New Frontiers in the Quality of Medicines

Workshop
Building a partnership for the investigation of counterfeit medicines

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Counterfeit of medicines an increasingly important issue for public health

- Need for better supervision
- Room for optimisation of current approaches
• Involvement of OMCLs is important
  – Investigations
  – Confirmation of suspect counterfeit

How to do it?
• Need of work sharing

• Need for rapid action
  – Proactive with interested stakeholders

• Need for skill / costly equipment
  – Libraries of results to ensure proper interpretation of testing data
  – Centres of expertise

• Building partnership:
  – Between authorities: Customs, police, health authorities
  – Between health authorities and industries
  • Access to essential information
    – Analytical procedure designed for the purpose
    – Finger print
    – Reference samples
• Networking is essential
  – Interactivity a prerequisite
  – Work sharing
  – Security of communication an absolute need
    -> appropriate data bases

Through specific contacts
Building a partnership for the investigation of counterfeit medicines

Experience and viewpoint of an OMCL

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Medical Products Agency
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OMCL – Official Medicines Control Laboratories

Role:
independent testing of

• medicines in market surveillance programs
• products with suspected quality defect, e.g. counterfeit medicines
OMCL-network

- 35 Countries
- 90 Laboratories
- The network is co-ordinated by EDQM, Council of Europe

OMCL network

- co-operation is based on mutual recognition
- has a uniform Quality Assurance systems based on ISO 17025
- common guidelines
- databases for communication and exchange of results
OMCL-network

- expertise in testing all kinds of medicines e.g. chemical, herbal, vaccines, blood products, biotech
- more than 1000 experts in the network
- benefits using the network, e.g. sharing results, saving resources and increasing the scientific knowledge

OMCL network in test of counterfeit medicines

- Perform test on medicinal products and API
  - identification
  - content
  - impurities
  - pharmaceutical parameters
Legal basis

- a number of countries have national legislation regarding sampling and analysis of medicinal products
- no uniform approach
- no legal basis for exchange of data between the various members of the network
- a common legal environment on counterfeit medicines would be helpful

Stakeholders and interactions

- Competent authority
- OMCL
- Police
- Customs
- Industry

Interdisciplinary interactions needed
Counterfeit medicines – global issue

• To combat counterfeit cooperation with industry (API and Medicines) will be necessary

OMCL needs reference material and exchange of analytical knowledge

OMCL network in test of counterfeit medicines

• ordinary laboratory instrument is often sufficient
• occasionally sophisticated and expensive instrumentation is needed, e.g. Masspectrometry, NMR and NIR
• laboratories acting as competence centres may be needed
OMCL network involvement in “counterfeit medicines”

Systems for exchange of information

• sample information
• tests results
• analytical methods

but not enforcement information

Examples of counterfeit testing at OMCL

• Viagra and Cialis
• Numerous of samples were tested in the Netherlands and in the UK
• Example from the Netherlands 2000 - 2004
• 400 samples tested
Examples of counterfeit testing at OMCL – Viagra samples

Total number of samples (325)

- Genuine (10)
- Counterfeit (92), falsification look-alike genuine
- Imitation (195), do not look like genuine but claim similar pharmacological effect
- Analogue (28), new similar type of active substance

Experince from the Swedish OMCL

Strategy

1. Samples from the Internet are taken in co-operation with the police
2. NMR; identity and quantification
3. LC-MS; confirm identity
4. LC; assay and impurity profile
Rimonabant

- medicine for weight loss
- at the time of sample collection the product was under assessment in the Central procedure
- sold on the Internet as food supplement

Rimonabant -1H-NMR
Rimonabant -LC

Rimonabant –LC-MS
Rimonabant - results

- the identity was confirmed using NMR and LC-MS
- the content was 18.0 - 21.3 mg/tablet (declared content 20 mg/tablet)
- the products are imitations
- the results are reported to the police

