The Quality System for Drugs in Germany

Prof. Dr. Harald G. Schweim
Head of Department for Drug Regulatory Affairs
Institute for Pharmacy, University of Bonn

Former President of the German Federal Institute for Drugs and Medical Devices (BfArM)
Former Director of the German Institute of Medical Documentation and Information (DIMDI)
## Steps for a quality system

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>1996</td>
<td>Decision for a quality system</td>
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<tr>
<td>1999</td>
<td>Draft documents for a Quality Assurance System in GMP</td>
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<td>2000</td>
<td>Approval of Quality Policy</td>
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<td>1999</td>
<td>Implementation and Test Phase</td>
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<tr>
<td>2001</td>
<td>First Revision of Documents; ongoing</td>
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</table>
| 2005 | Extension of System planned for supervision of  
- GCP  
- veterinary medicinal products  
- wholesalers  
- pharmacies |
Underlying standards

1. PIC/S: Recommendations on quality system requirements for GMP inspectorates (PH 7/94; current updated version http://www.picscheme.org)

2. European Norms
   EN 45004 (1995)
   EN 45012 (1989)

3. DIN/ISO Norms
   ISO 9002 (1994)

EU- Compilation of Community procedures cover...

- Training of inspectors
- Manufacturing authorisations
- Inspection planning
- Inspection performance, follow-up
- Inspection report
- Action in cases of non-compliance/ defect products (RAS*)
- Sampling
- Internal Audits

*Rapid Alert System
Structure of Quality System

- Policy Statement
  - Statement for quality policy
- Quality Management Manual (QMM)
  - 17 Quality guidelines
- Quality Assurance Manual (QAM)
  - SOPs AIMS
QM-Manual: Quality Guidelines

- Frame conditions for a detailed quality system (responsibilities, organisation and management, personnel, documentation, change control, inspection systems, equipment, quality manuals, transparency, audits, complaint handling, sub-contracting, cooperation, sampling and testing, certificates)

- Decided and approved on political level
Quality Guidelines (1)

1. Responsibility of the upper management
2. Administrative provisions
3. Organisation and management
4. Personnel
5. Documentation
6. Change control
7. Inspection procedures
8. Required equipment / resources
9. Quality assurance manual
10. Confidence building and transparency
Quality Guidelines (2)

11. Internal quality audit and regular checks (management review)
12. Administrative actions for deficiencies and defects
13. Handling of mistakes, complaint management
14. Delegation of tasks
15. Licensing
16. Cooperation
17. Testing of samples
QA-Manual: SOPs /Aide mémoires

• **32 SOPs (Standard Operating Procedures)**
  (qualification and training of inspectors, manufacturing / import authorisation, inspection performance, inspection planning, certificates, ...)

• **8 Aide mémoires**
  (sterile drugs, biotechnology, computerized systems, blood products, active ingredients, ...)

• *Developed on an expert level*
Specific Procedures
Staff

- 041101 training and designation of GMP inspectors
- 041102 ongoing training
- 041105 job descriptions
- 041106 appointment of QA responsibilities
- 041110 assessment and maintenance of qualification
- 021101 avoidance of conflict of interest
Inspections

071101 inspection plan
071102 conduct of inspections
071108 inspection report
071107 Site Master File
071106 teams
071111 sampling
Aides memoire
Aides mémoire for Inspections

- 071201 inspection of manufacturers
- 071205 inspection of blood banks
- 071207 API manufacturers
- 071210 biotechnology
- 071206 manufacturers of sterile products
- 071211 qualification and validation
- 071212 computerised systems
Quality Defects

121101 management of drug risks/ incidents, consumer complaints, other complaints

121103 evaluation of deviations, deficiencies and defects

121104 corrective action in case of defects and deficiencies
Authorisations/Certificates

- 151101 manufacturing authorisation
- 151102 import authorisation
- 151103 certificate acc. section 72a AMG
- 151104 WHO certificate
- 151106 certificate for API
Drug Testing

171101 official testing of samples

171105 validation of analytical procedures

171106 OOS results
041101 Training and Designation of GMP Inspectors

1. Basic qualification: pharmacists
   veterinarian (only for vet. prod.)

2. Baseline Training: 2 years in an inspectorate
   of which 6 months may be in
   OMCL, Länder ministry,
   Federal Ministry, quality lab (ZLG)

3. Theory: as in „Compilation of
   community procedures...“

4. Practical training: at least 10 joint inspections
   with senior inspector

5. Final exam inspection

6. Formal designation
041102 Ongoing Training

1. At least 10 days per year, e.g.:
   • Conferences (e.g. PIC/S, commercial conferences)
   • German annual conference
   • Expert group trainings
   • Joint inspections/joint visits
   • Local SOP training sessions

2. Formal documentation in personal file
041110 Assessment and Maintenance of Qualification

- Every 5 years by head of inspectorate
- Assessment may be covered by:
  - Quality audit
  - Evaluation of inspection reports
  - Participation in inspections
- Possible actions:
  - Specific training
  - Participation in inspections in other inspectorates
  - Suspension or revocation of designation
SOP 07111102: Sampling

• Sampling plan by OMCL in cooperation with inspectorate
• Analytical evaluation of „risk products“ within 5 years after approvals
• „Risk products“:
  – New chemical entity
  – API with narrow therapeutic range
  – API with low stability
  – Dosage form with specific technological properties/ problems
Audit Systems 111101: Audits

1. Subject: Inspectorates

2. Biannual cycle: Organisation
   Procedures
   Quality System

3. Auditors: at least 2
   at least 1 GMP inspector

4. Corrective Action: to be proceeded to management
   to be evaluated by auditors
Inspections of API* manufacturers in Germany

**Legal requirements:**

- Under scope of centralised procedure
- National level:
  - only APIs of human and animal origin; biotec APIs
  - After publication of Ordinance: all APIs

**Practical implementation**

- Voluntary inspections of API manufacturers
- Voluntary 3rd country inspections

* Advanced Pharmaceutical Industry
Conclusions:
What we learnt about the process...

• to give enough time for discussions on all levels
• to make sure that all parties involved have enough time to make contributions
• to make sure that contributions are clearly evaluated
• to allow for 70% accuracy at the beginning
• to allow for a pilot phase in order to collect practical experiences
• to intensively monitor the implementation phase
• to adjust immediately where necessary
Thank you for your attention!