New Frontiers in the Quality of Medicines

Workshop
Partnership developed within the Official Medicines Control Laboratories (OMCLs)

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Strasbourg, France
ROLE AND IMPORTANCE OF OMCLs

WHAT IS AN OMCL?

IN EUROPE:
- COMMON DEFINITION PROPOSED BY THE « OMCL NETWORK »

KEYS WORDS:
- ANALYSE SAMPLES OF MEDICINES
- ENSURE THAT LEGAL PRESCRIPTIONS ARE RESPECTED
- PUBLIC INSTITUTION
- FOR A COMPETENT AUTHORITY
- INDEPENDANTLY FROM THE MANUFACTURER
- ALSO CONTRIBUTES TO ACTIVITIES OF OTHER GOVERNMENTAL AUTHORITIES RELATED TO HEALTH PRODUCTS
ROLE AND IMPORTANCE OF OMCLs

GENERAL ORGANIZATION OF THE OMCL NETWORK

NATIONAL LEVEL
- EVALUATION / REGISTRATION
- INSPECTION
- OMCL(s)

EUROPEAN LEVEL
- EMEA London
- EDQM Strasbourg
- HMA(s)
- OMCL network
- BRP, CAP, MRP programmes
- OMCLs
- EU
- PHEUR
- PTS, MSS studies

NATIONAL PROGRAMMES

ROLE AND IMPORTANCE OF OMCLs

CONDITIONS OF EFFICIENCY

INTERACTIVITY

EVALUATION
- ASSESSORS BODIES

INSPECTION
- INSPECTORATES BODIES

CONTROL
- OMCLs

COMMON TOPICS OF INTERESTS
- PRIORITIES
- RISK ORIENTED STRATEGIES

**EXAMPLE OF INTERACTIVITY FOR THE BENEFIT OF PUBLIC HEALTH / GENERIC DRUGS**

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>INSPECTION</th>
<th>CONTROL BY OMCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARMACEUTICAL DOSSIER</td>
<td>MANUFACTURING SITE</td>
<td>CONTROL OF SAMPLES</td>
</tr>
<tr>
<td>BIOEQUIVALENCE STUDY</td>
<td>BIOEQUIVALENCE SITE/FILE</td>
<td></td>
</tr>
</tbody>
</table>

**ROLE AND IMPORTANCE OF OMCLs**

**THE RENEWED INTEREST FOR QUALITY CONTROL**

- GENERIC COMPOUNDS
- IMPURITIES IN ACTIVE INGREDIENTS
- NEW MANUFACTURING APPROACHES
- PARALLEL IMPORTATION
- NEW « INTEREST » (i.e.: herbal medicinal compounds)
- COUNTERFEITING...

**NATIONAL / EUROPEAN / INTERNATIONAL**

- INTEREST EXPRESSED BY AUTHORITIES AND MANUFACTURERS
- MORE THAN 80 OMCLs AVAILABLE
ROLE AND IMPORTANCE OF OMCLs
BENEFITS OF A NETWORK APPROACH

→ OPTIMAL USE OF TECHNICAL EXPERTISE : EFFICIENCY OF THE SYSTEM

→ LABORATORIES : TIME AND RESOURCES CONSUMING

→ COMMON TOPICS OF INTERESTS

→ SAME PRODUCTS AUTHORIZED

→ ALL THE NEEDS NOT COVERED

→ PREVENT THE RISK OF MAJOR IMBALANCE AMONG 27 MS

ROLE AND IMPORTANCE OF OMCLs
BENEFITS OF A NETWORK APPROACH

EXAMPLE

<table>
<thead>
<tr>
<th>PROGRAMME</th>
<th>FRENCH OMCL</th>
<th>RESULTS AVAILABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP 2001-2006</td>
<td>50</td>
<td>210</td>
</tr>
<tr>
<td>MRP 2006</td>
<td>38</td>
<td>238</td>
</tr>
</tbody>
</table>

