General Inspection Trends in Europe: Current Systems and Future Perspectives

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Topics...

2. Inspection Systems
3. Types of Inspection in the EU
4. Former Programs with EU-Candidate Countries
<table>
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<th>Institutions &amp; Cooperations</th>
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<tr>
<td><strong>EMEA</strong></td>
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<td>European Agency for the</td>
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<tr>
<td>Evaluation of Medicinal</td>
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<tr>
<td>Products</td>
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<tr>
<td>[<a href="http://www.emea.eu.int">http://www.emea.eu.int</a>]</td>
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<td><strong>EDQM</strong></td>
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<td>European Directorate for the</td>
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<td>Quality of Medicines</td>
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<td>[<a href="http://www.pheur.org">http://www.pheur.org</a>]</td>
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<td><strong>PIC/S</strong></td>
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<td>Pharmaceutical Inspection</td>
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<td>Cooperation Scheme</td>
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<tr>
<td>[<a href="http://www.picscheme.org">http://www.picscheme.org</a>]</td>
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</table>

http://pharmacos.eudra.org
### Relevant European Legislation

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

<table>
<thead>
<tr>
<th>Inspection Request</th>
<th>Responsibility</th>
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<tbody>
<tr>
<td>• Member State (MS)</td>
<td>Competent MS authority</td>
</tr>
<tr>
<td>• Commission</td>
<td></td>
</tr>
<tr>
<td>• EMEA</td>
<td></td>
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<tr>
<td>• Starting material manufacturer</td>
<td></td>
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<td>• EDQM in the context of CEP (via Commission or EMEA)</td>
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* veterinary directive correspondingly
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<th></th>
<th>Description</th>
<th>Date</th>
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<tbody>
<tr>
<td>6</td>
<td>Manufacture of Medicinal Gases</td>
<td>Rev. 07/2002</td>
</tr>
<tr>
<td>13</td>
<td>Manufacture of Investigational Medicinal Products</td>
<td>Currently under rev.</td>
</tr>
<tr>
<td>14</td>
<td>Manufacture of Products derived from Human Blood or Human Plasma</td>
<td>Rev. 10/2000</td>
</tr>
<tr>
<td>15</td>
<td>Qualification and Validation</td>
<td>Rev. 07/2001</td>
</tr>
<tr>
<td>16</td>
<td>Certification by a Qualified Person and Batch release</td>
<td>New 07/2001</td>
</tr>
<tr>
<td>17</td>
<td>Parametric Release</td>
<td>New 07/2001</td>
</tr>
<tr>
<td>18</td>
<td>GMP for APIs (ICH Q7a)</td>
<td>New 07/2001</td>
</tr>
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</table>
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

Manufacturer

Submission of Dossier

EDQM

Acknowledgement of receipt

Designation of Rapporteur & Co-Rapporteur

Samples? Inspections?

Report A
Confidential Report

Report B
Request for revision of monograph

Report C
Comments for inspectors

EDQM
Advisory board

CEP
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

Ø Product specific inspections
– Pre Approval:
  • GMP and dossier related
– Post Approval:
  • Routine Inspection (every 2-3 years)
  • For Cause Inspection

Ø 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...

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

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

Ø **CADREAC:**
Collaboration *Agreement of Drug Regulatory Authorities in European Associated Countries*
Ø 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 ...

Ø Install regular cooperation
Ø Ensure joint training
Ø First steps to introduce
  Ø EU-legislation
  Ø 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?