Public Health Issues of SUBSTANDARD MEDICINES

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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

Clinical data

Preclinical data
Pharmaceutical data

Generic medicine
Proof of bioequivalence
Pharmaceutical data

Administrative and summarizing data, including GMP
3.2.2. DRUG SUBSTANCE:
3.2.2.1 General Information
3.2.2.2 Manufacture
3.2.2.3 Characterization
3.2.2.4 Control of drug substance
3.2.2.5 Reference standards or Materials
3.2.2.6 Container closure system
3.2.2.7 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

<table>
<thead>
<tr>
<th>Maximum daily dose</th>
<th>Reporting threshold</th>
<th>Identification threshold</th>
<th>Qualification threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 g/day</td>
<td>0.05 %</td>
<td>0.10 % or 1 mg/day intake whichever is lower</td>
<td>0.15 % or 1 mg/day intake whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g/day</td>
<td>0.03 %</td>
<td>0.05 %</td>
<td>0.05 %</td>
</tr>
</tbody>
</table>
## QUALITY OF TRIMETHOPRIM

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Impurities detected by HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rt min 2.8</td>
</tr>
<tr>
<td>ROCHE (Switzerland)</td>
<td>&lt; 0.1 %</td>
</tr>
<tr>
<td>Source 1 (KOREA)</td>
<td></td>
</tr>
<tr>
<td>Source 2 (INDIA)</td>
<td></td>
</tr>
<tr>
<td>Source 3 (CHINA)</td>
<td>&lt; 0.1 %</td>
</tr>
<tr>
<td>Source 4 (CHINA)</td>
<td></td>
</tr>
<tr>
<td>Source 5 (CHINA)</td>
<td>&lt; 0.1 %</td>
</tr>
</tbody>
</table>
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 which 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**

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

* 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**
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

<table>
<thead>
<tr>
<th>Maximum daily dose</th>
<th>Qualification threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mg</td>
<td>1,0 % or 50 µg TDI whichever is lower</td>
</tr>
<tr>
<td>10 mg – 100 mg</td>
<td>0,5 % or 200 µg TDI whichever is lower</td>
</tr>
<tr>
<td>&gt; 100 mg – 2 g</td>
<td>0,2 % or 3 mg TDI whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g</td>
<td>0,15 %</td>
</tr>
</tbody>
</table>
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

**EVALUATION (M.A Dossier)**

**ISPECTION**
- GMP, GLP, GCP ...
- Products related

**CONTROL**
National control Lab