→ BATCH RELEASE OF VACCINES
6 OMCLs → BR CERTIFICATES → 27 COUNTRIES
× MICROBIOLOGY
× PHYSICO-CHEMISTRY
× ANIMAL HOUSING FACILITIES
ROLE AND IMPORTANCE OF OMCLs
BENEFITS OF A NETWORK APPROACH

EXEMPLE OF COUNTERFEITING

1 PHARMACOLOGICAL CLASS
ALL THE AUTHORIZED PRODUCTION
« LIBRARY » OF THE AUTHORIZED PRODUCTION
IDENTIFICATION OF AN « UNKNOWN » PRODUCTION

HOW DO WE DO IF WE DO NOT COOPERATE?

ROLE AND IMPORTANCE OF OMCLs
CONDITIONS OF CREDIBILITY

→ A COORDINATION STRUCTURE
   EDQM
   DOCUMENTATION
   TRAININGS
   EXCHANGE OF INFORMATION

→ A STANDARD QUALITY ISO 17025
   MUTUAL JOINT AUDITS
   MUTUAL RECOGNITION OF CONTROLS

→ A FULL SUPPORT OF THE « PARTNERS »
   EMEA – HMAs – WHO
Control and testing of biologicals

Biologicals for human use are of central importance to public health
Vaccines and blood products are a striking example
Biologicals are products derived from biological sources
Control and testing of biologicals

- Nature of biologicals raises particular control questions and requires an eternal vigilance against their considerable potential hazards
- This is due to
  - Inherent variability of most of the products
  - Inbuilt opportunities for contamination with adventitious agents
  - Variability inherent in biological test methods

Control and testing of biologicals

- Quality control of biologicals covers four major areas:
  1. the product is sufficiently characterised with regards to its composition and potency
  2. the product does not contain impurities or contaminants that make it harmful
  3. the test performed have been carried out according to recognised standards
  4. the testing is carried out at appropriate stages of production
Types of control and testing of biologicals (1)

- **Preventive testing**
  - Checking manufacturer’s control methods, i.e. during the assessment of a marketing authorisation application
  - Pre-marketing testing, i.e. batch release of vaccines (human and veterinary) and blood products
  - Post-marketing testing (supervision of quality)

Types of control and testing of biologicals (2)

- **Reactive testing**
  - Independent testing of quality after corresponding pharmacovigilance reports
  - Experimental investigation of suspected counterfeit biologicals
Control and testing of biologicals

- OMCL/EDQM network plays a key role in checking and monitoring the compliance of biologicals with their marketing authorisation ensuring that:
  - the product is what it claims to be in terms of composition and potency
  - the product does not contain impurities/adventitious agents
  - the tests performed have been carried out according to E.P. standards
  - the tests are performed with “biological standard” reference material

Control and testing of biologicals

- Supervision of the quality of biologicals
  - Within the programme for Official Control Authority Batch Release (OCABR) of vaccines and blood products
  - Within the programme for Sampling and Testing of CAP’s
  - Close cooperation with the EMEA for CAP’s
  - By National Control Authorities
Specific issues related to immuno-biologicals for veterinary use

- Ways have also been found on a European level how to discover and avoid as good as possible the risks inherent to biologicals, e.g.
  1. quality assurance of the raw materials, in-process and final product tests by the manufacturers of veterinary vaccine batches
  2. GMP inspections

- Risk-oriented Official Control Authority Batch Release (OCABR) testing
- Long-term statistics by the Paul-Ehrlich-Institut demonstrate that the OCABR helps to detect deficiencies and risks that would not be revealed by any of the other safety assurance systems
Control and testing of biologicals

- Monographs on human and veterinary biological medicinal products in the European Pharmacopoeia help to guarantee consistent manufacture and testing throughout Europe.

