

# **Quality on the move at the EDQM**

**Lisboa, 11 October 2004**

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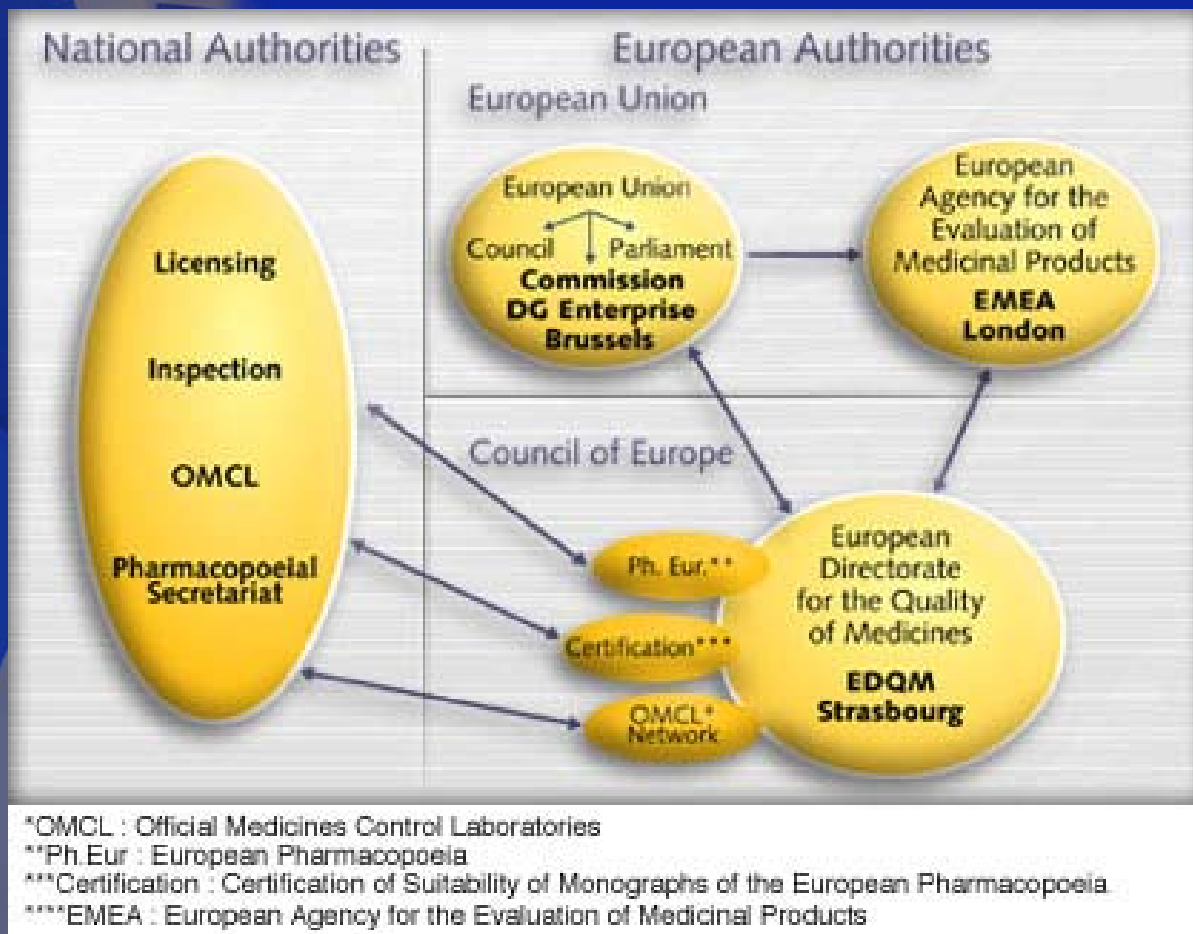
**Quality is never an accident.  
It is always the results of high intention,  
sincere effort, intelligent direction and  
skillfull execution ; it represents the wise  
choice of many options.**

**John Ruskin**

# AGENDA

- **Partnership European framework**
- **Standardisation Ph. Eur.**
- **Certification of suitability of monographs for API**
- **European Biological Standardisation Programme**
- **European OMCLs Network**

