Introduction to EU Regulatory system and GMP Inspection system. The Qualified Person.

DJ Cockburn
Head of Manufacturing and Quality Compliance
European Medicines Agency

Any views expressed may not necessarily be those of the Agency

Agenda

- Overview of the EU regulatory system
- Authorisations (Licences)
- GMP in the EU
  - Requirements and responsibilities
  - Inspections
  - Harmonisation within EU
- International collaboration
- Qualified Person

The EU(EEA) Regulatory Framework

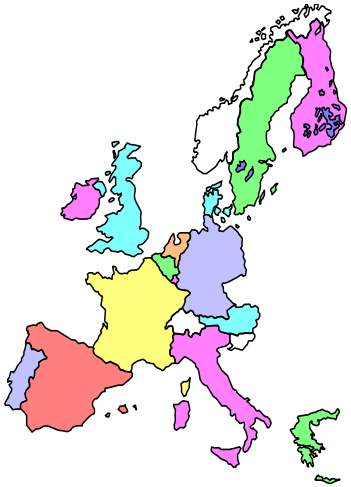
European Regulatory Structure

Treaties	**Signed by all Member States.**
Directives	**Defines objectives to be achieved. Member States have to define compliance in their own law.**
Regulations	**Directly applicable to all Member States.**
Decisions	**Applicable to a specific case, person, organisation…**
Opinions	**Does not need to be enforced, but MSs can use them to support national law**

Authorisations

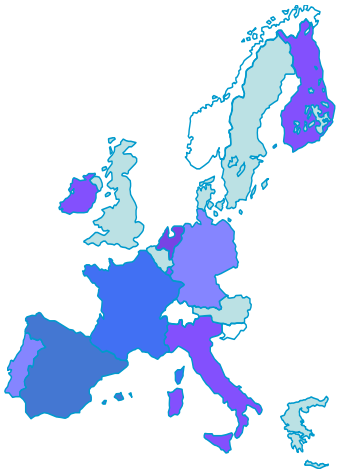
- The regulation of medicinal products in the EU is based on three types of licence
  - Marketing Authorisation: Granted for each product following assessment of quality, safety and efficacy.
    - **Authorises the placing of the medicinal product onto the market**
  - Manufacturing authorisation: Granted following inspection for GMP
    - **Authorises the manufacture (or import) of categories of medicinal product**
    - **Subject to repeated inspections**
  - Wholesale distribution authorisation: Granted following inspection for Good Distribution Practice (GDP)
    - **Authorises distribution by way of wholesale dealing**
    - **Subject to repeated inspections**
- Changes to these authorisations are processed as Variations

Procedures for Marketing Authorisation for medicinal products in EEA



Pre-1995

National applications, assessments, standards and authorisations



Post-1995

Mutual Recognition/ Decentralised

1 assessment
2-25 similar national authorisations

Centralised

1 assessment

1 authorisation in EU

Same Quality, Safety and Efficacy standards

Responsibilities of Marketing Authorisation Holder

- Must be established in the EEA
- Ensure that the product is manufactured in accordance with the marketing authorisation (e.g. specifications, methods, authorised manufacturer(s))
- Take account of scientific and technical progress
- Have a system of pharmacovigilance (including having a qualified person available)
- Where required, to submit samples to an official laboratory prior to batch release (OCABR)

Manufacturing authorisation

- Granted by the Competent Authorities of each member state for all manufacturing activities (including import) occurring in their territory.
  - Regardless as to which marketing authorisation procedure the products concerned are subject to.
- A Manufacturing authorisation is also required for products produced solely for export.
- Manufacturing authorisations follow a Community format and are mutually recognised by all Member States.

Responsibilities of Manufacturer

- Have suitable premises, personnel, equipment and control facilities
- Have a Qualified Person (QP)
- Ensure compliance with GMP, manufacturing authorisation and relevant marketing authorisations
- Review manufacturing methods in light of scientific and technical progress
- Apply for approval of any changes
  - keep Marketing authorisation holder informed
- Allow access for inspection
- Only use active substances that have been manufactured in accordance with GMP

Wholesale Distribution Authorisation

- A Manufacturing authorisation covers the distribution of products manufactured under that authorisation.
- Otherwise a wholesale distribution authorisation is required
- Granted by the Competent Authorities of each member state to wholesalers operating in their territory
- These are mutually recognised by all Member States.

Responsibilities of a wholesale distribution authorisation holder

- Have suitable and adequate premises
- Have a designated qualified person responsible for meeting the requirements
- Provide access for inspections
- Obtain medicinal products only from authorised sources
- Supply medicinal products only to authorised recipients
- Have an emergency plan to ensure effective implementation of any recall
- Keep records of purchases and sales
- Comply with GDP

EMEA

What is the EMEA?

