



UNIVERSITÀ DEGLI STUDI DI MILANO  
DIPARTIMENTO DI  
SCIENZE FARMACEUTICHE

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# *Corso di Laurea Magistrale in Chimica e Tecnologia Farmaceutiche - E25*

## *Fabbricazione Industriale dei Medicinali - 4 CFU*

*Dott. Matteo Cerea*

*Le GMP e il Sistema di Qualità nella produzione farmaceutica*

*Alessandro Regola*

## **Le tre basi delle attività in uno stabilimento farmaceutico**

- Autorizzazione alla Produzione (API o Medicinali)
- Autorizzazione alla Immissione in Commercio (Medicinali)
- Good Manufacturing Practices (GMP) e Sistema di Qualità Farmaceutico

## Tre obiettivi

- Qualità (corrispondenza alle specifiche, regolare disponibilità per il paziente)
- Sicurezza (purezza, dosaggio)
- Efficacia (corrispondenza agli studi clinici, dosaggio, performance tecnologica)

## **GMP (Good Manufacturing Practices)**

Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently **produced** and **controlled** to the **quality standards** appropriate to their intended use and as required by the **Marketing Authorisation, Clinical Trial Authorisation** or **product specification**. Good Manufacturing Practice is concerned with both **production** and **quality control**.

(EU GMP, Part I, Chapter 1)

## **GMP (Good Manufacturing Practices)**

The minimum regulations for **methods** to be used in, and the **facilities** and **controls** to be used for, the **manufacture, processing, packing or holding** of a drug to assure that such drug meets the requirements of **safety, identity, strength, quality and purity** (US CFR 21, 210-211)

## US GMP History (1)

- 1938 : Sulfanilamide syrup with diethylene glycol as solvent (107 deaths, mostly children)

### **1938 : Federal Food, Drug & Cosmetic Act (USA)**

- 1941 : Sulfathiazole tablets tainted with phenobarbital (300 deaths)
- 1955 : Antipolio vaccine with incompletely inactivated virus causes 149 individuals to develop polio

### **1978 : cGMP Final Rules for Drugs and Devices (CFR 21, 210-211)**

## US GMP History (2)

- 1982 : Tylenol (paracetamol) capsules poisoned by cyanide causes 7 deaths
- ↪ **1982 : Tamper resistant packaging regulations issued for OTC products (USA)**
- 1992 : Generic drug scandal (fraud and bribery)
- ↪ **1992 : Generic Drug Enforcement Act (USA)**

## US GMP History (3)

- 2000 – 2013 :
  - Materials adulteration / contamination (glycerine, heparin, milk)
  - Drug product shortages (due to GMP reasons)

### **2013 : FDA Safety and Innovation Act (FDASIA)**

- 2013 – oggi :
  - Data Integrity (falsificazione dati, mancanza di adeguata protezione dei dati)

### **2016 : FDA Guideline on Data Integrity and Compliance with cGMP**



## EU GMP - Storia

- **1989** : prima edizione, incluso l'**annex 1 sui medicinali sterili**
- **1991** : seconda edizione con recepimento delle Direttive 91/356 (medicinali a uso umano) e 91/412 (medicinali a uso veterinario), inclusi **12 allegati**
- **2005** : ristrutturazione del documento con divisione in **parte I (medicinali)** e **parte II (principi attivi)** e con recepimento delle Direttive 2004/27/EC (medicinali a uso umano) e 2004/28/EC (medicinali a uso veterinario), inclusi **17 allegati**
- **2010** : aggiornamento del testo e introduzione della **parte III (documenti correlati, di supporto e best practices)**

## **EU GMP – Basi legali**

### **Direttive 2001/83/EC (umano) e 2001/82/EC (veterinari)**

- Normativa europea sui medicinali (Codice Comunitario) :  
registrazione, produzione, importazione, etichettatura, distribuzione, farmacovigilanza

### **Regolamento 2017/1569 (farmaci sperimentali)**

- Normativa europea sui farmaci sperimentali

### **Regolamento 1394/2007 (farmaci di derivazione biologica)**

- Normativa europea sui farmaci di derivazione biologica

### **Direttiva 2017/1572 (umano) e 91/412/EEC (veterinari)**

- Norme di buona fabbricazione (Good Manufacturing Practices)

## Altre GMP (nazionali e sovranazionali)

- **Canada (Health Canada)** : medicinali
- **Australia (TGA)** : medicinali, principi attivi, sangue umano, derivati del sangue, tessuti umani e terapia cellulare
- **Cina (CFDA)** : medicinali
- **Brasile (ANVISA)** : medicinali
- **Messico (COFREPIS)** : medicinali e principi attivi
- **Sud Corea (KFDA)** : medicinali e principi attivi
- **Arabia Saudita (SFDA)** : medicinali e principi attivi
- **Russia (Roszdravnadzor)** : medicinali e principi attivi
  
