Regulatory and Legal Basis for Good Manufacturing Practices

APV Training Course

GMP Requirements

June,10th to11th 2004

Istanbul, Turkey

Dr. Jürgen Mählitz
GMP Inspector
District Government of Swabia
Fronhof 10
D-86152 Augsburg
Germany

First, who am I?

- German citizen
- Working for the Regional Government of Swabia for almost two years
- Previously worked
    - for more than two years at Hoffmann La Roche, Bale,Switzerland as Head of Laboratory for powder milling and analyzing
    - for more than two years at GGU GmbH as Head of Production;development, scale up and production of a new dry powder inhalation system
- PhD in Pharmaceutical Technology/Pharmacology

Aims of EU-GMP (1)

- guaranteeing that manufacturers of medicinal products will consistently and reproducibly manufacture products of a high predefined quality and standard
- protecting public health against pharmaceuticals of substandard quality
- providing an operational system for the recall of defective medicinal products

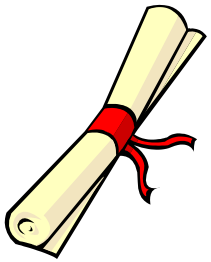
Aims of EU-GMP (2)

- Contribution of a single market for pharmaceuticals within the EU by elimination of duplicate laboratory testing and inspection
- supporting both of the European authorisation procedures for medicinal products

Germany

The Federal Republic of Germany

- **structure defined in the Basic Law (Constitution)**
- **16 Laender**
- **all together forming the Federal Republic**
- **competence of Federation and of the Laender**



Basic Law *(„Grundgesetz“)*
-The German Constitution-

23 May 1949

- **defines functions of the state bodies**
- **distribution of competence between Federation and the Laender**
- **Execution of national power and ful-filment of national duties on Laender level (Art. 30 Basic Law)**

Federation  **Laender**

German Basic Law

- **<u>Federal Laws</u> in areas of common interest (e.g. Drug Law, Law on Medical Devices, Transfusion Act)**
  - **executed by the Laender as matters on their own (Art. 84) on basis of Laender laws**
- **<u>Laws on level of the Laender</u>**

German Drug Authorities

Structure and Organisation

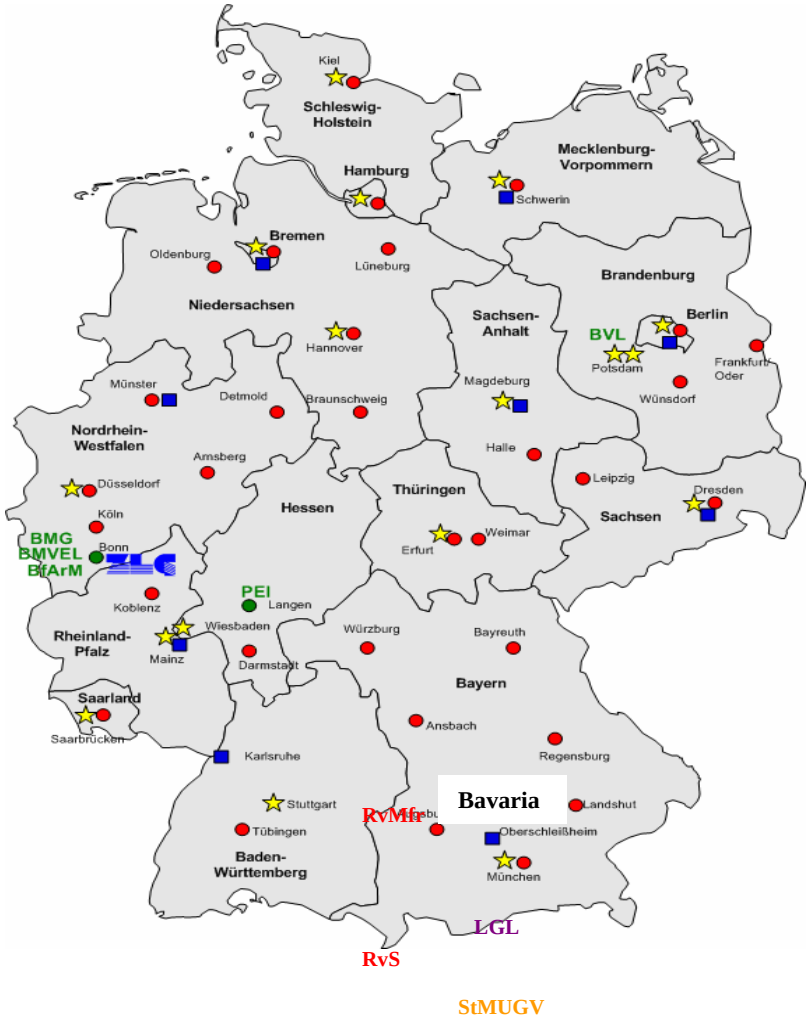
Federal level:

