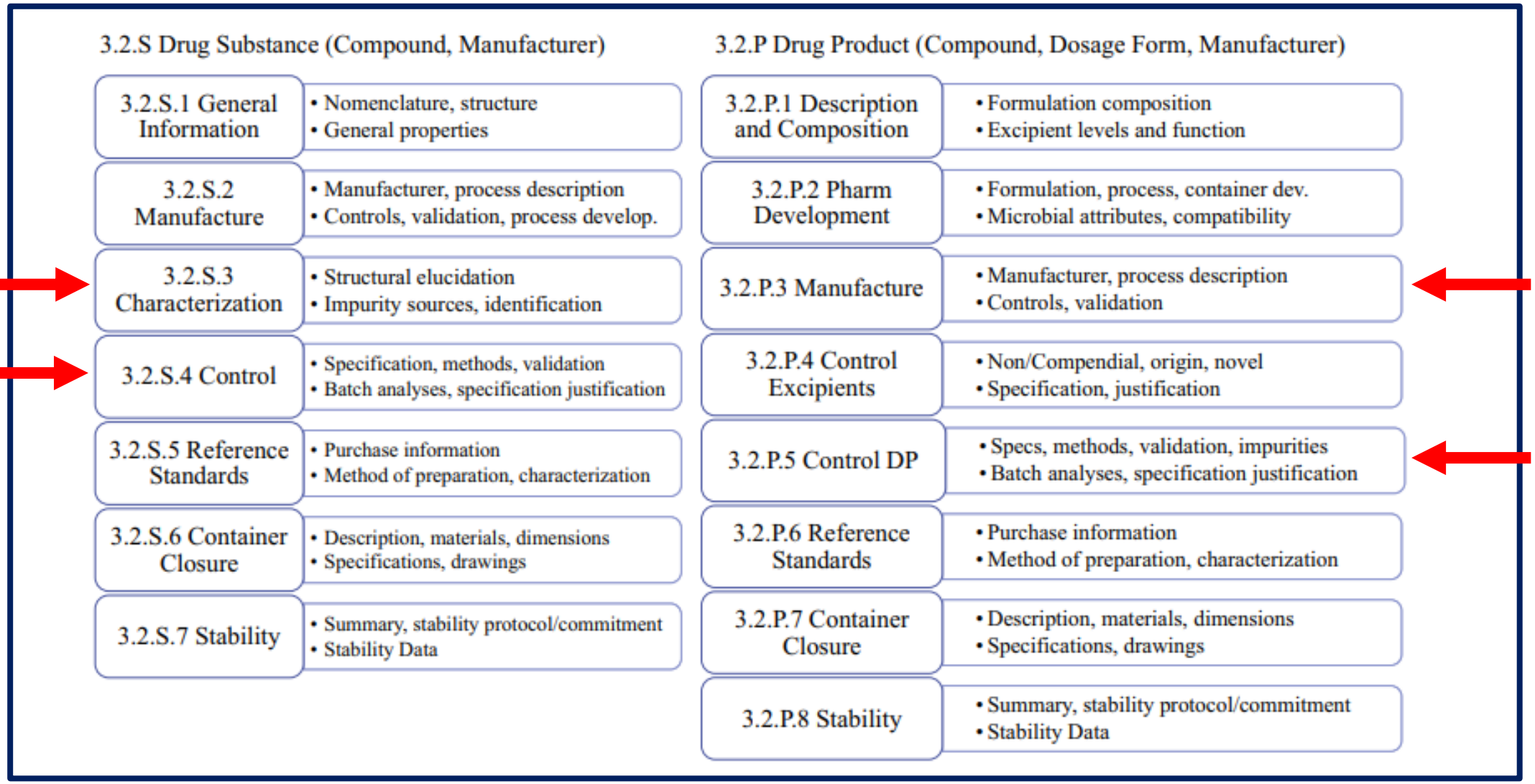
Current *Step 4* version
dated June 15, 2016

*Organisation of The Common Technical Document*

**Diagrammatic Representation of the Organization of the ICH CTD Common Technical Document**



# Quality : Module 3 CTD sections



# Quality : Module 3 CTD sections

The quality of **drug substances** and **drug products** is determined by

- Their design, development, in-process controls, GMP controls, and process validation
- specifications applied to them throughout development and manufacture

# Quality : Specifications /criteria

- A **specification** is defined as a list of **tests**, **references** to analytical procedures, and appropriate **acceptance criteria**, which are numerical limits, ranges, or other criteria for the tests described.