- **WHO** : medicinali e principi attivi; (principi generali + diversi allegati su argomenti specifici)
- **PIC/S (Pharmaceutical Inspection Convention)** : analoghe alle EU GMP

# **EU GMP**

## ***Struttura***

- ***Parte I (medicinali) (9 capitoli)***
- ***Parte II (principi attivi)***
- ***Parte III (documenti correlati, di supporto e best practices) (5 documenti)***
- ***Parte IV (terapie avanzate)***
- ***Allegati (18)***
- ***Glossario***

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines - European Commission - IE configured for Business use.


http://ec.europa.eu/health/documents/eudralex/vol-4/index\_en.htm

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### EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines.

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.

#### Introduction

- Introduction (33 KB) (7/02/2011)
- Commission Directive 2003/94/EC, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use  
Replacement of Commission Directive 91/356/EEC of 13 June 1991 to cover good manufacturing practice of investigational medicinal products.
- Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

#### Part I - Basic Requirements for Medicinal Products

- Chapter 1 Pharmaceutical Quality System (65 KB) (into operation since 31 January 2013)
- Chapter 2 Personnel (58 KB)(into operation since 16 February 2014).
- Chapter 3 Premise and Equipment (171 KB) (into operation since 1 March 2015)
  - See transitional arrangement for toxicological evaluation on page 1 of Chapter 3
  - Previous (34 KB)

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# **EU GMP**

## ***Parte I (medicinali) (9 capitoli)***

- 1. Pharmaceutical Quality System***
- 2. Personnel***
- 3. Premises and Equipment***
- 4. Documentation***
- 5. Production***
- 6. Quality Control***
- 7. Outsourced Activities***
- 8. Complaints, Quality Defects and Product Recall***
- 9. Self inspections***

# EU GMP – Parte I – Capitolo 1 (2013)

## *Pharmaceutical Quality System*

### **Principle**

*The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, **comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation**, as appropriate and do not place patients at risk due to inadequate **safety, quality or efficacy**. The attainment of this quality objective is the responsibility of **senior management** and requires the participation and commitment by **staff** in many different departments and **at all levels within the company**, by the company's **suppliers** and by its **distributors**.*

# EU GMP – Parte I – Capitolo 1 (2013)

## *Pharmaceutical Quality System*

### **Principle**

*.....To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented **Pharmaceutical Quality System** incorporating **Good Manufacturing Practice** and **Quality Risk Management**. It should be **fully documented** and its effectiveness monitored. All parts of the Pharmaceutical Quality System should be **adequately resourced** with competent **personnel**, and suitable and sufficient **premises, equipment** and **facilities**. .....*



# **EU GMP – Parte I – Capitolo 1 (2013)**

## ***Pharmaceutical Quality System***

- ***Pharmaceutical Quality System***
- ***Good Manufacturing Practice for Medicinal Products***
- ***Quality Control***
- ***Product Quality Review***
- ***Quality Risk Management***

# EU GMP – Parte I – Capitolo 2 (2014)

## *Personnel*

### ***Principle***

*The correct manufacture of medicinal products relies upon people. For this reason there must be sufficient **qualified personnel** to carry out all the tasks which are the responsibility of the manufacturer. Individual **responsibilities** should be **clearly understood** by the individuals and recorded. All personnel should be **aware of the principles of Good Manufacturing Practice** that affect them and receive **initial and continuing training**, including hygiene instructions, relevant to their needs.*

# **EU GMP – Parte I – Capitolo 2 (2014)**

## ***Personnel***

- ***General***
- ***Key Personnel (Qualified Person, Head of Production, Head of Quality Control)***
- ***Training***
- ***Personnel Hygiene***
- ***Consultants***

# EU GMP – Parte I – Capitolo 3 (2014)

## *Premises and Equipment*

### ***Principle***

*Premises and equipment must be located, **designed, constructed, adapted and maintained** to suit the operations to be carried out. Their layout and design must aim to **minimise** the risk of **errors** and permit effective **cleaning and maintenance** in order to **avoid cross-contamination, build-up of dust or dirt** and, in general, any **adverse effect on the quality of products.***

# EU GMP – Parte I – Capitolo 3 (2014)

## *Premises and Equipment*

- **Premises**
  - *General*
  - *Production Area*
  - *Storage Areas*
  - *Quality Control Areas*
  - *Ancillary Areas*
- **Equipment**

