Lebanese Society for Quality and Safety in Health Care

الجمعية اللبنانية للجودة والسلامة الصحية

Public Health Issues of SUBSTANDARD MEDICINES

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RÉPUBLIQUE FRANÇAISE

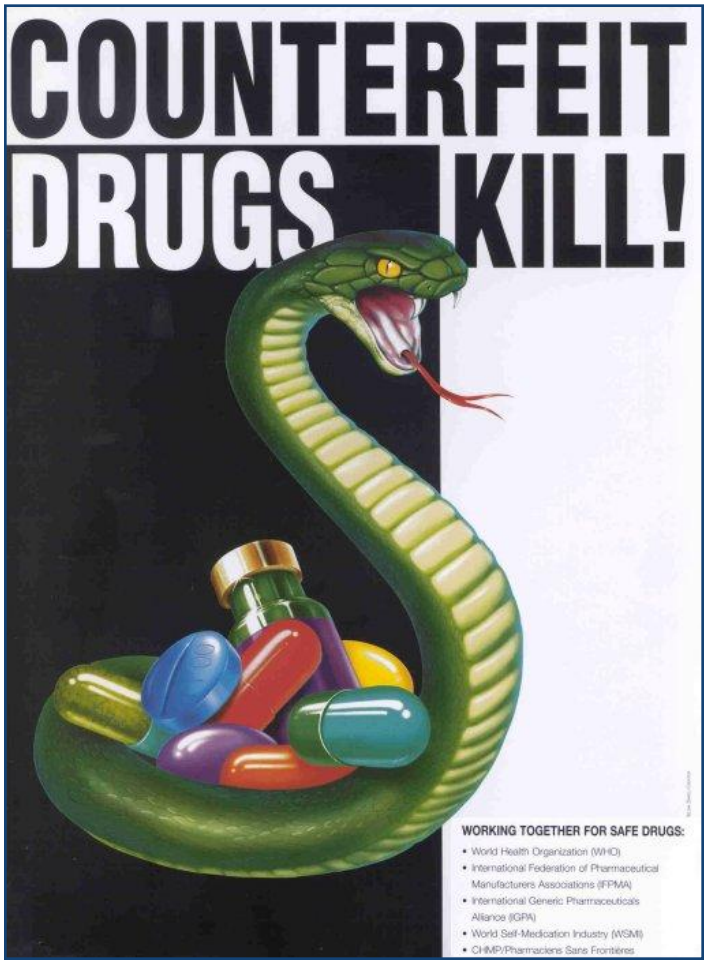
Is quality of medicines still Globally a problem?

- 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

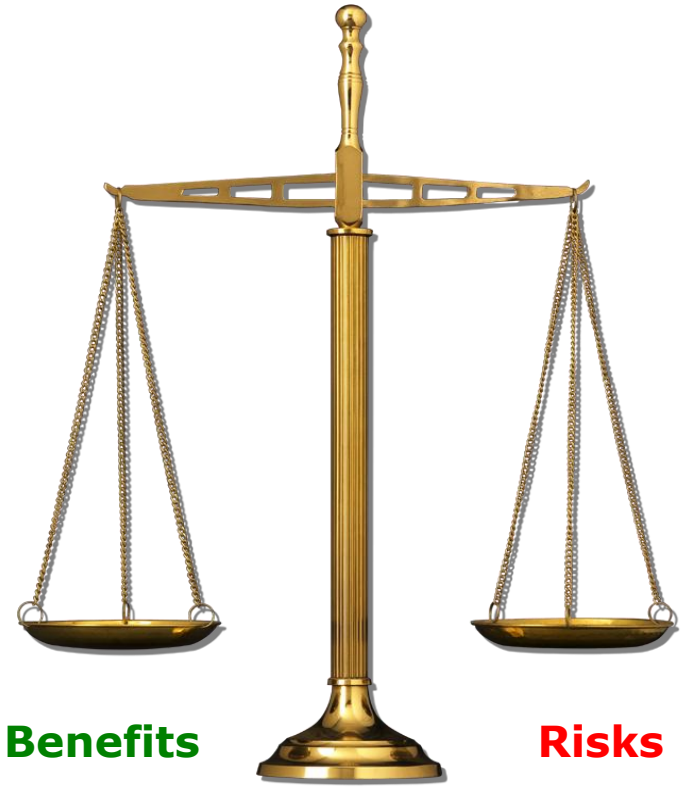
No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State