Federal Ministries

Laender level:

16 Laender => Ministries

Responsibilities in Germany



- BMGS German Ministry of Health
  - "Bundesoberbehörden"
    - BfArM
      - Marketing authorisation, (general)
    - PEI
      - MA for blood, sera, vaccines etc.)

- ✸ 16 Federal States Ministries ("Laender")
  - ✸ (in Bavaria StMGUGV, Munich)

- ⇔ with 1 Central Co-ordination Unit (ZLG)

in Bavaria

- 7 Regional Governments (e.g. RvS)
  - Manufacturing and Import Licenses
  - Supervision of companies
  - WHO Certificates
- ■ Laboratory (OMCL Oberschleissheim)
- ⇔ with 1 Central Co-ordination Unit (LGL)

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 med. products 2309/93/EC	directly binding
Decision	e.g. related to BSE/ TSE	directly binding
Guidelines/ Guidances/ „Soft Law“	GMP – Guide „Rules governing med. products“ Compilation of Community Procedures	current standard

Agencies of the EC

Cedefop	**European Centre for the Development of Vocational Training**
EUROFOUND	**European Foundation for the Improvement of Living and Working Conditions**
EEA	**European Environment Agency**
ETF	**European Training Foundation**
EMCDDA	**European Monitoring Centre for Drugs and Drug Addiction**
EMEA	**European Agency for the Evaluation of Medicinal Products**
OHIM	**Office for Harmonisation in the Internal Market (Trade Marks and Designs)**
EU-OSHA	**European Agency for Safety and Health at Work**
CPVO	**Community Plant Variety Office**
CdT	**Translation Centre for the Bodies of the European Union**
EUMC	**European Monitoring Centre on Racism and Xenophobia**
EAR	**European Agency for Reconstruction**
EFSA	**European Food Safety Authority New**
EMSA	**European Maritime Safety Agency New**
EASA	**European Aviation Safety Agency New**

Compilation of Community Procedure

- Rapid alerts, recalls
- GMP inspections:
  - »Conduct
  - »Third country inspections
  - »Training of inspectors
- GMP Inspection report format