# EUROPEAN REGULATORY FRAMEWORK



# Partnership EDQM-CoE/EU

- EP Convention
  - 1964: EU Observer
  - 1975-2004: EU Dir, Reg. refers to EP
  - 1994: EU signs the Convention
- Contracts
  - 1992: Biological standardisation
  - 1994: setting up the Eur. Network of OMCLs
- 1997: EMEA post marketing control of centrally authorised products

# **MISSIONS OF THE EDQM <sup>(1)</sup>**

## **SECRETARIAT OF THE PHEUR COMMISSION**

### **Goals of the Pheur:**

- **Harmonise the Q and the C of medicines for human and veterinary use in Europe**
- **Contribute to the protection of Public health**
- **Promote free movement of medicines in Europe**

**Activities based on an international convention from the Council of Europe**

# Secretariat of Ph. Eur. Commission



# Ph. Eur. MEMBER & OBSERVERSHIP (including EU)



# Purpose of a monograph?

- **Public standard**
- **Independent evaluation of quality specification**
- **Applicable by all laboratories**
- **Regulators need uniform quality standard**
- **Sets standard for future products**

# The European Pharmacopoeia

## Recent development

- 5th Edition (2004), general monographs
- International harmonisation among JP, EP, USP
- Functionality-related characteristics in excipient monographs
- Control of impurities in API's
- The Certification scheme
- Electronic communication

# General monographs 1.1

- Cover classes defined by different criteria: production method, origin, risk factors
- Deal with aspects that cannot be treated in each individual monograph
- Residual solvents, polymorphism, pesticides in herbals, etc.

# Scope of monographs

- Aim is to cover all sources of a product approved for use in EP Member States
- Monograph does not necessarily cover other sources
- Suitability to be demonstrated (CEP)

# Ph. Eur.: Work Programme

Based on inquiries on needs of users

- Licensing authorities
- Industries, hospitals

Monographs

- Pharmeuropa (4 issues/year)
- Internet
- Scientific seminar

# Ph. Eur. and new technologies <sup>(1)</sup>

- **Products of Recombinant DNA Technology (5th Edition)**
- **Alternative methods for control of microbiological quality (Pharmeuropa No 16.4)**
- **Cell & gene Therapy (Pharmeuropa No 16.4)**

# Ph. Eur. and new technologies <sup>(2)</sup>

- Adenovirus vectors for human use
- Plasmid vectors for human use
- Poxvirus vectors for human use
- Human haematopoietic progenitor cells
- Gene transfer medicinal products for human use
- Bacterial cells used for the manufacture of plasmid vectors for human use (5.2.10)
- Numeration of CD34 + cells in haematopoietic products (2.7.23)
- Microbiological control of cell therapy products (2.6.27)

# EDQM Laboratory



# MISSIONS OF THE EDQM <sup>(2)</sup>

- **Publication of the Eur. Pharm. Texts (F+E)**
- **5th Edition, updated 3 times a year (Book, CD-ROM and Online versions)**
- **A forum: PHARMEUROPA (4 issues per year) & PHARMEUROPA BIO (2 issues per year) ;**
- **An official guideline: THE LIST OF STANDARD TERMS (pharmaceutical dosage forms, route of admin, containers) to be used in MA dossiers (27 languages) ;**
- **Technical guide for elaboration of monographs**

# 5th Edition



# Implementation dates

|                     | <b>Adoption</b> | <b>Publication</b> | <b>Implementation</b> |
|---------------------|-----------------|--------------------|-----------------------|
| <b>5 th Edition</b> | <b>11/2003</b>  | <b>July 2004</b>   | <b>Jan. 2005</b>      |
| <b>Suppl. 5.1</b>   | <b>03/2004</b>  | <b>Oct. 2004</b>   | <b>April 2005</b>     |
| <b>Suppl. 5.2</b>   | <b>06/ 2004</b> | <b>Dec. 2004</b>   | <b>July 2005</b>      |

# MISSIONS OF THE EDQM <sup>(3)</sup>

- Producing and distributing  
Pharmaceutical RS , Biological RS  
described in the standards

**More than 1600 reference substances  
available**

# **MISSIONS OF THE EDQM <sup>(4)</sup>**

**Certification of suitability  
of Ph. Eur. monographs**

**Participating in the European regulatory system by a centralised  
evaluation of the quality that the quality of material is suitably  
controlled by monograph (API & excipients)**

