



# Public Health Issues of SUBSTANDARD MEDICINES

SAWAYA Antoine,  
Pharm D; Ph D.

**ansm**  
Agence nationale de sécurité du médicament  
et des produits de santé

RÉPUBLIQUE FRANÇAISE



# Is quality of medicines still Globally a problem?

- Facts :
  - Diethylene glycol poisonings continue
  - Viracept (nelfinavir) case
  - Heparin case
  - ...

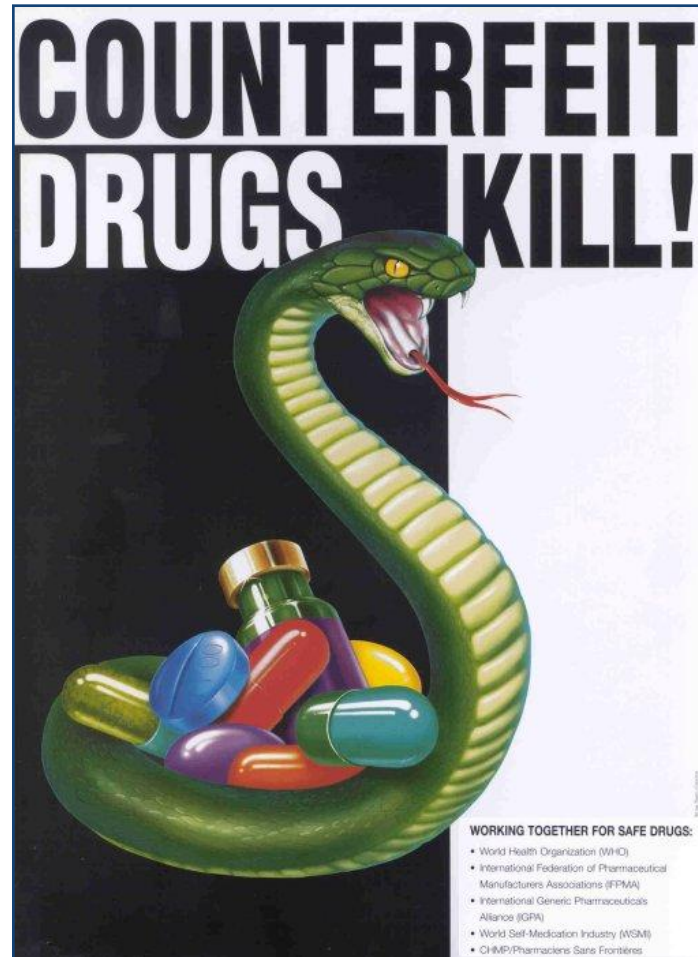


# Quality issues with essential medicines against TB

- Quality defects found in:
  - Botswana: 4/13 FDCs
  - Nigeria: 4/4 INH, 5/15 Rif and 10/19 Strep inj
  - India: Amikacin, Etham (2x), Rif (2x), INH (2x)
  - Myanmar: Rifampicin
  - Hong Kong, Pakistan, Germany: Ofloxacin



# Counterfeiting medicines is a major public health concern





# Counterfeit Medicines

Medicines which are deliberately and fraudulently mislabelled with respect to identity and/or source ...

Counterfeit products may include products with correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.



# Substandard Medicines

- Substandard medicines (or OOS products) are genuine medicines produced by manufacturers authorized by NMRA which do not meet quality specifications set for them by national standards



# What is the problem with Substandard Medicines ?

- Under treatment or non treatment
  - ➔ ineffective medicines
- Intoxication
  - ➔ harmful medicines

Substandard medicines are a Major Public Health concern



# European Regulation

The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health





# Marketing Authorization of Medicines

No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State



# Criteria for Authorising Medicines

- Evidence of :
  - Quality,
  - Safety,
  - Efficacy,of the Medicine



# Criteria for Authorizing Medicines



MA is granted when the Benefit-Risk balance of a product is positive, meaning that benefits from use of this product outweigh risks associated with its use.