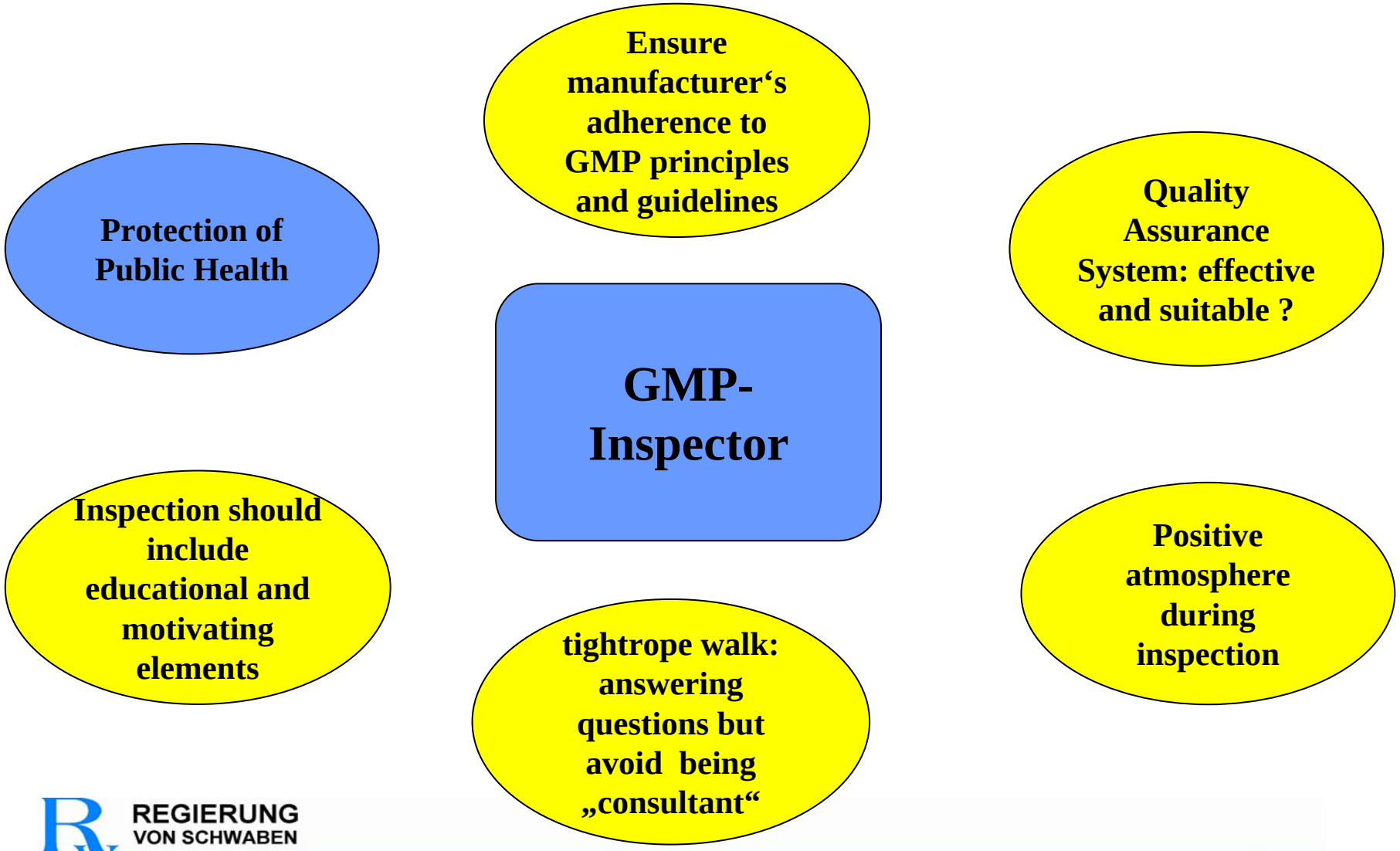
Compilation of Community Procedure

- Format for manufacturing authorization
- Exchange of information within the EU
- Batch certificates in the context of an MRA
- Inspections within the centralized procedure