**Directives 2001/83/EC, 2003/63/EC & 2001/82/EC**

# How to demonstrate the suitability of monographs for a substance ?

- Improve up-date and transparency of monographs
- Procedure of centralised evaluation elaborated with
  - The licensing authorities in Europe
    - Recognition of its validity
  - Industries -> assurance on the protection of the information provided

**Certification of suitability**

# Certification Unit



# The CEP Steering Committee

- **Chairman of the Eur.Ph. Commission**  
**Chairmen of technical groups**  
**CPMP/CMV (QWP/BioWP/IWP/HPWP)**
- **1 représentant enregistrement Etats non UE**
- **1 représentant de l'EMEA (Inspection)**
- **1 représentant EDQM**
- **Chairs of TAB**

# Certification - Inspection

- Applicant to agree to be inspected
- Inspection by national inspector + 2nd from another country + EDQM
- 2 European inspectors outside Europe
- 1999 Pilot programme
- 2001 established inspection
- 48 sites inspected (18 in 2003, 7 in 2004)

# Inspection

- **Inspection inside and outside Europe**
- **Inspection of**
  - **Chemicals including sterile bulk**
  - **TSE risk**
  - **Manufacturers**
  - **Brokers**
- **Authorities notified of issues arising**

# Certification: benefits

- **Single assessment**
- **Uniformity of assessment**
- **Replaces Drug Master File**
- **Savings of time and cost**
- **Updating of monographs (impurities)**
- **Revision of monographs (new or replacement test methods)**

# MISSIONS OF THE EDQM <sup>(5)</sup>

## The European Biological Standardisation Programme (BSP)

### Goals

- The establishment of European working standards;
- The development and validation of new analytical methods;
- the validation of alternative methods in the framework of the 3Rs concept (Refine, Reduce, Replace animal experiments);

# Recent achievements

- **Viral markers for blood HCVRnA, B19**
  - Testing methods
  - Standard
- **Alternative methods**
  - Tetanus
  - Diphtheria/Serological methods
  - Hormones
- **Standards**
  - EPO, IGg, Fact VIII/IX IG antiD

**Established together with WHO, FDA**

# MISSIONS OF THE EDQM <sup>(6)</sup>

## The European network of the Official Medicines Control Laboratories (OMCL network)

Created in 1994 in close collaboration with the E.U.

### Goals of the OMCL network:

To develop exchanges and know-how, facilitate mutual recognition of controls of national laboratories and promote the future development of harmonised common standards and foster further work-sharing.

# Definition of OMCL

- Public Institution which **ONLY** performs laboratory testing for a Competent Authority, independently from the manufacturer, for medicinal products, prior to and/or after marketing for the general surveillance of medicines in relation to the safety of human patient and/or animals

# OMCL Network: composition

- **OMCL Network is composed of public OMCLs and, when appropriate, representatives of Competent Authorities**
- **Criteria :**
  - **establishing a formal QA System based on ISO 17025**
  - **Implementing European Pharmacopoeia**
  - **Independency (see definition)**

# OMCL Network: objectives

- Harmonise the administrative and technical activities of common interests
- Mutual recognition of national quality control tests
- OMCL tests samples of medicinal products and/or its components to check whether they comply with the specifications in the MA application or in official documents such as Ph Eur or specific guidelines

# OMCL Network - Where are we ?

already in place:

- Common QA system
- Official Control Authorities Batch Release with **formal** mutual recognition
- Centrally authorised products  
**true** work-sharing

# OMCL Network - Quality Assurance

- **Development and maintenance of QA system initiated in 1998**
- **Implementation of QA System based on**
  - **Commonly agreed standard Iso 17025**
  - **Peer review (audit)**
  - **Specific procedures**
  - **PTS (performance measurements)**

# OMCL Network - Work-sharing

- For techniques that are rarely used or require on-going use

**create centres of expertise**

- For other products **cut costs** by work-and information **sharing**

for e.g. Mutual Recognition products (MRP)