# EU GMP – Parte I – Capitolo 4 (2011)

## *Documentation (1)*

### ***Principle***

*Good documentation constitutes an **essential part** of the quality assurance system and is key to operating in compliance with GMP requirements.....*

***Documentation may exist in a variety of forms, including paper-based, electronic or photographic media.** The main objective of the system of documentation utilized must be to **establish, control, monitor and record all activities** which directly or indirectly impact on all aspects of the quality of medicinal products. ....*

# EU GMP – Parte I – Capitolo 4 (2011)

## Documentation (2)

### **Principle**

*.... The Quality Management System should include sufficient **instructional detail** to facilitate a common understanding of the requirements, in addition to providing for **sufficient recording of the various processes and evaluation of any observations**, so that ongoing **application of the requirements may be demonstrated**.*

*There are **two primary types of documentation** used to manage and record GMP compliance: **instructions (directions, requirements) and records/reports**. .....*

# EU GMP – Parte I – Capitolo 4 (2011)

## *Documentation (3)*

### **Principle**

*....Suitable controls should be implemented to ensure the **accuracy, integrity, availability and legibility** of documents.*

*Instruction documents should be free from errors and **available in writing**.*

*The term ‘**written**’ means **recorded**, or **documented on media** from which data may be **rendered in a human readable form**.*



# EU GMP – Parte I – Capitolo 4 (2011)

## *Documentation (4)*

- ***Required GMP Documentation***
  - *Site Master File*
  - *Instructions type*
  - *Records / Reports type*
- ***Generation and Control of Documentation***
- ***Good Documentation Practice***
- ***Retention of Documents***

# **EU GMP – Parte I – Capitolo 4 (2011)**

## ***Documentation (5)***

- ***Specifications (starting and packaging materials, intermediate, bulk products, finished products)***
- ***Manufacturing Formula and Processing Instructions***
- ***Packaging Instructions***
- ***Batch Processing Record***
- ***Batch Packaging Record***
- ***Procedures and Records***

# EU GMP – Parte I – Capitolo 5 (2014)

## *Production (1)*

### ***Principle***

*Production operations must follow **clearly defined procedures**; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the **requisite quality** and be **in accordance with the relevant manufacturing and marketing authorisations**.*

# **EU GMP – Parte I – Capitolo 5 (2014)**

## ***Production (2)***

- ***General***
- ***Prevention of cross-contamination in production***
- ***Validation***
- ***Starting Materials***
- ***Processing operations : intermediate and bulk products***
- ***Packaging Materials***
- ***Packaging Operations***
- ***Finished Products***
- ***Rejected, Recovered and Returned Materials***
- ***Product Shortage due to Manufacturing Constraints***

# EU GMP – Parte I – Capitolo 6 (2014)

## *Quality Control (1)*

### ***Principle***

*Quality Control is concerned with **sampling, specifications and testing** as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that **materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.***

*..... The **independence of Quality Control from Production** is considered fundamental to the satisfactory operation of Quality Control.*

# EU GMP – Parte I – Capitolo 6 (2014)

## *Quality Control (2)*

- ***General***
- ***Good Quality Control Laboratory Practice***
  - *Documentation*
  - *Sampling*
  - *Testing*
  - *On-going Stability Programme*
- ***Technical Transfer of Testing Methods***

# EU GMP – Parte I – Capitolo 7 (2013)

## *Outsourced Activities (1)*

### ***Principle***

*Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to **avoid misunderstandings** which could result in a product or operation of unsatisfactory quality. There must be a **written Contract** between the **Contract Giver** and the **Contract Acceptor** which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the **Qualified Person** certifying each batch of product for release **exercises his full responsibility**.*

# EU GMP – Parte I – Capitolo 7 (2013)

## *Outsourced Activities (2)*

- ***General***
- ***Contract Giver***
- ***Contract Acceptor***
- ***Contract***



# EU GMP – Parte I – Capitolo 8 (2014)

## *Complaints, Quality Defects and Product Recall*

### *Principle (1)*

In order to protect public and animal health, a system and appropriate procedures should be in place to **record, assess, investigate and review complaints** including **potential quality defects**, and if necessary, to effectively and promptly **recall** medicinal products for human or veterinary use and investigational medicinal products from the distribution network. **Quality Risk Management principles should be applied** to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventative actions and other risk-reducing actions. ....

## EU GMP – Parte I – Capitolo 8 (2014)

### *Complaints, Quality Defects and Product Recall*

#### ***Principle (2)***

All concerned competent **authorities should be informed** in a timely manner **in case of a confirmed quality defect** (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the **recall** of the product or an **abnormal restriction in the supply**.

.....