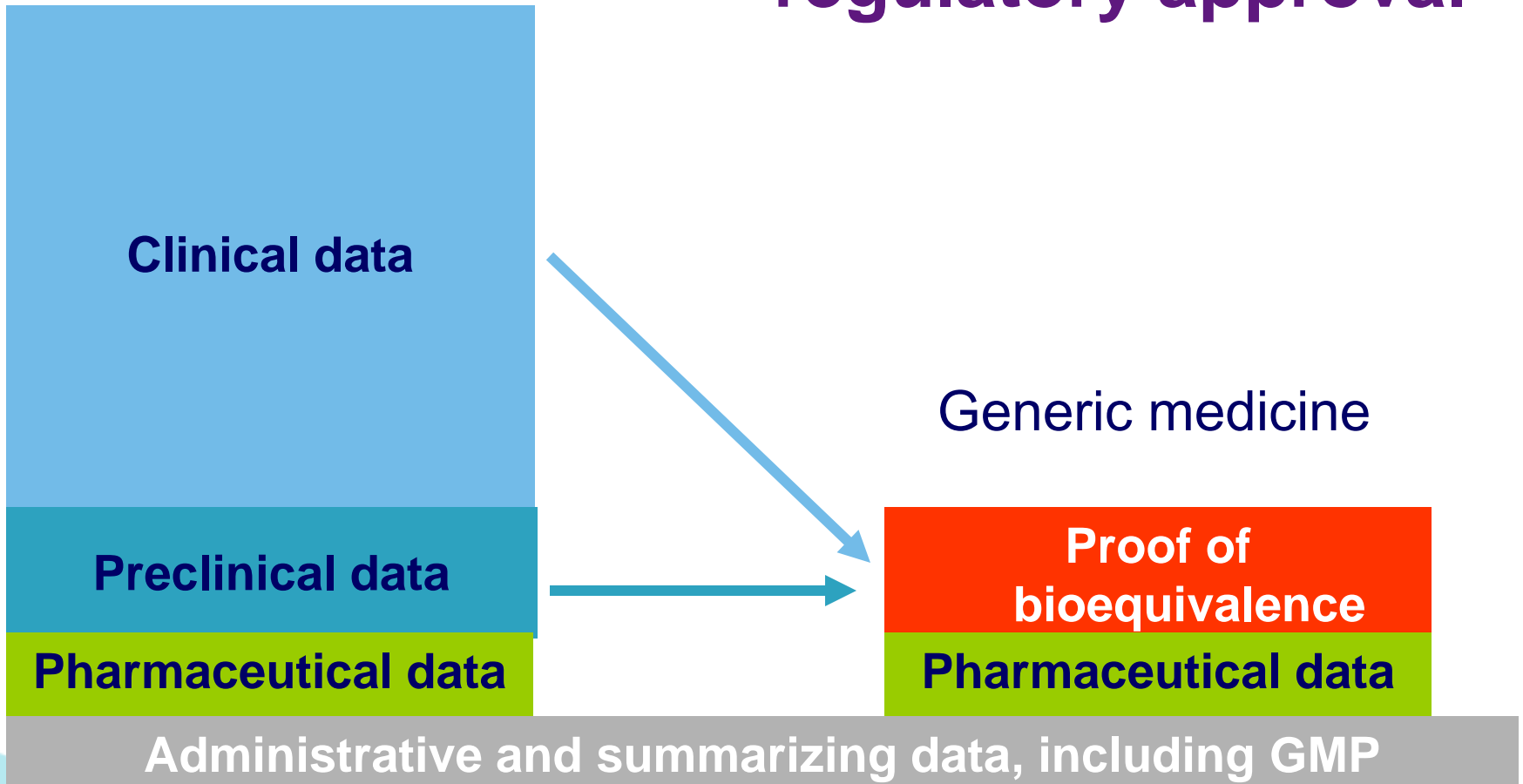
# Marketing Authorisation Applications

- Full Application,
- Bibliographical (or Well Established Use) Application,
- Abridged Applications :
  - Generic Application,
  - Hybrid Application



Innovative medicine  
Experimental data/ Literature

# Data required for regulatory approval





# Marketing Authorization Dossier : Quality Requirements

## **3.2.S DRUG SUBSTANCE :**

**3.2.S.1 General Information**

**3.2.S.2 Manufacture**

**3.2.S.3 Characterization**

**3.2.S.4 Control of drug substance**

**3.2.S.5 Reference standards or Materials**

**3.2.S.6 Container closure system**

**3.2.S.7 Stability**



# **Marketing Authorization Dossier : Quality Requirements**

## **3.2.P DRUG PRODUCT**

**3.2.P.1 Description and composition of the drug product**

**3.2.P.2 Pharmaceutical Development**

**3.2.P.3 Manufacture**

**3.2.P.4 Control of excipients**

**3.2.P.5 Control of drug product**

**3.2.P.6 Reference standards or materials**

**3.2.P.7 Container closure system**

**3.2.P.8 Stability**



# Quality Evaluation

- General and specific monographs of the European Pharmacopeia
- ICH guidelines
- CHMP/QWP notes for guidance





# IMPURITIES IN DRUG SUBSTANCES

- impurities from synthesis.
- impurities from degradation



# IMPURITIES FROM SYNTHESIS

- Related organic impurities :
  - starting materials
  - by-products
  - intermediates



# IMPURITIES FROM DEGRADATION

- Impurities from hydrolysis
- Impurities from oxidation
- Impurities from light exposure
- Impurities from epimerisation, racemisation ...