- It establishes **the set of criteria** to which a drug substance or drug product should conform to be considered acceptable for its intended use.

# Quality : Specifications /criteria

- "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will **meet the listed acceptance criteria**.

- **Specifications** are **critical quality standards** that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

# Quality : Specifications /criteria

ICH HARMONISED TRIPARTITE GUIDELINE

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

Q6A

Current *Step 4* version

dated 6 October 1999

| | Universal Test/Criteria | Specific Tests / Criteria |
|---|---|---|
| **Drug Substance** | Description | Physicochemical properties |
| | Identification | Particle size |
| | Assay | Polymorphisme form |
| | impurities | Tests for chiral new drug substances |
| | | Inorganic impurities |
| | | Microbial limits |
| | | Water content |

# Quality : Specifications /criteria

ICH HARMONISED TRIPARTITE GUIDELINE

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

Q6A

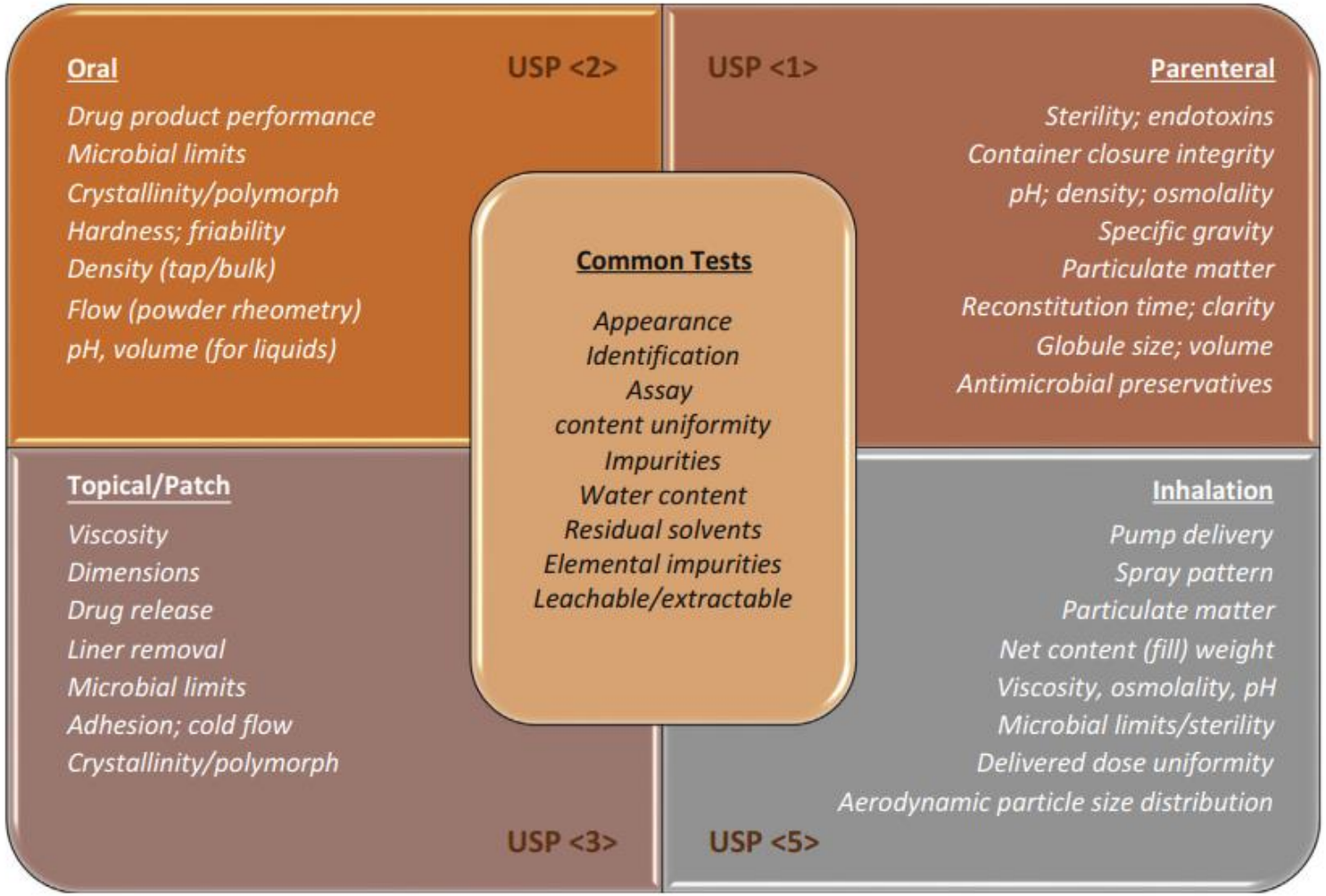
Current *Step 4* version

dated 6 October 1999

| | Universal Test/Criteria | Specific Tests / Criteria |
|---|---|---|
| **Drug Product** | Description | Dissolution: |
| | Identification | Disintegration |
| | Assay | Antimicrobial preservative content |
| | Impurities | Antimicrobial preservative content |
| | | pH |
| | | Alcohol content … |