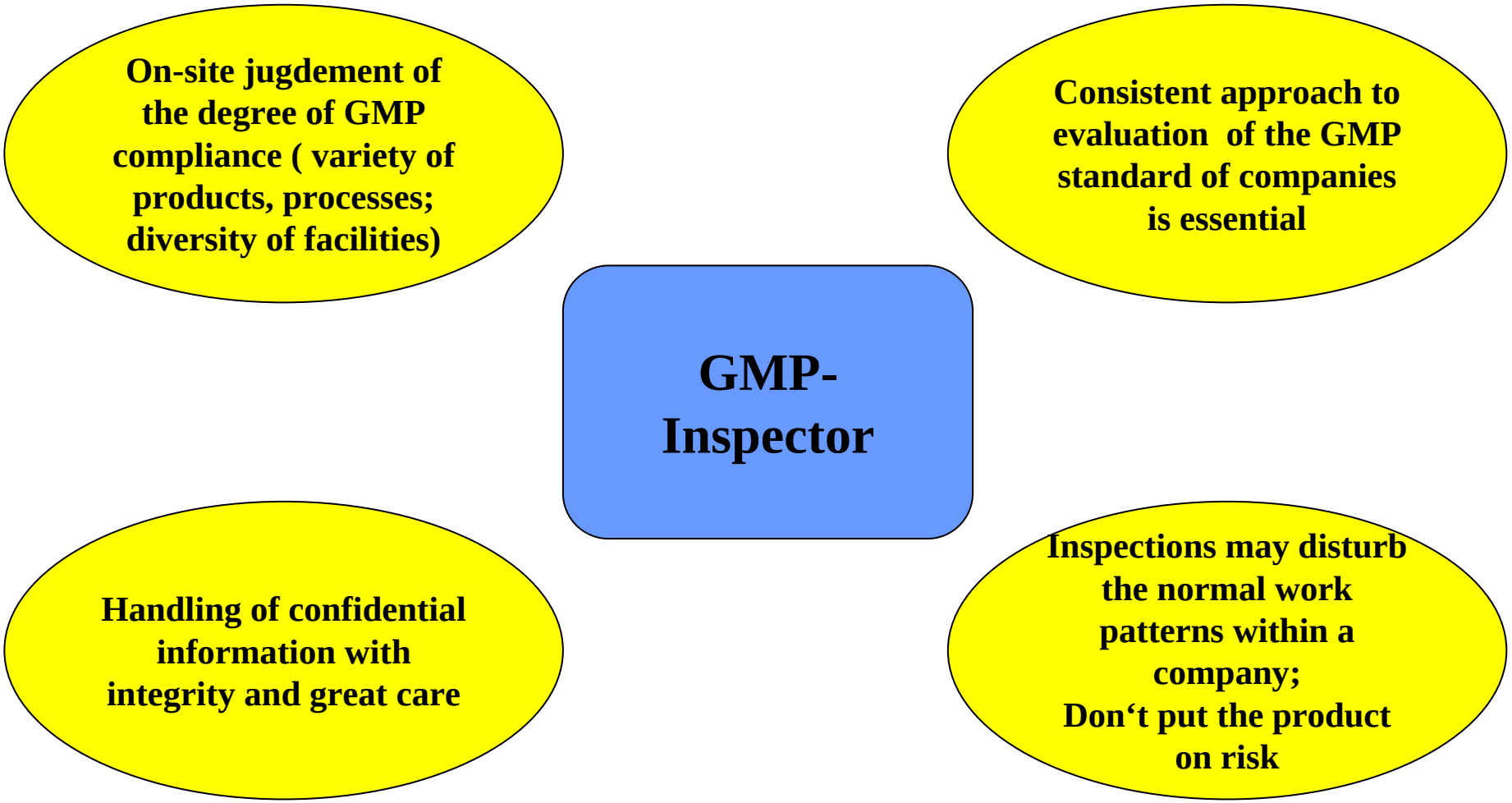
Compilation of Community Procedure

Verknüpfung mit Compilation of Communitiy Procedures 2001.pdf.lnk

General Considerations on Inspections (1)



General Considerations on Inspections (2)



General Aspects of National GMP Inspections (1)

- Checking GMP-compliance of manufacturers
- requirements are defined in 2003/94/EC (replaces 91/356/EEC) and 2001/83/EC for manufacturing of human medicinal products
- 91/412/EEC and 2001/82/EC for veterinary medicinal products

General Aspects of National GMP Inspections (2)

- Inspections should be carried out at least every two years
- large companies may be visited department by department being completed at least every five years
- interval between inspection should never exceed 3 years

Types of Inspections (1)

- National Inspections
- Inspections in third countries
- inspections requested by EMEA (CPMP/CVMP) due to a centrally authorised medicinal product

Types of Inspections (2)