- The European Pharmacopoeia has proven to be of greatest value for the production and control of biologicals.
Control and testing of nonbiologica ls (post-marketing surveillance)

Tom Wikberg
National Agency for Medicines
Finland
14 June 2007

Testing as part of surveillance

Marketing authorisation (pre-marketing) → Illegal

Industry → wholesaler → pharmacy → patient

GXP (pre- and post-marketing) → OMCL testing (post-marketing)

Pharmacovigilance (pre- and post-marketing)
Testing as part of surveillance

- Testing complement assessment of MA applications by verifying scientifically the feasibility of the methods for testing the quality of medicines.
- The reproducibility and reliability of production and the quality control of the pharmaceutical industries can be monitored through testing products put on the market. This complement the surveillance through inspections.
- Testing validates the effectiveness of the other surveillance activities: assessment, inspection, and pharmacovigilance.

Nonbiologicals vs. biologicals

<table>
<thead>
<tr>
<th>Nonbiologicals</th>
<th>Biologicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typically synthetic organic compounds MW 200 – 2000</td>
<td>Typically proteins MW 20 000 – 200 000</td>
</tr>
<tr>
<td>Often absorbed after oral dosing _ tablets, capsules, oral solutions etc.</td>
<td>Not absorbed through membranes, often destroyed in GI-tract _ peramens.</td>
</tr>
<tr>
<td>Structure well characterized and can be produced reproducibly in relatively pure form _ easy to identify .</td>
<td>Structure complex and variable _ more difficult to identify .</td>
</tr>
<tr>
<td>Efficacy related to the content of active pharmaceutical ingredient: and quality of pharmaceutical form</td>
<td>Efficacy of medicinal product: often determined by the biological activity = potency</td>
</tr>
<tr>
<td>Impurities may be toxic as such or after biotransformation .</td>
<td>Impurities may cause an immune response .</td>
</tr>
</tbody>
</table>
Quality requirements and specifications

- The quality requirements are set as part of the marketing authorisation and by the pharmacopoeia
- A specification is a set of criteria to which a substance/medicinal product should conform to be considered acceptable for its intended use.
- Specification:
  - list of tests
  - reference to analytical procedures
  - acceptance criteria
- The control of the quality of raw materials and finished products is primarily the responsibility of the manufacturer releasing the product on the market

Typical tests for nonbiologics

- **Chemical active substances**
  - Universal tests
    - identification
    - assay
    - impurities (synthetic)
  - Specific tests
    - particle size
    - polymorphic forms
    - enantiomeric purity
    - inorganic impurities
    - water
    - microbial limits

- **Medicinal products**
  - Universal tests
    - identification
    - assay
    - impurities (degradation)
  - Specific tests
    - dissolution
    - uniformity of dosage units
    - pH
    - microbial limits
    - endotoxins
Surveillance at EU and national level

- Centrally approved medicinal products (CAP)
  - EMEA has the responsibility to coordinate the supervision

- Nationally approved medicinal products
  - With EU and national level surveillance
    - Mutual recognition procedure (MRP)
    - Decentralised procedure (DCP)
  - With national level surveillance
    - Purely nationally approved
    - Special surveillance programs, e.g. samples taken from inspection sites

Centrally approved medicines
Centrally approved medicines

Co-operation in MRP/DCP product testing
Benefits of co-operation in OMCL testing

- For medicinal products with the same quality specifications in many countries, work sharing and co-operation enables the OMCLs to test a larger number of medicinal products per year!
- No single OMCL has the expertise / equipment to perform all possible tests. Within the OMCL-network almost every medicinal product can be tested!
- CAP
  - EMEA and EDQM utilize the existing OMCLs for testing
- MRP/DCP
  - Voluntary co-operation between OMCLs
  - Economical and efficient scheme including sample exchange
Benefits of sample exchange in MRP/DCP surveillance