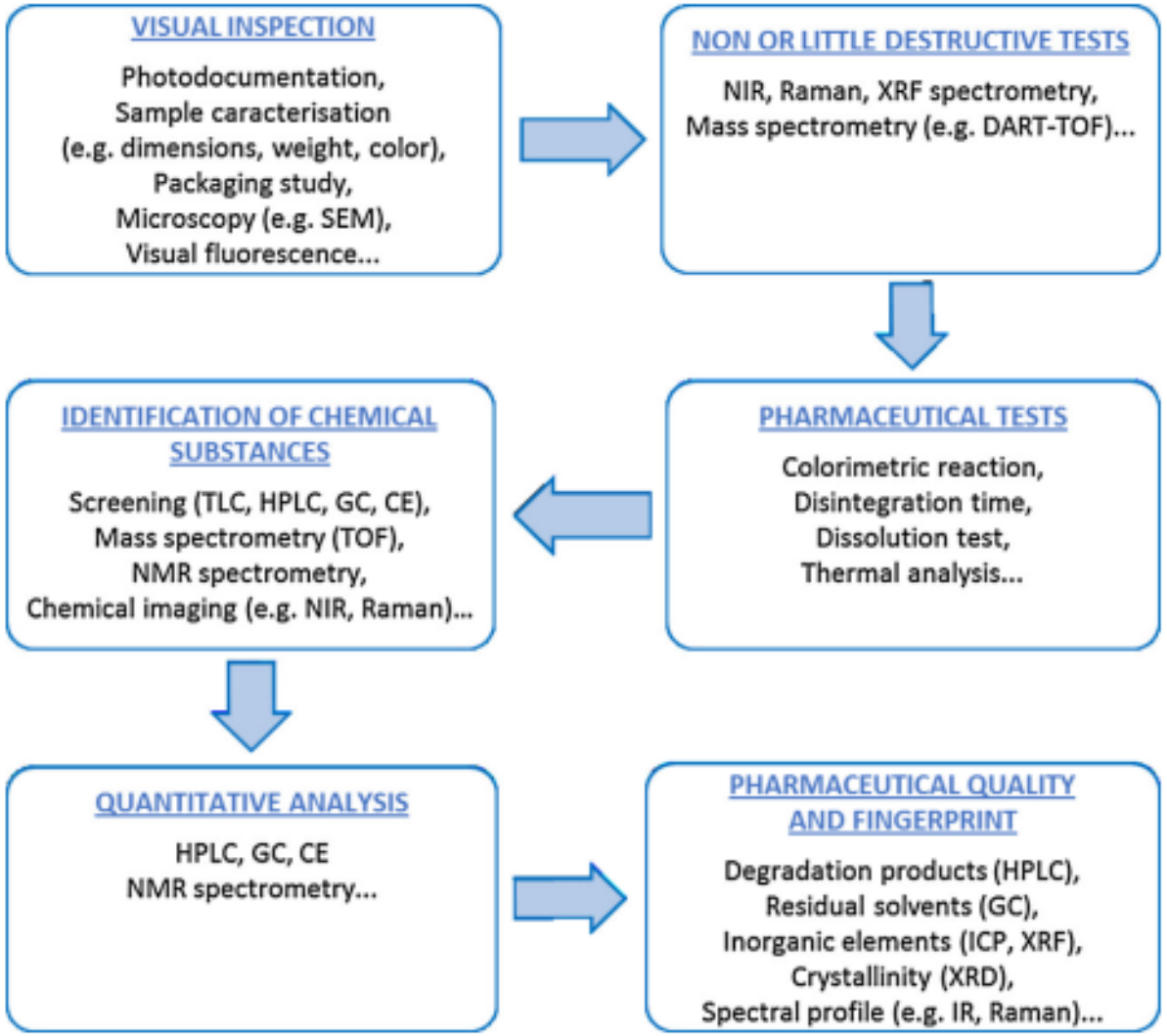
# Specification tests by dosage form

- ICH Q6
- EP, USP




Analytical methods in the clinical phase of development John D. Orr , George L. Reid