- General GMP-Inspection
- Re-Inspections
- product- or process related inspections
- inspections caused by an actual event (in this case the visit could be unannounced)

Conditions for unannounced inspections (1)

- Release not according to marketing authorisation
- Recalls
- Complaints
- Changing of key personnel or important premises/equipment without notifying the inspectorate

Conditions for unannounced inspections (2)

- Verifying the corrective actions when many deficiencies were found
- company tries to hide something

Planning of Inspections

- Elaboration of a programme
- Ensure that frequency of inspection of individual manufacturers can be adhered to as planned
- Sufficient resources must be determined and available

Preparation of Inspection

- Type and scope of inspection
- Review of latest Site Master File
- Previous reports, pending issues
- New products, equipment or premises
- preparing agenda, length of visit
- composition of inspection team (experts needed eg. for sterile products, blood)

Site Master File (1)

- Prepared by the manufacturer
- contains specific information about the quality assurance, the production and quality control of pharmaceutical manufacturing operations
- wherever possible, simple plans, outline drawings or schematic layouts should be used

Site Master File (2)

- General information on the firm (including name and Address) and its structure
- description of pharmaceutical activities (dosage forms)
- personnel (organisation chart)
- premises and equipment
- documentation

Site Master File (3)

- Brief description production operations
- arrangement for the handling of starting and packaging materials, bulk and finished products
- sampling, quarantine, release and storage
- arrangements for reprocessing or rework
- handling of rejected materials and products

Site Master File (4)

- Brief description of general policy for process validation
- quality control system
- contract manufacture and analysis
- Distribution, complaints and recalls
- Self inspection

Announcement of Inspection

- Competent Authorities have the right to inspect at any time (including during shift work)
- Normally is it useful to announce in advance
  - Date and length of inspection
  - Objectives
  - Special documents

Procedure during Inspection

- Opening meeting
- Short orientation tour (new companies)
- Inspection
- Review of documents requested in the opening meeting
- Internal meeting of GMP team
- Closing meeting

Opening Meeting (1)

- Participants: inspection team; personnel responsible for production and quality control, representative of the management of the pharmaceutical company
- scope and timeline of inspection
- check of quality management structure
- qualifications, experience, responsibilities of key personnel

Opening Meeting (2)

- organisation chart
- GMP-training plan and documents about training
- request for documents that will be reviewed later
- general questions about products (new dosage forms,different active ingredients, equipment, facilities ...)

Inspection Tour

- Normally: following the material flow
- beginning with income of starting and packaging materials
- Production
- Quality control
- handling of finished products
- rejected, recovered, returned materials

Document Review

- Qualification, Validation (Validation Master Plan, Protocols...)
- Standard Operation Procedures (SOP)
- Batch processing records (examples)
- analytical protocols
- procedure for batch release

Document Review (2)

- Written contracts for contract manufacturing and analysis
- procedure for handling recalls and complaints
- procedure for self-inspections

Closing Meeting

- The inspection team presents the found deficiencies
- definition of the severity of the deficiencies (critical, major, minor)
- discussion about corrective actions
- timelines

Classification of deficiencies (1)

- Probability of severe risk for public health ?
- **Critical** (may cause death or severe illness)
- **Major** (severe quality defect**)**
- **Minor** (e.g. significant non compliance to EU-GMP)

Procedure after inspection

- In case of critical deficiencies: official request for immediate action
- Report preparation (ASAP, up to 2 months)
- Distribution
- Time for company response
- Correction action plan or follow-up-inspection

To whom is the report send

- Original to QP or management of company with a cover letter with a time frame for answering and corrective actions
- copies to agencies responsible for certificates and issuing of marketing authorisation

Follow up (1)

- Correspondence with company or re-inspection (follow-up-inspection)
- criteria for time frames:
- proposals for critical deficiencies in closing meeting agreed

Follow up (2)

- Time frames for critical e.g. 5 days, major 10 days for proposals for corrective actions (deficiencies related to investment)
- time frame 28 days for procedures