# MJA/MJV Programme

- **1999 - OMCL Network starts MJV/MJA system to help each other implementing and maintaining a Quality System**
- **Standard ISO/IEC 17025 was selected**
- **MJA are intended to evaluate the competence of the labs in an equivalent way to the External Accreditation Bodies**
- **MJA/MJV highly appreciated - sharing of technical knowledge, meeting other experts, independent evaluation**

# MJA Process <sup>(1)</sup>

- The interested OMCL makes an "Audit request" to EDQM Div. IV
- 5 types of Audit scope:
  - Blank audit (all elements covered, only recommendations given)
  - Initial audit (all elements of ISO 17025 are assessed)
  - Surveillance audit (only specific topics are covered)
  - Reassessment audit (every 5 years, all elements covered)
  - Follow up of non-conformities
- Audit team: one or more trained auditors from the OMCL Network + audit team coordinator from EDQM (+ experts if needed)
- Auditors sign a Confidentiality statement prior to the audit
- OMCL is requested to send QS documentation for evaluation

# MJA Process <sup>(2)</sup>

- **“Audit Notification” sent to the OMCL**
- **“Audit plan” agreed with the OMCL**
- **Audit check list based on ISO/IEC 17025 requirements**
- **Closing meeting: findings are discussed with OMCL Management**
- **Draft Audit Report is sent to OMCL for comments**
- **OMCL decides on corrective action + informs Division IV on its status**
- **When all non-conformities are solved, Div IV sends a MJA Attestation**

# Tutorial Scheme

- Tutors: qualified experts from the OMCL Network or from EDQM carrying out tuition in the field of interest
- Objective: to coach personnel on QA topics (general, specific, implementation of the Quality system, etc)

## TUTORIAL PROCESS

- Interested OMCL makes a “QA Tutorial request” to EDQM Division IV
- Coaching is given in the form of lessons, seminars, discussion groups, etc
- Tutorial planning established by Division IV + QA Officer of OMCL
- Tutors are bound by confidentiality agreement
- Tutorial Report is written on site: topics discussed + recommendations

# Proficiency Testing Studies PTS

# Proficiency testing

Proficiency testing is the use of inter-laboratory comparison for the determination of laboratory testing or measurement performance

Participation in proficiency testing schemes provides laboratories with an objective means of assessing and demonstrating the reliability of the data they are producing

Use as a complement of the QA system in place as requested by the standard ISO 17025

# Some data

- Scheme initiated in 1995 (OMCLs + EP lab)
- Open to non OMCL labs since 2000 (2004 bio)
- 3-4 (bio) & 5-6 (physico-chemical) studies/year
- Average of 13 (bio) and 45 (physico-chemical) participants/study
- Use of compendial methods: EP, BP& USP (for finished products only)

# Physico-Chemical PTS Studies in 2004

- Assay of tablets (UV-VIS)
- RELS by HPLC
- Water semi-micro determination
- Assay of tablets (titration)
- Chiral purity of essential oils by GC
- Acetic acid in synthetic peptides

# Physico-Chemical PTS studies for 2005

- Assay of injections (HPLC)
- Assay of suppositories (titration)
- Residual solvents (GC)
- Refractive index
- Assay of tablets (HPLC)
- Impurity profile

# Physico-Chemical PTS programme with WHO

- Contractual collaboration with WHO since 2000
- Programmes are run for a 1,5-2 year's period
- On going programme: 5 studies planned between July 2004 and June 2006
- 42 control laboratories of the WHO regional offices in Asia, Africa, South America, East Europe
- Protocol based on IP & using essential medicines

# Bio PTS Studies in 2004 (1)

**PTS052: Testing human blood (plasma pools) for contamination with B19 virus DNA by *quantitative* Nucleic Acid Amplification (NAT)**

- 1st PTS on topic (testing mandatory since 1/04)
- Participation OMCLs and manufacturers
- 1/2 available test kits not appropriate  
==> **information of kit manufacturer**
- feedback to users of EP and regulators

# Bio PTS Studies in 2004 <sup>(2)</sup>

## PTS054: Testing human blood (plasma pools) for contamination with Hepatitis B RNA by *qualitative* NAT

- Performed 1-2 per year
- Significant decrease of number of failing labs over time
- First participation of manufacturers