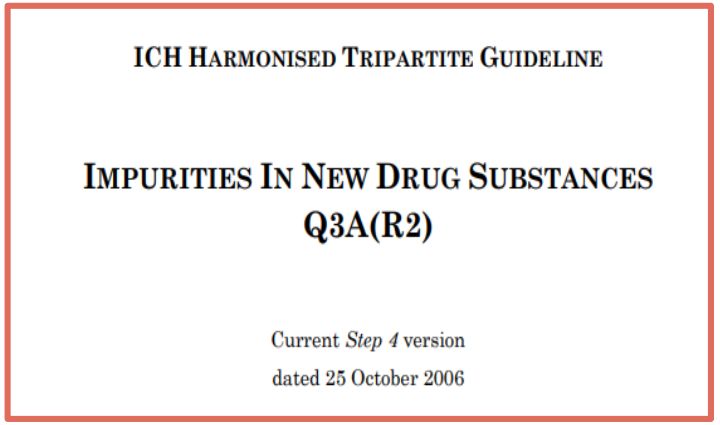
# Physico-chemical methods




H. Rebiere et al. / Journal of Pharmaceutical and Biomedical Analysis 142 (2017) 286–306

# Impurities

- **Organic impurities** *( process and drug related)*
- **Inorganic impurities** *(from manufactoring process, dentified and known)*
- **Residual solvents** *(organic or inorganic liquids)*


ICH HARMONISED TRIPARTITE GUIDELINE

IMPURITIES IN NEW DRUG SUBSTANCES
Q3A(R2)

Current *Step 4* version
dated 25 October 2006

# Classification of impurities

| | |
|---|---|
| Organic impurities | ❖Starting materials |
| | By-products |
| | Intermediates |
| | Degradation product |
| | Reagents, ligands and catalysts |

# Organic impurities : regulation and methods

| Organic Impurities | | | | |
|---|---|---|---|---|
| **Sub Type** | **Process related** | **degradants** | **Chiral impurities** | **Genotoxic impurities** |
| **Common analytical technique** | **HPLC, GC, GCMS, LCMS, TLC** | **HPLC, GC, GCMS, LCMS, TLC** | **HPLC, GC, CE** | **HPLC, GC, GCMS, LCMS, NMR, IC** |
| **API**<br><br>**Guidance Reference and limits** | **ICH Q3A ( 0,03% to 0,15% as per dose), ICH Q6, USP, EP** | **ICH Q3A ( 0,05% to 0,15% as per dose), ICH Q6, USP, EP** | **ICH Q3A ( 0,05% to 0,15% as per dose), ICH Q6, FDA guidance, USP, EP** | **ICH M7, S9, FDA guidance, as per TTC limit and duration of treatment** |
| **Drug product**<br><br>**Guidance Reference and limits** | **Usually not monitoring in drug product** | **ICH Q3A ( 0,2% to 1% as per dose), ICH Q6, USP** | **Usually not monitoring in drug product. Evaluation study done in few cases** | **Usually not monitoring in drug product. Evaluation study done in few cases** |

# Classification of impurities

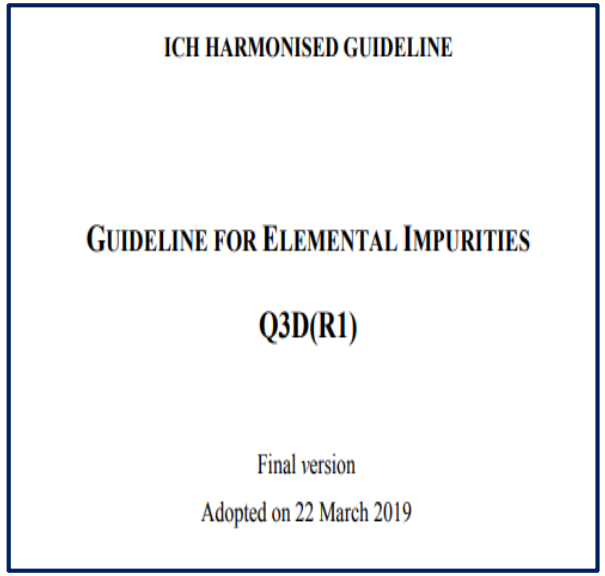
| | |
|---|---|
| Inorganic impurities | ❖Reagents, ligands and catalysts |
| | Heavy metals or oyher residual metals |
| | Inorganic salts |
| | Other materials (e.g., filter aids, charcoal) |