## **EU GMP – Parte I – Capitolo 8 (2014)**

### ***Complaints, Quality Defects and Product Recall***

- ***Personnel and Organization***
- ***Procedures for handling and investigating complaints including possible quality defects***
- ***Investigation and Decision-making***
- ***Root Cause Analysis and Corrective and Preventative Actions***
- ***Product Recalls and other potential risk-reducing actions***

# EU GMP – Parte I – Capitolo 9 (1989)

## *Self Inspection*

### *Principle*

*Self inspections should be conducted in order to **monitor** the implementation and compliance with Good Manufacturing Practice principles and to propose necessary **corrective measures**.*

# **EU GMP – Parte II (2014)**

## **Basic Requirements for Active Substances used as Starting Materials (1)**

- **Introduction**
- **Quality Management**
- **Personnel**
- **Buildings and Facilities**
- **Process Equipment**
- **Documentation and Records**
- **Materials Management**
- **Production and In-Process Controls**
- **Packaging and Identification Labelling**

**EU GMP – Parte II (2014)**  
**Basic Requirements for Active Substances  
used as Starting Materials (2)**

- **Storage and Distribution**
- **Laboratory Controls**
- **Validation**
- **Change Control**
- **Rejection and Reuse of Materials**
- **Complaints and Recalls**
- **Contract Manufacturers (including Laboratories)**
- **Agents, Brokers, Traders, Distributors,  
Repackers and Relabellers**

**EU GMP – Parte II (2014)**  
**Basic Requirements for Active Substances  
used as Starting Materials (3)**

- **Specific Guidance for APIs Manufactured by Cell Culture/Fermentation**
- **APIs for Use in Clinical Trials**
- **Glossary**

## **EU GMP – Parte III (2010)**

### **GMP related documents**

- **Explanatory Notes on the preparation of a Site Master File**
- **Quality Risk Management (ICH Q9)**
- **Pharmaceutical Quality System (ICH Q10)**
- **Internationally harmonised requirements for batch certification**
- **Template for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use**



# **EU GMP – Parte III (2010)**

## **Pharmaceutical Quality System (ICH Q10) (2008)**

- **Pharmaceutical Quality System**
  - **Objectives :**
    - **Achieve product realization**
    - **Establish and maintain a state of control**
    - **Facilitate continual improvement**
  - **Enablers :**
    - **Knowledge management**
    - **Quality risk management**

# **EU GMP – Parte III (2010)**

## **Pharmaceutical Quality System (ICH Q10) (2008)**

- **Management Responsibility**
  - **Management commitment**
  - **Quality planning**
  - **Resource management**
  - **Management review**
- **Continual Improvement of Process Performance and Product Quality**
- **Continual Improvement of the Pharmaceutical Quality System**

# **EU GMP – Parte IV (2017)**

## **Advanced Therapy Medicinal Products**

- **Introduction**
- **Risk based approach**
- **Personnel**
- **Premises**
- **Equipment**
- **Documentation**
- **Starting and raw materials**
- **Seed lot and cell bank system**
- **Production**

## **EU GMP – Parte IV (2017)**

### **Advanced Therapy Medicinal Products**

- **Qualification and validation**
- **Qualified Person and batch release**
- **Quality Control**
- **Outsourced activities**
- **Quality defects and product recalls**
- **Environmental control methods for ATMPs containing or consisting of GMOs**
- **Reconstitution of product after batch release**
- **Automated production of ATMPs**

## **EU GMP – Annexes**

- 1. Manufacture of Sterile Medicinal Products (2009)  
(*in revisione*)**
- 2. Manufacture of Biological active substances and Medicinal Products for Human Use (2013)**
- 3. Manufacture of Radiopharmaceuticals (2009)**
- 4. Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Products (1991)**
- 5. Manufacture of Immunological Veterinary Products (1991)**
- 6. Manufacture of Medicinal Gases (2010)**
- 7. Manufacture of Herbal Medicinal Products (2009)**

## **EU GMP – Annexes**

- 8. Sampling of starting and packaging materials (1991)**
- 9. Manufacture of liquids, creams and ointments (1991)**
- 10. Manufacture of pressurised metered dose aerosol preparations for inhalation (1991)**
- 11. Computerized Systems (2011)**
- 12. Use of ionizing radiation in the manufacture of medicinal products (1991)**
- 13. Investigational Medicinal Products (2010)**
- 14. Manufacture of Medicinal Products Derived from Human Blood or Plasma (2011)**

## **EU GMP – Annexes**

**15. Qualification and validation (2015)**

**16. Certification by a Qualified Person and Batch Release (2015)**

**17. Parametric Release (2002) (*in revisione*)**

**19. Reference and Retention Samples (2006)**

**Grazie !**

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