- One of the 23 European Community agencies
- Mobilises existing scientific resources of the EEA to
  - Deliver Opinions on granting/amending of Marketing Authorisations for Centralised Products through its Scientific Committees, CHMP or CVMP
  - Delivers scientific opinions on any matter referred to it
  - Facilitates harmonisation between EU Member States
  - Provides guidelines to applicants
- The Agency has 6 Scientific Committees (CHMP, CVMP, COMP, PDCO, HMPC, CAT)

EMEA and its Europartners

- Over 40 national competent authorities
- Network of over 3,500 European experts
- European Commission
  - Proposes legislation
- European Pharmacopoeia (Council of Europe)
  - Official Medicines Control Laboratories (OMCL) Network
  - Certification scheme for APIs subject to monographs of the Ph. Eur. (CEP)

GMP Inspections

Responsibilities of Member States

- Must ensure by repeated inspections that legal requirements are complied with
- Inspectors must be empowered to:
  - Inspect manufacturing or commercial establishments or laboratories
  - Take samples
  - Examine documents
  - Prepare reports after each inspection
  - Communicate reports to the manufacturer
  - Place information in the EudraGMP database

EudraGMP Database

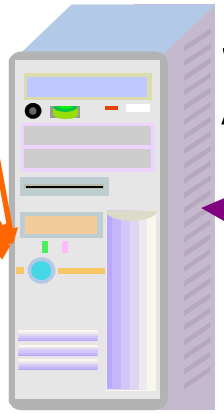
Manufacturing Authorisations (v1)

GMP Certificates (v1)

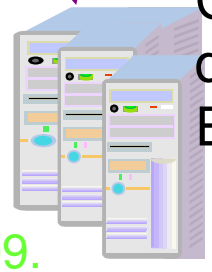
GMP non-compliance (v2)

Inspection plans
in 3rd countries (v3)

Information on “faulty Manufacture” (v4)



Search capabilities
Alert on event capabilities



Links to other Community databases e.g. EudraCT

- 1st release April 2007 (v1). v2 release July 2009.
- Limited public access phased in from 2009-2011.
- Access by MRA partners and other regulatory agencies in progress.

Key concepts

"Supervisory authority"

The competent authority that grants the manufacturing authorisation. For third country imports, the competent authority that grants the manufacturing authorisation to the importer.

- **Free movement between member states - no duplication of controls between Member States**

GMP inspections

- Type of inspections:
  - **General GMP**:
    - where GMP compliance is unconfirmed or routine surveillance (can be targeted to product or process).
  - **Product related:**
    - To assess compliance with the marketing authorisation
  - Both types can be performed pre- or post-authorisation
  - **Other:**
    - E.g. Follow-up of earlier inspection, complaint, sampling, quality defect or recall

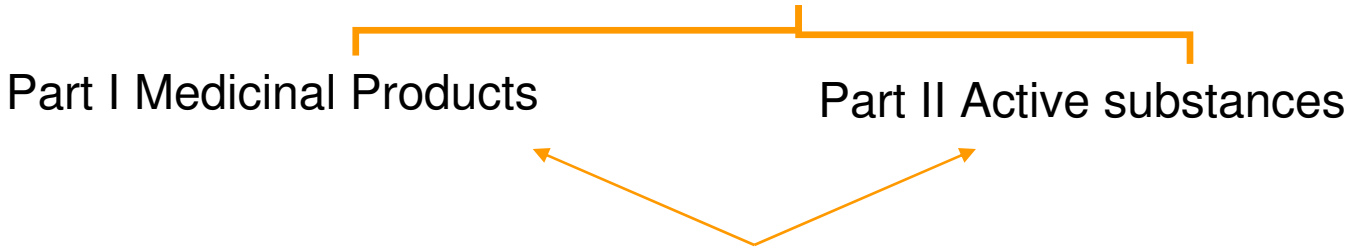
EU GMP Structure

Principles and Guidelines

Laid down in Directives 91/412/EEC and 2003/94/EC. Compliance mandatory.

Detailed Guidelines

EC GMP Guide Basic Requirements. Interpretation of Principles and Guidelines.



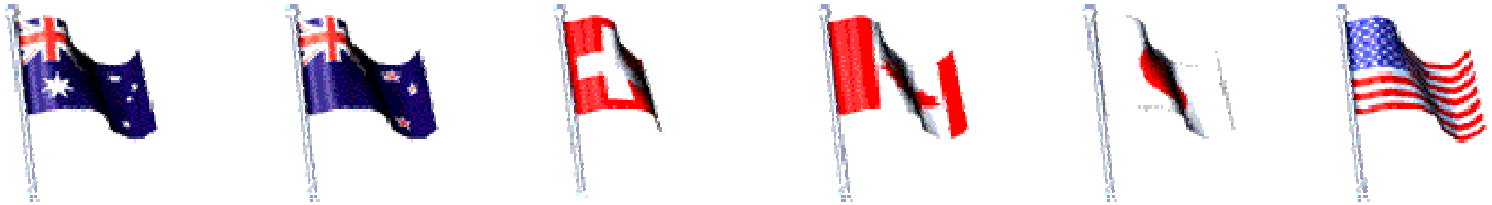
Supplementary Guidelines

Annexes to EC GMP Guide. Provide detail on specific areas and modify detailed guidelines.