# Inorganic impurities : regulation

- Normally detected and quantified using pharmacoepial or other appropriate procedures

- Carry-over of catalysts to the new drug substance should be evaluated during development

# Inorganic impurities : regulation


ICH HARMONISED GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

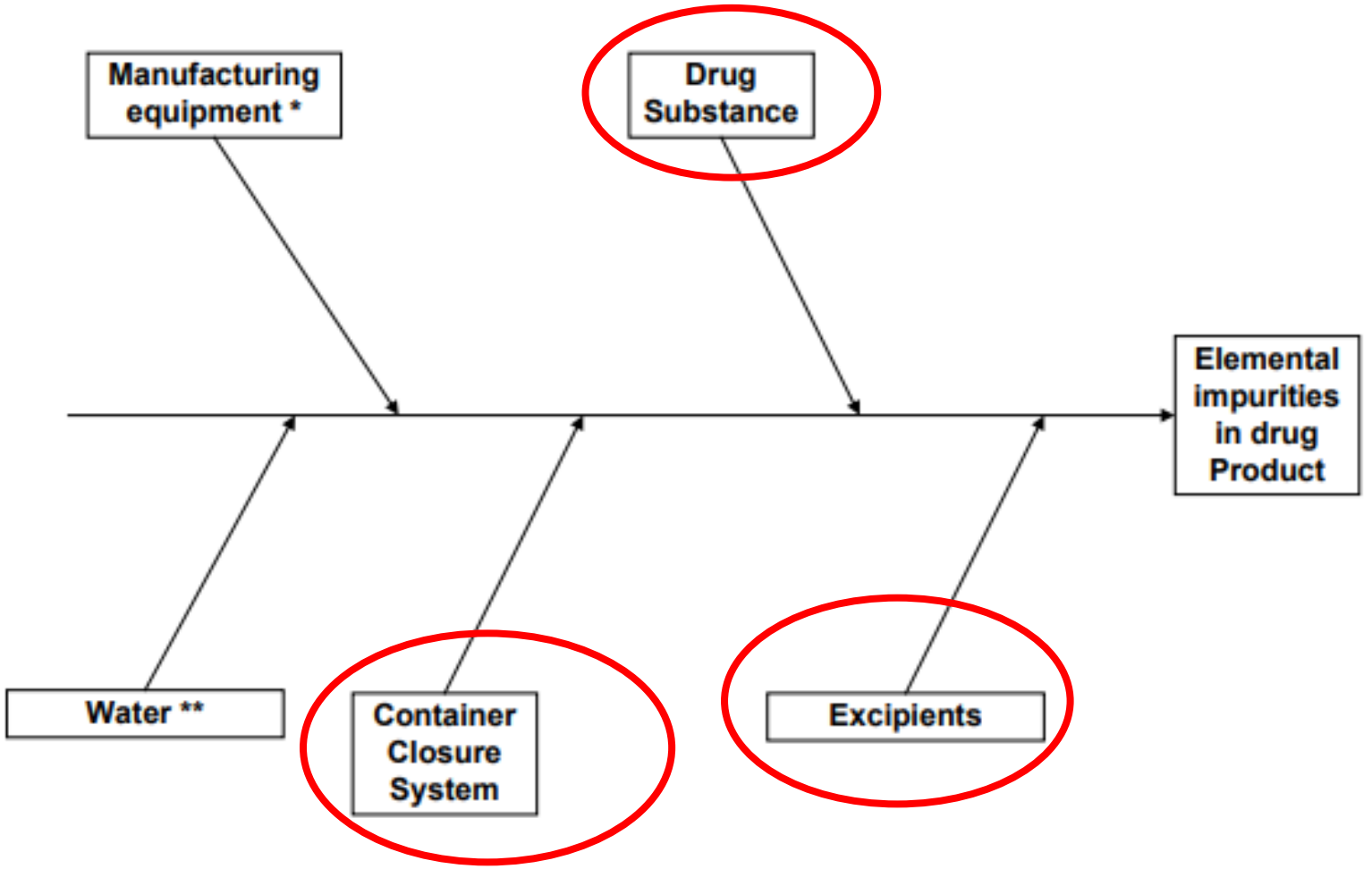
Q3D(R1)

