General Inspection Trends in Europe: Current Systems and Future Perspectives

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Topics...

1. Current Pharmaceutical Legislation
2. Inspection Systems
3. Types of Inspection in the EU
4. Former Programs with EU-Candidate Countries

Institutions & Cooperations

EMEA	European Agency for the Evaluation of Medicinal Products http://www.emea.eu.int	EC European Commission	Marketing authorization in centralized procedures
EDQM	European Directorate for the Quality of Medicines http://www.pheur.org	Council of Europe; inter-govern-mental	• EP monographs • Certificate of EP • OMCL network
PIC/S	Pharmaceutical Inspection Cooperation Scheme http://www.picscheme.org	Cooperation	Joint standards and trainings

1. Current Pharmaceutical Legislation

http:// pharmacos.eudra.org

Relevant European Legislation

Directives	Pharmaceuticals: 2001/83/EC (hum.) & 2001/82/EEC (vet.) GMP-Directives: 91/356/EEC (hum) & 91/412/EEC (vet)	transferred into 15 national member state laws
Regulation	EMEA, central authorization & supervision of medicinal products 2309/93/EC	directly binding
Decision	e.g. related to BSE/ TSE	directly binding
Guidelines/ Guidances/ „Soft Law“	GMP – Guide „Rules governing medicinal products“ Compilation of Community Procedures	current standard

Modification & Review Process EC Pharmaceutical Legislation

1. Modification of Directive 2001/82/EC on the Community Code relating to medicinal products for **human use**,

2. Modification of Directive 2001/83/EC on the Community Code relating to medicinal products for **veterinary use**

3. Modifications of Council Regulation (EEC) **No.2309/93**

Modification of Human Directive
Article 47*

- Detailed GMP guidelines for active substances used as starting materials

- Commission to publish guidelines on
  - format and content of authorization
  - inspection reports
  - format and content of GMP certificate

* veterinary directive correspondingly

Modification of Human Directive
Articles 46 & 46a*

- GMP for active substances used as starting materials requested as a necessary provision for manufacturing authorization

- with respect to
  - total & partial manufacture
  - import

- for wholesalers, brokers, traders for e.g. processes as
  - dividing up
  - packaging

* veterinary directive correspondingly

Modification of Human Directive:
Supervision & Sanction - Article 111*

Inspection Request	Responsibilty
• Member State (MS) • Commission • EMEA	Competent MS authority
• Starting material manufacturer • EDQM in the context of CEP (via Commission or EMEA)	

* veterinary directive correspondingly

News in EC GMPs (Annexes)

6	Manufacture of Medicinal Gases	Rev. 07/2002
13	Manufacture of Investigational Medicinal Products	Currently under rev.
14	Manufacture of Products derived from Human Blood or Human Plasma	Rev. 10/2000
15	Qualification and Validation	Rev. 07/2001
16	Certification by a Qualified Person and Batch release	New 07/2001
17	Parametric Release	New 07/2001
18	GMP for APIs (ICH Q7a)	New 07/2001

Inspection Systems

References for Inspectorate Quality Systems

- PIC/S Quality System Requirements for Pharmaceutical Inspectorates (PI 002-1)
- EN 45000 - Series
- ISO 9000 - Series
- Compilation of Community Procedures
- EU Joint Audit Program

Compilation of Community Procedures

- Rapid alerts, recalls
- GMP inspections:
  - » Conduct
  - » Third country inspections
  - » Training of inspectors
- GMP inspection report format
- Format for manufacturing authorization
- Exchange of information within the EU
- Batch certificates in the context of an MRA
- Inspections within the centralized procedure

European Expert Cooperation

Besides formal cooperation in the legislative process:

- Ad hoc Working Groups of GMP/ GCP Inspection Services hosted by EMEA
- Working Groups at EMEA
- Exchange between EU and PIC/S
- European Network coordinated by EDQM

Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP) by EDQM

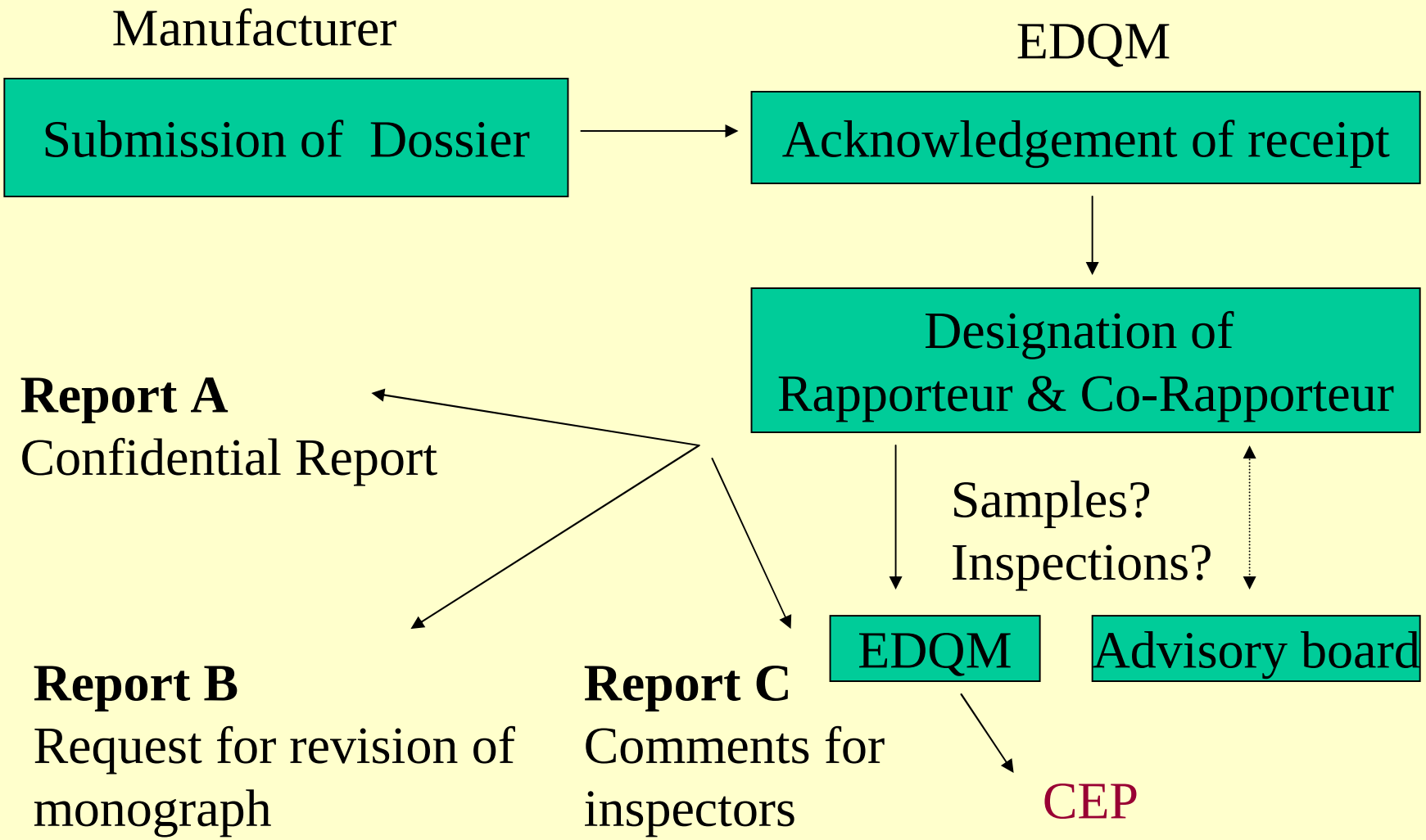
Manufacturer must ensure that ...

- all possible impurities and contamination from this particular route of manufacturer (including source material) can be fully controlled by the monograph.

CEP certifies that ...

- by applying the relevant monographs of European Pharmacopoeia (EP) ...
- it is possible to check whether or not the quality of the substance is suitable for use in medicinal products.

CEP - Procedure



Types of Inspections in the EU

Pre Marketing Authorization GMP Inspections

- Pre manufacturing authorization inspection
- Dossier related inspections
  (up to Member States legislation)

Post Marketing Authorization GMP Inspections

- *Routine inspection*
  (every 2 – 3 years with the scope of covering all production areas every 5 years)
- *Product specific* inspection
- Inspections *related to importations*
  (in third countries)
- *For cause* inspections (e.g. in case of known product defects)

Inspections in the Context of a Centrally Authorized Product

- *Product specific inspections*
  - Pre Approval:
    - GMP and dossier related
  - Post Approval:
    - Routine Inspection (every 2-3 years)
    - For Cause Inspection
- *Lead Inspectorate from EU authority responsible for importing site*

(Former) Programs with EU Candidate Countries*

* Maybe this could be a model for „Mediterranean Sea“ surrounding countries ?

PHARE - Program (Regulation 3906/89)

Financial and technical cooperation program of EU with central and eastern European countries

- Implementation of European legislation
- Support of institutions
- Support of investment
- Twinning programs
- Joint programs

Programs in GMP...

- ***PECA:***
  Protocol to the Europe Agreement on Conformity Assessment and Acceptance of Industrial Product
  - „MRA“ with EU Candidate countries

- ***PERF:***
  Pan European Regulatory Forum
  http://perf.eudra.org
  - Joint Training Activities (main focus: GMP)

- ***CADREAC:***
  Collaboration Agreement of Drug Regulatory Authorities in European Associated Countries
  - Main focus: marketing authorizations

PECAs – Objectives...

Objectives comparable to those with MRAs:

- Standardized batch certificates
- Exchange of GMP certificates
- No requirement for retesting upon import in EU

... in the view of a future EU membership

PERF - Objectives ...

- Install regular cooperation
- Ensure joint training
- First steps to introduce
  - EU-legislation
  - Harmonize systems with the EU

on the long term:

Mutual recognition of authorities

Mutual recognition of marketing authorizations

Steps in PERF

1. Implementation of EC legislation related to medicinal products
2. GMP Training
3. Pharmaco-vigilance/ RAS
4. Marketing authorization
   Assessment of dossiers
5. Telematics

The End or
The Beginning?