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GMP e Quality System

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GMP : Introduzione e aspetti generali

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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, strenght, quality** and **purity**

(US CFR 21, 210-211)

GMP (Good Manufacturing Practices)

EU Directive 2003/94/CE (art. 2 Definizioni)

5) «**Garanzia della qualità farmaceutica**», la somma di tutte le precauzioni messe in atto per garantire che i medicinali o i medicinali in fase di sperimentazione abbiano la qualità richiesta per l'uso cui sono destinati.

6) «**Buone prassi di fabbricazione**», la parte di garanzia della qualità che assicura che i medicinali siano prodotti e controllati secondo norme di qualità adeguate all'uso cui sono destinati.

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

1962 : Thalidomide causes birth defects in thousands of European babies

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)**

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 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 2001/83/EC (veterinari)

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

Direttiva 2001/20/EC (farmaci sperimentali)

- Normativa europea sui farmaci sperimentali

Direttiva 2003/94/EC (umano) e 91/412/EEC (veterinari)

- Norme di buona fabbricazione (Good Manufacturing Practices)

Altre GMP

WHO : medicinali (2011) e principi attivi (2010); (principi generali + diversi allegati su argomenti specifici)

Canada (Health Canada) : medicinali (2011)

Cina (CFDA) : medicinali (2011)

Brasile (ANVISA) : medicinali (2010)

Australia (TAG) : sangue umano, derivati del sangue, tessuti umani e terapia cellulare (2013)

Messico (COFREPIS) : medicinali e principi attivi (2013)

Sud Corea (KFDA) : medicinali e principi attivi (2007)

Arabia Saudita (SFDA) : medicinali e principi attivi

PIC/S (Pharmaceutical Inspection Convention) : uguali 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)***
- ***Allegati (18)***
- ***Glossario***

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, in vigore da marzo 2015)

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, in vigore da marzo 2015)

Premises and Equipment (revisione)

Reasons for changes:

The only change is to section 6 as part of the improved guidance on **prevention of cross-contamination** involving also Chapter 5 and includes reference to a new complementary **toxicological assessment** guidance.

(“**Dedicated facilities**”)

EU GMP – Parte I – Capitolo 3
(2014, in vigore da marzo 2015)

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. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System.
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****. Appropriate good documentation practice should be applied with respect to the type of document. ……*

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***
- ***Specifications (starting and packaging materials, intermediate, bulk products, finished products)***

EU GMP – Parte I – Capitolo 4 (2011)

Documentation (5)

- ***Manufacturing Formula and Processing Instructions***
- ***Packaging Instructions***
- ***Batch Processing Record***
- ***Batch Packaging Record***
- ***Procedures and Records***
  - *Receipt (of materials)*
  - *Sampling*
  - *Testing*
  - *Other (next page)*

EU GMP – Parte I – Capitolo 4 (2011)

Documentation (6)

- ***Procedures and Records / Other***
  - *Release and Rejection (materials and products)*
  - *Batch distribution*
  - *Validation and Qualification*
  - *Equipment assembly and calibration*
  - *Technology Transfer*
  - *Maintenance, cleaning, sanitation*

EU GMP – Parte I – Capitolo 4 (2011)

Documentation (7)

- ***Procedures and Records / Other***
  - *Personnel (signature list, training, clothing, hygiene)*
  - *Environmental monitoring*
  - *Pest Control*
  - *Complaints*
  - *Recalls*
  - *Returns*
  - *Change Control*

EU GMP – Parte I – Capitolo 4 (2011)

Documentation (8)

- ***Procedures and Records / Other***
  - *Investigations into deviations and non-conformances*
  - *Internal Quality / GMP Compliance Audits*
  - *Product Quality Reviews*
  - *Supplier audits*
  - *Operating Procedures for Manufacturing and Test Equipment*
  - *Log books (for major manufacturing and test Equipment and areas)*
  - *Inventory of documents*

EU GMP – Parte I – Capitolo 5
(2014, in vigore da marzo 2015)

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, in vigore da marzo 2015)

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 5
(2014, in vigore da marzo 2015)

Production (revisione)

Reasons for changes:

- prevention of cross-contamination / toxicological assessment guidance (“Dedicated facilities”)
- qualification of suppliers / manufacture of active substances in accordance with GMP / supply chain traceability
- testing of starting materials (use of test results of supplier)
- notification of restrictions in supply (“Product Shortage”)

EU GMP – Parte I – Capitolo 6
(2014, in vigore da ottobre 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**. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The **independence of Quality Control from Production** is considered fundamental to the satisfactory operation of Quality Control.*

EU GMP – Parte I – Capitolo 6
(2014, in vigore da ottobre 2014)

Quality Control (revisione)

Reasons for changes:

- Technical transfer of testing methods
- Out of specification results

EU GMP – Parte I – Capitolo 6
(2014, in vigore da ottobre 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, in vigore da marzo 2015)

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. Guidance in relation to these principles is provided in Chapter 1.

EU GMP – Parte I – Capitolo 8
(2014, in vigore da marzo 2015)

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**. In situations where product on the market is found to be non-compliant with the marketing authorisation, there is no requirement to notify concerned competent authorities provided the degree of non-compliance satisfies the Annex 16 restrictions regarding the handling of unplanned deviations.

EU GMP – Parte I – Capitolo 8
(2014, in vigore da marzo 2015)

Complaints, Quality Defects and Product Recall

Principle (3)

In case of **outsourced activities**, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and/or sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing actions relating to a defective product. Guidance in relation to contracts is provided in Chapter 7. Such contracts should also address how to contact those responsible at each party for the management of quality defect and recall issues.

EU GMP – Parte I – Capitolo 8
(2014, in vigore da marzo 2015)

Complaints, Quality Defects and Product Recall (revisione)

Reasons for changes:

- Quality Risk Management principles to be applied when investigating quality defects/complaints and when making decisions in relation to product recalls or other risk-mitigating actions.
- the cause(s) of quality defects/complaints to be investigated and determined, and that appropriate preventative actions are put in place to guard against a recurrence of the issue.
- clarify expectations and responsibilities in relation to the reporting of quality defects to the Supervisory Authority.

EU GMP – Parte I – Capitolo 8
(2014, in vigore da marzo 2015)

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 – Annexes

1. Manufacture of Sterile Medicinal Products (2009)
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 (2001) (*in revisione*)**
16. **Certification by a Qualified Person and Batch Release (2002) (*in revisione*)**
17. **Parametric Release (2002)**
19. **Reference and Retention Samples (2006)**

Grazie !

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