Final version

Adopted on 22 March 2019

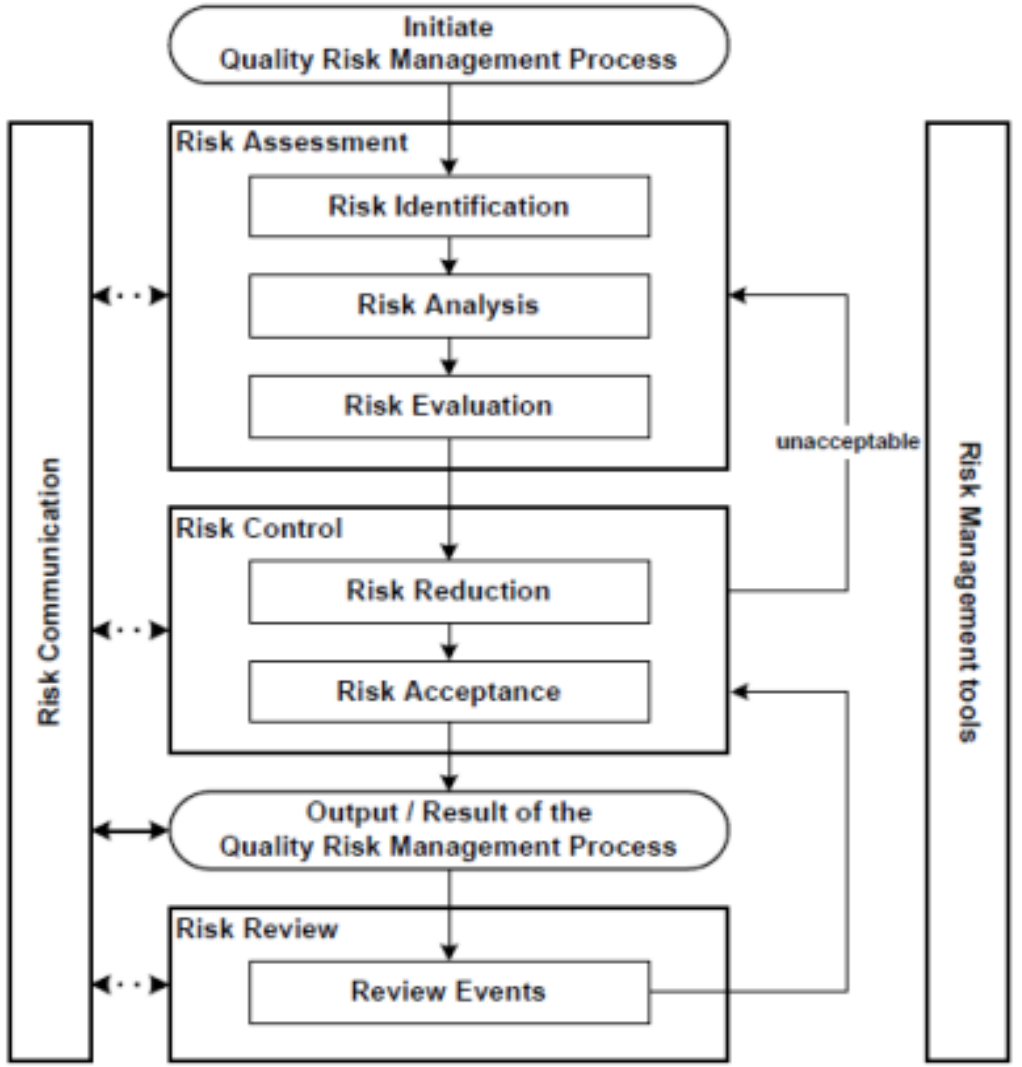
| CLASS 1 | CLASS 2 | CLASS 3 |
|---|---|---|
| • Human toxicants that have limited or no use in the manufacture of pharmaceuticals.<br>• Their presence in drug products typically comes from commonly used materials. require evaluation during the risk | • Generally considered as route-dependent human toxicants :<br>  • **Class 2A** : **high** probability of occurrence, require evaluation during the risk assessment<br>  • **Class 2B** : **reduced** probability of occurrence | • The elements in this class have relatively low toxicities by the oral route of administration.<br>• Require consideration in the risk assessment for inhalation and parenteral routes |