Criteria for Authorising Medicines

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

  of the Medicine

Criteria for Authorizing Medicines

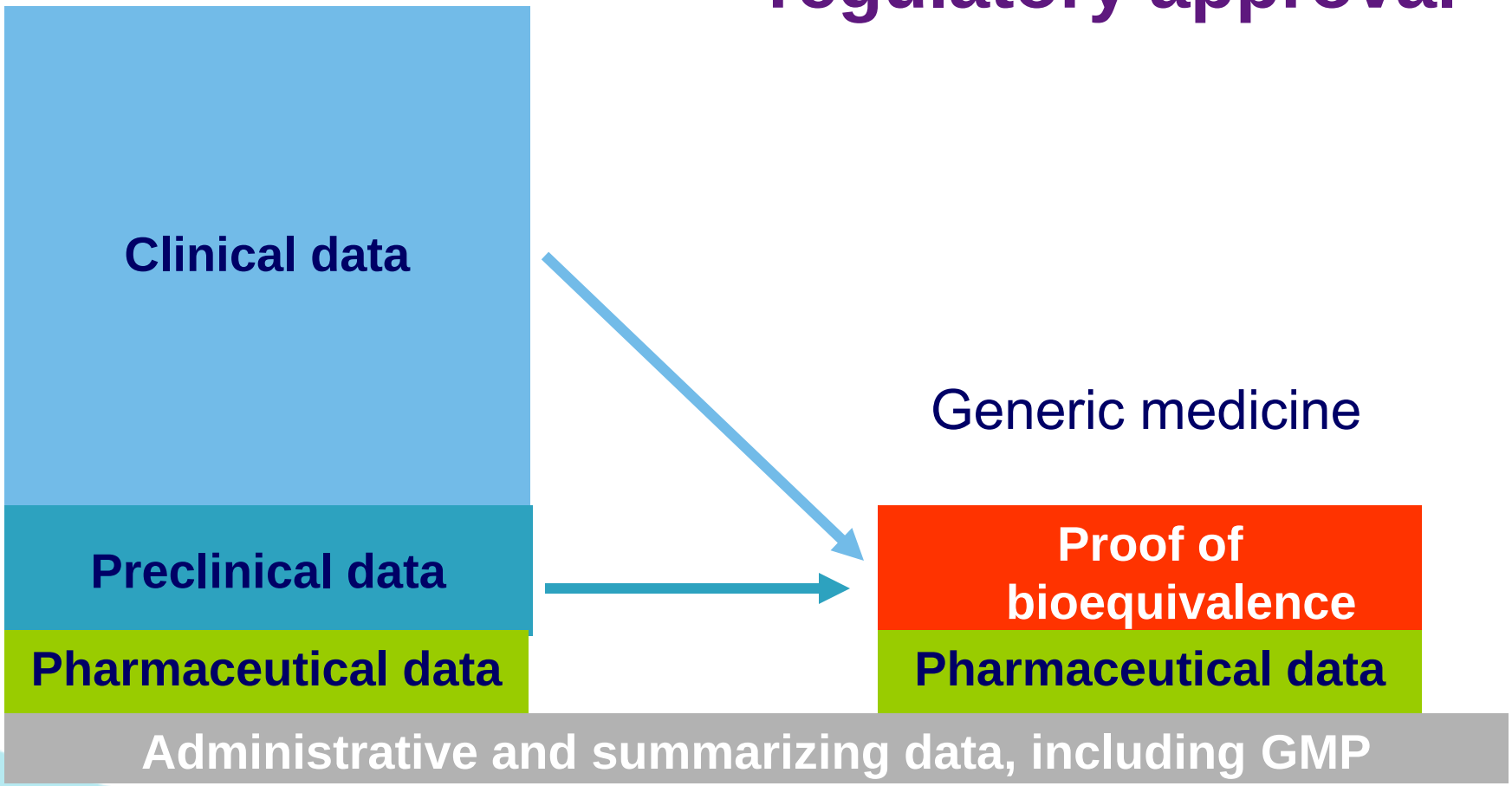


MA is granted when the Benefit-Risk balance of a product is positive, meaning that benefits from use of this product outweigh risks associated with its use.

Marketing Authorisation Applications

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

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
≤ 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
ROCHE (Switzerland)	< 0.1 %				< 0.1 %
Source 1 (KOREA)			< 0.1 %	< 0.1 %	< 0.2 %
Source 2 (INDIA)				0.17 %	0.17 %
Source 3 (CHINA)	< 0.1 %	0.95 %			0.95 %
Source 4 (CHINA)		0.95 %			0.95 %
Source 5 (CHINA)	< 0.1 %	0.92 %	0.1 %	0.47 %	1.49 %

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)
Class 1A: **Pt, Pd**	100	10	10	1	Pt: 70 *
Class 1B: **Ir, Rh, Ru, Os**	100**	10**	10**	1**	
Class 1C: **Mo, Ni, Cr, V** Metals of significant safety concern	250	25	25	2.5	Ni: 100 Cr (VI): 10
Class 2: **Cu, Mn** Metals with low safety concern	2500	250	250	25	
Class 3: **Fe, Zn** 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