# IMPURITIES IN DRUG SUBSTANCES

## Reporting, identification and qualification thresholds for related impurities

### ICH Q3A

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
$\leq 2$ g/day	0.05 %	0.10 % or 1 mg/day intake whichever is lower	0.15 % or 1 mg/day intake whichever is lower
$> 2$ g/day	0.03 %	0.05 %	0.05 %



# QUALITY OF TRIMETHOPRIM

Manufacturer	Impurities detected by HPLC				
	Rt min 2.8	Rt min 6.0	Rt min 9.2	Rt min 11.2	Sum
<b>ROCHE (Switzerland)</b>	<b>&lt; 0.1 %</b>				<b>&lt; 0.1 %</b>
<b>Source 1 (KOREA)</b>			<b>&lt; 0.1 %</b>	<b>&lt; 0.1 %</b>	<b>&lt; 0.2 %</b>
<b>Source 2 (INDIA)</b>				<b>0.17 %</b>	<b>0.17 %</b>
<b>Source 3 (CHINA)</b>	<b>&lt; 0.1 %</b>	<b>0.95 %</b>			<b>0.95 %</b>
<b>Source 4 (CHINA)</b>		<b>0.95 %</b>			<b>0.95 %</b>
<b>Source 5 (CHINA)</b>	<b>&lt; 0.1 %</b>	<b>0.92 %</b>	<b>0.1 %</b>	<b>0.47 %</b>	<b>1.49 %</b>



# IMPURITIES IN DRUG SUBSTANCES

## Residual solvents

- 4 classes of solvents :
  - Class 1 : Solvents to be avoided
    - ex : Benzene            2 ppm
    - Dichloroethane        5 ppm
  - Class 2 : Solvents to be limited
    - ex : Chloroform    60 ppm (option1)
    - 0,6 mg/day PDE (option 2)
  - Class 3 : Solvents with low toxic potential
    - ex : Ethanol        500 ppm or 0,5 %
  - Class 4 : Solvents for wich no adequate toxicological data was found
    - ex : Isooctane, diethoxypropane...



# IMPURITIES FROM SYNTHESIS

- Inorganic impurities :
  - non toxic common ions : chlorides, sulphates...:  
limited by sulphated ash test
  - toxic ions : barium, cyanides...  
limited by specific tests
  - heavy metals : limited by heavy metal test
  - residues of catalysts : Platinum, Palladium, Rhodium, Nickel... limited by specific tests



# IMPURITIES FROM SYNTHESIS

## Residue of catalysts : which limits

Classification	Oral Exposure		Parenteral Exposure		Inhalation exposure *
	PDE (µg/day)	Concentration (ppm)	PDE (µg/day)	Concentration (ppm)	PDE (ng/day)
<b>Class 1A:</b> <b>Pt, Pd</b>	100	10	10	1	Pt: 70 *
<b>Class 1B:</b> <b>Ir, Rh, Ru, Os</b>	100**	10**	10**	1**	
<b>Class 1C:</b> <b>Mo, Ni, Cr, V</b> Metals of significant safety concern	250	25	25	2.5	Ni: 100 Cr (VI): 10
<b>Class 2:</b> <b>Cu, Mn</b> Metals with low safety concern	2500	250	250	25	
<b>Class 3:</b> <b>Fe, Zn</b> Metals with minimal safety concern	13000	1300	1300	130	

\* see section 4.4 and the respective monographs, Pt as hexachloroplatinic acid

\*\* Subclass limit: the total amount of listed metals should not exceed the indicated limit





# IMPURITIES IN DRUG SUBSTANCES

## Toxic Impurities

**WARNING !!!**

The ICH thresholds for impurities apply only to «Ordinary impurities» and not to those which are unusually toxic.



# **IMPURITIES IN DRUG SUBSTANCES**

## **genotoxic and/or carcinogenic impurities**

- **The chemical synthesis of active substances uses several reagents, which are known to be potentially genotoxic and/or carcinogenic.**
- **The applicant should justify that no other alternative is available.**
- **In some cases the use of genotoxic or potential genotoxic reagents is unavoidable.**



# IMPURITIES IN DRUG SUBSTANCES

## genotoxic and/or carcinogenic impurities

- Impurities suspected to be genotoxic :  
maximum daily dose : 1.5 µg / day of impurity  
e.g. :  
daily dose of API 10 mg/day ➔ ≤ 150 ppm in the API  
daily dose of API 300 mg/day ➔ ≤ 5 ppm in the API
- Impurities known to be genotoxic :  
maximum daily dose : 0.15 µg / day of impurity  
e.g. :  
daily dose of API 10 mg/day ➔ ≤ 15 ppm in the API  
daily dose of API 300 mg/day ➔ ≤ 0.5 ppm in the API



# IMPURITIES IN DRUG PRODUCTS

## Impurities from degradation

- Impurities from hydrolysis
- Impurities from oxidation
- Impurities from light exposure ...
- Impurities from interaction between API and  
Excipients



# IMPURITIES IN DRUG PRODUCTS

## Qualification thresholds for degradation products

Maximum daily dose	Qualification threshold
< 10 mg	1,0 % or 50 µg TDI whichever is lower
10 mg – 100 mg	0,5 % or 200 µg TDI whichever is lower
> 100 mg – 2 g	0,2 % or 3 mg TDI whichever is lower
> 2 g	0,15 %



# Quality aspects in Benefit-Risk balance

- Quality always will influence outcome of treatment and therefore Quality aspects should be included in the discussion about Benefit-Risk balance
- Quality aspects may be beneficial and important for the patients or may introduce additional risks



# How can we ensure the quality of Medicines ?

- Control over the entire chain of manufacturing and distribution of medicinal products
- Withdrawal of defective products
- Effective efforts against counterfeit and substandard products



# Strong National Medicines Authorities