# Inorganic impurities : potentials sources




https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf

# Inorganic impurities




*https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf*

# Inorganic impurities : regulation

**Table 5.1: Elements to be Considered in the Risk Assessment**

| Element | Class | If intentionally added (all routes) | If not intentionally added | | |
|---|---|---|---|---|---|
| | | | Oral | Parenteral | Inhalation |
| Cd | 1 | yes | yes | yes | yes |
| Pb | 1 | yes | yes | yes | yes |
| As | 1 | yes | yes | yes | yes |
| Hg | 1 | yes | yes | yes | yes |
| Co | 2A | yes | yes | yes | yes |
| V | 2A | yes | yes | yes | yes |
| Ni | 2A | yes | yes | yes | yes |
| Tl | 2B | yes | no | no | no |
| Au | 2B | yes | no | no | no |
| Pd | 2B | yes | no | no | no |
| Ir | 2B | yes | no | no | no |
| Os | 2B | yes | no | no | no |
| Rh | 2B | yes | no | no | no |
| Ru | 2B | yes | no | no | no |
| Se | 2B | yes | no | no | no |
| Ag | 2B | yes | no | no | no |
| Pt | 2B | yes | no | no | no |
| Li | 3 | yes | no | yes | yes |
| Sb | 3 | yes | no | yes | yes |
| Ba | 3 | yes | no | no | yes |
| Mo | 3 | yes | no | no | yes |
| Cu | 3 | yes | no | yes | yes |
| Sn | 3 | yes | no | no | yes |
| Cr | 3 | yes | no | no | yes |

https://database.ich.org/sites/default/files/**Q3D**-R1EWG_Document_Step4_Guideline_2019_0322.pdf

# Inorganic impurities : regulation

- The data that support this risk assessment can come from a number of sources that include :
  - Prior knowledge
  - Published literature
  - Data generated from similar processes
  - Supplier information or data
  - **Testing of the components of the drug product;**
  - **Testing of the drug product.**

# Inorganic impurities : methods

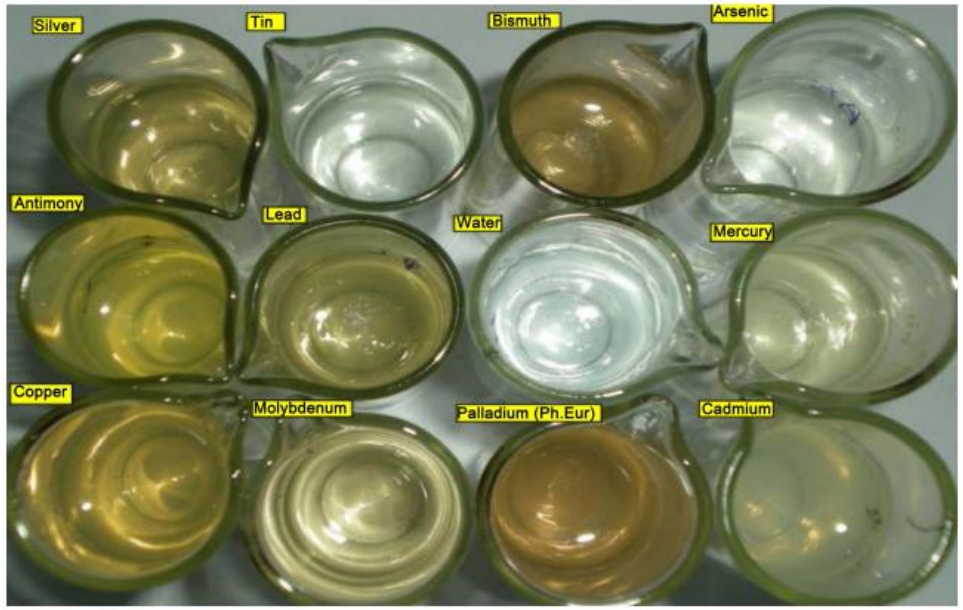



**Figure 5.** Erroneous reporting of heavy metals as per USP <231> heavy metals [45].

DOI: 10.4236/ajac.2018.94016 196 American Journal of Analytical Chemistry

**Non specific !!**

Current requirements changed and

replaced **nonspecific heavy metal tests**

with specific quantifying techniques

and specifications were included

# Inorganic impurities : methods
# USP

## ⟨233⟩ ELEMENTAL IMPURITIES—PROCEDURES

**INTRODUCTION**

This chapter describes two analytical procedures (*Procedures 1* and *2*) for the evaluation of the levels of the elemental impurities. The chapter also describes criteria for acceptable alternative procedures. By means of validation studies, analysts will confirm that the analytical procedures described herein are suitable for use on specified material.

**Use of Alternative Procedures**

The chapter also describes criteria for acceptable alternative procedures. Alternative procedures that meet the validation requirements herein may be used in accordance with *General Notices, 6.30 Alternative and Harmonized Methods and Procedures*. Information on the *Requirements for Alternate Procedure Validation* is provided later in this chapter.

**Speciation**

The determination of the oxidation state, organic complex, or combination is termed *speciation*. Analytical procedures for speciation are not included in this chapter, but examples may be found elsewhere in *USP–NF* and in the literature.