Tamiflu capsules from the Internet

German
Bulgarian
Tamiflu capsule - 1H-NMR

Tamiflu – LC impurity profile
Tamiflu capsules – results

• genuine product, verified by NMR and LC

• labelled in a foreign language

• the results are reported to the police

ViaMax power Tabs

• Ami-nord Gmbh, Bremen, Germany.
  – Imidazotriazinone, a precursor to Vardenafil.
  – BioNordica

\[\text{Imidazotriazinone} \rightarrow \text{Vardenafil}\]
Sample from Internet

ViaMax power Tabs

• Analysis
  – LC-UV-MS och LC-UV-MS/MS
  – NMR (\(^1\)H, \(^{13}\)C-APT, COSY, HSQC och HMBC).
ViaMax power Tabs

UV-spectrum of the unknown substance compared with sildenafil

Sildenafil

large peak LC

ViaMax power Tabs

Sildenafil

MS/MS

Product ionspectrum of m/z 475@ 35 eV

-192 Da

-164 Da

Unknown substance

MS/MS

Product ionspectrum of m/z 491@ 35 eV

-192 Da

-164 Da
ViaMax power Tabs

• Proposal
  – molar weight ok
  – UV can be explained
    • thiooxo compounds have higher UV max
  – MS/MS fragmentation can be explained
  – NMR-data support the proposed structure

Conclusion, national perspective

• The Swedish OMCL is well prepared both regarding equipment and competence in order to analyse samples of suspected counterfeit medicines
Conclusion OMCL perspective

• OMCL-network play an important role in the combat of counterfeit medicines
• International coordination of testing and sharing of test results will be helpful
• It may be of need to establish competence centres when the use of sophisticated testing methodology is necessary
• a common legal system would be helpful
API Counterfeiting**: WHO MAY BE INVOLVED?

- The API Manufacturer*
- The Trader/Broker exporting/importing/selling the API
- The Drug Product Manufacturer
- The Marketing Authorisation Holder

** Counterfeit APIs are active pharmaceutical ingredients for which source and/or quality are falsely represented on the label, on the Certificate of Analysis or otherwise

* Especially Commodity APIs for older products
WHAT CAN BE DONE?

• Effective Laws and Regulations must be implemented and enforced
• More API-focused inspections are needed in all markets
• Focus on the entire supply chain - seek out fraud and counterfeiting practices
• Sanctions must be tough and enforced
• Industry can work in partnership with regulators
• Report unusual labels, damaged/tampered with containers, suspected trading of illicit APIs
• Only use reputable brokers/traders
• Full transparency back to the API manufacturer
• Utilise analytical techniques i.e. fingerprinting

ROLE OF THE AUTHORITIES

• EDQM inspections: Many serious API issues observed in China & India. So coming authority inspection efforts should focus on producers, traders and users of APIs from such high risk regions
• National Authorities must collaborate across the supply chain
• Involve international policing agencies i.e. Interpol also in API matters
• Make sanctions very tough - withdraw involved MAs, prosecute and jail perpetrators
• Highlight those sanctioned
• Support and fund anti-counterfeit measures i.e. RFID
• Explore security checks at all borders
• Surveillance of integrity of API-part of supply chain with major focus on traders
RECENT DEVELOPMENTS

• Joint Position Paper issued by US/European Industry- 'Uneven enforcement leads to sub-par drugs and National Security Risk'-EFCG/SOCMA

• Written Declaration tabled by MEPs

• Position paper submitted by CEFIC-'Impact of fraud,counterfeiting and severe non-compliance on EU Medicines'

• Council of Europe-Moscow Meeting/Declarations

• European Parliament Symposium on Counterfeit of Pharmaceuticals-co-sponsored by CEFIC-May 2007

THE FUTURE?

• Difficult to apportion an exact percentage of counterfeit to API, however the gentamicin study would lead one to estimate that up to 30% of API used in older product comes from unknown sources

• The major fear- the so-called API time bomb:...It is e.g. estimated that annually 90,000 tonnes of paracetamol are consumed worldwide- this is equivalent to 180 Billion tablets..imagine the effects of a sub-standard product on this supply chain...many thousands could suffer, even die...the content of only one drum of API reaches a few thousand patients

• The time to act is now; Industry, Authorites and Governments must come together