Market surveillance studies

- Studies within the OMCL-Network
- Interlaboratory evaluation based on a common testing sample
  - transferability of testing methods
  - evaluation of interlaboratory variability of the method.
- Knowledge of the quality of groups of medicinal products of special interest
  - all participating laboratories take samples from the national market, test them, and report the results to be evaluated by the scientific adviser/EDQM
- E.g. active substances, herbals, groups of medicinal products, dosage forms…
## Outcome of testing

- Problems with the quality of products seldom seen
  - Typical problems: stability, content slightly outside the specified range, dissolution of extended release preparations.
  - Indicates that the present system for overall surveillance is effective
- Problems with the methodology used by the marketing authorisation holders are common
  - Indicates a need for more pre-approval testing, also for nonbiologics

## Future challenges in the field of nonbiologicals

- Priorities in OMCL-testing
  - Risk based approach?
- Illegal medicines (counterfeit drugs, internet, doping etc)
  - Co-operation with the customs and the police
- Scientific basis of tests as quality indicators
  - Pre-authorisation testing
Partnership developed within the OMCL Network

QA and PTS programme

Marta Miquel Figuerol
Karl-Heinz Buchheit
Silvia Muñoz Botella
EDQM, 14 June 2007

Quality Assurance Programme
OMCL Network

The Official Medicines Control Laboratory (OMCL) Network was established in the mid 90s, with the purpose of harmonisation and mutual recognition of the control tests performed at a national level.

The OMCL Network is currently composed of 70 laboratories located in 34 countries (31 European countries and 3 observer countries: Australia, Canada and Morocco).

Quality Management Systems in the OMCL Network

The OMCLs agreed that the Quality Management Systems (QMS) put in place in their laboratories should be harmonized and based on:

- ISO/IEC 17025: « General requirements for the competence of testing and calibration laboratories »
- OMCL Guidelines: created to respond to the specific activities of the OMCLs (drafted by groups of experts from the Network)
QA programmes in the OMCL Network

To guarantee this homogeneous approach in the implementation and maintenance of the QMS throughout the OMCL Network, several QA programmes have been put in place.

These QA programmes are coordinated by EDQM, Department of Biological Standardisation, OMCL Network and Healthcare (DBO).

QA programmes in the OMCL Network

MJA - MJV - TU - TV - PTS
## QA programmes in the OMCL Network

### Mutual Joint Audits (MJA)
Objective: to check compliance with ISO/IEC 17025 and with the specific OMCL guidelines requirements.
MJA are comparable to the audits performed by National Accreditation Bodies.

### Mutual Joint Visits (MJV)
Objective: to observe the QMS under development and give advice and recommendations for improvement.

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### Tutorials (TU)
Educational objective: to coach personnel on specific or general QA topics (performed at the OMCL site).

### Training Visits (TV)
Educational objective: members of an OMCL visit the facilities of another OMCL, with the aim of learning about technical or QA topics.
Proficiency Testing Schemes (PTS)

According to ISO/IEC 17025 (5.9), the laboratory shall have quality control procedures for monitoring the validity of tests and calibrations undertaken, e.g. by participating in interlaboratory comparisons or proficiency testing programmes.

EDQM-DBO organises PTS studies (both in the Physico-chemical and Biological fields), for laboratories that are members of the OMCL Network and also for non-members.

Note: participation in PTS is recommended at any level.
MJA and MJV in the OMCL Network
(Dec 1997 - June 2007)

TOTAL number of MJA and MJV in the OMCL Network
(Dec 1997 - June 2007)
TU and TV in the OMCL Network

Training courses for the OMCL Network
Training courses for the OMCL Network (2005-2007)

- General Quality Assurance (April 05): 54 participants from 26 countries
- Quality Assurance in the Chemical-Pharmaceutical field (Oct 05): 92 participants from 35 countries
- Quality Assurance in the Biological field (Feb 06): 112 participants from 29 countries
- Training course for technical auditors of the MJA Scheme (June & September 2006): 35 participants from 14 countries
- General Quality Assurance (September 2007)