**PROCEDURES**

- COMPENDIAL PROCEDURES 1 AND 2

  System standardization and suitability evaluation using applicable reference materials should be performed on the day of analysis.

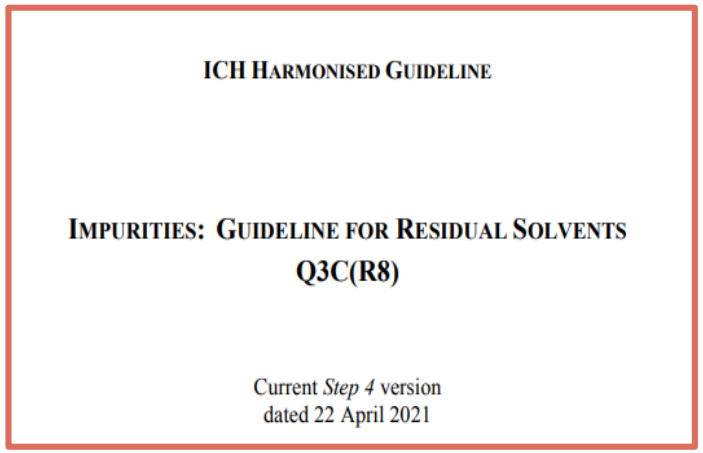
  **Procedure and detection technique:** *Procedure 1* can be used for elemental impurities generally amenable to detection by inductively coupled plasma–atomic (optical) emission spectroscopy (ICP–AES or ICP–OES). *Procedure 2* can be used for elemental impurities generally amenable to detection by ICP–MS. Before initial use, the analyst should verify that the procedure is appropriate for the instrument and sample used (procedural verification) by meeting the alternative procedure validation requirements below.

**ICP-OES**

**ICP-MS**

# Classification of impurities

## Residual solvents


ICH HARMONISED GUIDELINE

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS
Q3C(R8)

Current *Step 4* version
dated 22 April 2021

❖**Class 1** : Solvents to be avoided *(human carcinogens, environmental hazards*

**Class 2** : Solvents to be limited *(Non genotoxic animal carcinogen or possible causative agents for other irreversible toxicity)*

**Class 3** : Solvents with low toxic potential

# Residual solvents: regulation

**ICH HARMONISED GUIDELINE**

**IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS**
**Q3C(R8)**

Current *Step 4* version
dated 22 April 2021

**TABLE 1. Class 1 solvents in pharmaceutical products** (solvents that should be avoided).

| *Solvent* | *Concentration limit (ppm)* | *Concern* |
|---|---|---|
| Benzene | 2 | Carcinogen |
| Carbon tetrachloride | 4 | Toxic and environmental hazard |
| 1,2-Dichloroethane | 5 | Toxic |
| 1,1-Dichloroethene | 8 | Toxic |
| 1,1,1-Trichloroethane | 1500 | Environmental hazard |

# Residual solvents: regulation

**ICH HARMONISED GUIDELINE**

**IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS**
**Q3C(R8)**

Current *Step 4* version
dated 22 April 2021

**TABLE 2. Class 2 solvents in pharmaceutical products.**

| *Solvent* | *PDE (mg/day)* | *Concentration limit (ppm)* |
|---|---|---|
| Acetonitrile | 4.1 | 410 |
| Chlorobenzene | 3.6 | 360 |
| Chloroform | 0.6 | 60 |
| Cumene[1] | 0.7 | 70 |
| Cyclohexane | 38.8 | 3880 |
| Cyclopentyl methyl ether[2] | 15.0 | 1500 |
| 1,2-Dichloroethene | 18.7 | 1870 |
| Dichloromethane | 6.0 | 600 |
| 1,2-Dimethoxyethane | 1.0 | 100 |
| N,N-Dimethylacetamide | 10.9 | 1090 |

# Residual solvents: Methods

- Residual solvents are typically determined using chromatographic techniques such as **gas chromatography**. Any harmonised procedures for determining levels of residual solvents as described in the pharmacopoeias should be used

- If only **Class 3 solvents** are present, a non-specific method such as **loss on drying** may be used.

# Conclusion

- Protect the public health by ensuring the safety, efficacy, and security of human and veterinary drugs
- Speed innovations that make medical products more effective, safer, and more affordable

→ Possible only through regulatory watch and specific and innovative analysis methods in **collaboration** with **experts** and **scientists**

# The pharmaceutical industry in Tunisia

**Hanène Oueslati**

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**Head of the service of analytical chemistry, LNCM**

# Thank you for attention