# Future Bio PTS studies 2004-5

- **PTS063: Endotoxin content of human heparin preparations**
- **PTS065: Serological potency assay of acellular pertussis vaccines**
- **HCV-NAT (as PTS054 but other virus genotypes)**
- **B19 NAT (as PTS052)**
- **Pre-kallikrein activator content of human albumin preparations**
- **Anti-D immunoglobulin: potency assay**

# General activities

## Market Surveillance Studies

### MSS

# MSS 2003/2004

**MSS017 - Matricaria flower**

**MSS020 - Aciclovir tablets**

**MSS021 - Amoxicillin granules and powders**

**MSS022 - Ibuprofen tablets**

**MSS023 - Omeprazole tablets and capsules**

# **MSS 2004/2005 <sup>(1)</sup>**

**MSS025 - Tablets for which subdivision is authorised**

**MSS026 - Erythromycin liquid preparations and erythromycin esters preparations**

**MSS027 - Equisetum stem**

**MSS028 - Products containing sulfasalazines**

**Type of products: tablets / suppositories**

**Assay and impurity profile**

**MSS029 - Trimethopim**

**Control of impurities in API and tablets**

# EU/EEA EUROPEAN NETWORK OF OMCLs

- **OCABR**
  - **Common approach of batch release**
    - Administrative procedure
    - 39 guidelines product specific
    - mutual recognition
- **CAP (centrally authorised products)**
  - **Sharing sampling and testing**
  - **Reports to EMEA**

**CAP**  
**Regulation 726/2004 & Sampling  
and Testing Programme for  
centrally authorised products  
article 57r**

# Objectives of sampling and testing... (1)

- To supervise the quality of medicinal products
- To confirm compliance of the medicinal product placed on the market with its authorised specifications
- To monitor the quality of the finished product in all parts of the distribution chain throughout the authorised shelf-life
- To investigate suspected quality defects of CAPs -when requested
- To assist in testing of counterfeits of CAPs -when requested

# Objectives of sampling and testing... (2)

- To make use of existing systems and resources
- To avoid duplication`
- Provide for work sharing
- Mutual recognition of testing results in the EEA

# Organisational challenges

- Partnership with EMEA/EDQM for co-operation with OMCL network
- Support of GMP inspectors through ad hoc GMP inspectors group
- Dedicated EMEA staff member appointed
- EDQM strenghtens coordination team
- Regular feedback through Advisory Group

# EMA responsibilities

- Responsible for choice of medicinal products
  - adopted by scientific committees
- Liaison with (co) rapporteur/working parties
- Communication with Marketing Authorisation holder
- Co-ordination of communication of follow-up measures
- Overall responsibility

# EDQM responsibilities

- **Coordination of EEA OMCL network**
- **Organisation of QA system**
- **Coordination sampling and testing**
- **Receipt and reviewing of documentation**
- **Reference material and specific reagent request**
- **Define sampling and select inspectorates**
- **Provide samples to selected OMCLs**
- **Review and summaries results, report to EMEA**

# MAH responsibilities

- Provision of documentation
- Clarification of issues
- Supplies of reference material/reagents
- Pay for samples through voucher system
- Explaining deviations
- Implementing necessary follow-up measures

# National Authority Responsibilities

- As (coo) rapporteur/assessor - selection of test and advising on implications of outcome for dossier
- As inspectors, sampling and taking into account results in national inspection programmes
- As OMLC members, performing tests and advising on outcomes

# Examples of findings <sup>(1)</sup>

- **Products within specification limits**
- **In some cases, difficulties in setting up the test protocols**
  - **Problems in method transfer**
  - **Difficulty to fulfil system suitability criteria**
  - **Unclear descriptions in test methods**
  - **Incorrect or missing formulas for calculations**

# Examples of findings (2)

- Questioning method sensitivity, precision and robustness
- Unclear specifications and impurity limits
- Discrepancies between specifications and referring analytical procedures

# Origin of samples

- **Routine GMP-inspection of a contract manufacturer**
- **Observation of a major GMP-deficiency due to insufficient testing of incoming APIs**
- **Sampling of the API & Bulk and finished product for analysis in OMCL**

# Conclusions

- **Working in a network: the 3C**
  - **Consultation**
  - **Collaboration**
  - **Co-ordination**