OMCL Network QA BOOKLET
OMCL Network QA Booklet

Compilation of Quality Assurance documents, relevant for the maintenance of the Quality Management Systems in the OMCL Network:

1. SOPs to be used in the frame of MJA, MJV, TU, TV
2. OMCL Network Guidelines and other relevant documents

Publication of OMCL Guidelines
Go to EDQM website: http://www.edqm.eu
Go to: Downloads

- Publications
- Presentation material
- Reference standards
- Certification
- Events organised by the EDQM
- Press releases
- Press articles
- European Pharmacopoeia & PDG
- QMCL Activities & Guidelines
- HelpDesk
- Videos

PTS Programme
Contents

• Goals & Scope
• Organisation
• Method of Work
• Achievements
• Examples
• Plans

Goals (ISO/IEC Guide 43)

• Part of QA system
• Determination of performance of individual labs for specific tests
• Monitoring of labs’ continuing performance
**Scope**

- Physico-chemical methods
- Biological methods (no animal tests)
- Open to
  - OMCLs
  - Contract labs for OMCLs
  - Private labs (manufacturers)

**Organisation**

- Secretariat: EDQM/DBO
- Scientific Advisor: OMCL/EDQM Expert
- Sample procurement & processing: EDQM
- Sample testing: Scientific Advisor or EDQM
Method of Work (1)

- Selection of studies based on input from users, results previous studies, feasibility
- Appointment of Scientific Advisor (geographical distribution)
- Panel proposal
- Samples procurement/processing
- Panel check
- PTS study (10 - 90 participants)

Method of Work (2)

- Evaluation of results
- Report to participants for comments
  - Evaluation of each participant’s performance
  - Presentation of all data
  - Key information on methods
- Final report
- Follow-up activities
### Panel & Study

- Samples complying with EP
- Borderline- or non complying samples
- Pairs of identical samples
- Blinded
- Labs to use routine method for
  - Assay/test
  - Statistical evaluation

### Performance Evaluation

- Recalculation means, RSD
- Data summary, histograms, xy-graphs
  - Means, RSD
- Accuracy: consensus value
  - z-score, RSZ, RSSZ
- Repeatability
## Study Follow-up

- Additional samples for failing labs
- Feedback to EP Groups of Experts
  - Adaptation of monographs
  - Standards
  - Improvement of methods

## Achievements (1)

### Biological Studies

- 27 studies concluded since 1997
- 12 studies on vaccines, blood products
  - Potency assay: FVIII, FIX, influenza vaccine, Hep A Ig, acellular pertussis vaccine
  - SEC: Hib vaccine, albumins
  - Endotoxin in vaccines, heparins
  - Igs - protein content
- 12 studies on HCV-NAT
- 3 studies on B19-NAT
Achievements (2)

Physico-chemical Studies

- 54 studies proposed since 1997
- Liquid chromatography (assay and related substances): 14
- Titrations (all types): 10
- UV-VIS spectrophotometry: 7
- Gas chromatography (assay & residual solvents): 6
- Dissolution test: 4
- Other techniques: 14

Example

PTS Studies on HCV-NAT
**HCV-NAT: Results Since 1999**

**% undetected 100 IU/ml samples**

<table>
<thead>
<tr>
<th>Year</th>
<th>% Undetected</th>
</tr>
</thead>
<tbody>
<tr>
<td>017</td>
<td>50</td>
</tr>
<tr>
<td>019</td>
<td>69</td>
</tr>
<tr>
<td>029</td>
<td>27</td>
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<tr>
<td>050</td>
<td>0</td>
</tr>
<tr>
<td>054</td>
<td>5</td>
</tr>
<tr>
<td>061</td>
<td>4</td>
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</tbody>
</table>

**Plans**

- Cover all tests performed during OMCL batch release (if sufficient number of participants & no animal test)
- Accreditation after having settled in new building
Conclusion

PTS Studies
• help to improve performance of participants
• detect problems in application of monographs
• identify needs for standardisation