Mutual Recognition Agreements and related activities

Mutual Recognition Agreements

- Broad trade agreements including the recognition of equivalent GMP standards in the pharmaceuticals sector
  - Avoids duplication of GMP inspections
  - Inspection outcomes accepted based on the exchange of GMP certificates
- The scope varies depending on the individual agreement



USA agreement is partially operational

An enhanced agreement (ACAA) is being negotiated with Israel. This is based on the adoption of identical standards

Harmonisation in the EU/EEA

Harmonising factors

- Collective implementation of Directives into national legislation
  - National Manufacturing Authorisations
  - Concept of Supervisory Authority
  - Mutual recognition of inspection outcomes. All inspections "performed on behalf of the Community"
- Collective adoption of identical guidelines
- Harmonised practices
  - Compilation of Community Procedures
  - Joint audit programme
  - Regular meetings of the GMP/GDP Inspectors Working Group

EMEA's GMP/GDP Inspectors Working Group

Chaired by EMEA

Meets 4 x year

- **Develops GMP related guidelines**
- **Agrees on GMP related procedures**
- **Facilitates Exchange of information**
- **Harmonisation of GMP Inspections in the EEA**
- **Implementation of Mutual Recognition Agreements (MRAs)**
- **Liaison activities : QWP, BWP, GCP inspectors, Interested parties, PIC/S, WHO**

The Compilation of Procedures

Legal basis
Art. 3(1) Directive 2003/94

- Handling suspected defects and rapid alerts
- Dealing with GMP non-compliance
- Inspection procedures
- Formats for manufacturing authorisation, GMP certificates and inspection reports
- Exchange of information procedures
- Training and Qualifications of GMP Inspectors
- Triggers for API inspections
- Procedures for centralised inspections
- Verification of GMP in 3rd countries
- Risk-based inspection planning
- Quality System for GMP inspectorates

Joint Audit Programme

- Established in 2002 under the authority of the Heads of Medicines Agencies
- Programme of audits of member states' GMP Inspectorates by auditors from two other member states
- Audit tools are harmonised with those used in MRA evaluations and PIC/S assessments
  - The results of these audits are mutually recognised within PIC/S and EEA to avoid duplication
- Assesses the Implementation of Community legislation and the Compilation of procedures

Qualified Person (QP)
(Manufacturing Authorisation)

The legislative requirements (1)

- The QP must be permanently and continuously at the disposal of the manufacturing authorisation holder
- Manufacturing authorisation holder is obliged to put all necessary facilities at disposal of QP to enable him/her to fulfil duties
  - Must have a job description and be given sufficient authority to discharge their duties
- QP to have certain qualifications and practical experience

Qualifications of the QP

- 4 years study (e.g. pharmacy, medicine, veterinary medicine, chemistry)
- 2 years practical experience in industry in quality control
- Subject to administrative measures or code of conduct
- QP may be temporarily suspended

The legislative requirements (2)

- QP to secure (ensure) and certify that:
  - each batch of (investigational) medicinal product complies with laws in force and the marketing authorisation (or product specification file and request for clinical trial authorisation)
  - For imported products that analysis (in accordance with the marketing authorisation/request for clinical trial authorisation) has been carried out in the Community
    - Can be waived if an MRA/ACAA applies.
    - Only applies to IMPs as comparators when equivalent GMP standards at the third country manufacturer cannot be demonstrated.

The legislative requirements (3)

- Batches certified by a QP in one Member State can move freely into another Member State
- Records of batch certification must be kept for at least 5 years at the disposal of the Competent Authorities
- Member States are required to subject QPs to administrative measures or code of conduct
- Suspension and other administrative and disciplinary measures can be taken against a QP
  - National approaches may differ

GMP Annex 16

- The Annex provides guidance in particular when manufacture takes place at different locations
  - Does not cover every legally acceptable possibility
  - Introduces the concept of “confirmation” by QPs involved in intermediate stages
  - Requires arrangements to be underpinned by written agreements as appropriate to the relationship between the different parties
- The annex also gives guidance on what should be taken account of before certifying a batch
  - Similar guidance is given in Annex 13 for IMPs

What gives a QP the confidence to certify a batch?

- Elements listed in Annex 13 or 16
  - Ensure that these have been checked
- Is this sufficient?
- No, a QP needs to know that all aspects of production are in compliance

Operating in GMP Compliance

- GMP guidelines do not assume that nothing ever goes wrong
- GMP Compliance means:
  - Knowing what is ‘normal’ – e.g. Validation
  - Reacting appropriately when something goes wrong
- This demands an effective Quality System

What <u>really</u> gives a QP confidence to certify a batch?

- Familiarity with directives and guidelines
- Confidence and knowledge that relevant marketing/ clinical trial authorisations are being complied with
- Achieved through the establishment and maintenance of an effective Quality Assurance System
- Day to day involvement in manufacturing and quality operations
  - For QPs of importers: A thorough knowledge of the third country manufacturer

Further information

European Commission

http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

EMEA

http://www.emea.europa.eu/Inspections/GMPhome.html


T.C. SAĞLIK BAKANLIĞI
THE MINISTRY OF HEALTH OF TURKEY