Associazione Farmaceutici Industria

GMP – Introduzione e aspetti generali

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Associazione Farmaceutici Industria

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

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Tre obiettivi

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

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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)

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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)

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)**

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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

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)

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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)***
- ***Parte IV (terapie avanzate)***
- ***Allegati (18)***
- ***Glossario***

EUDRALEX : https://ec.europa.eu/health/documents/eudralex/vol-4

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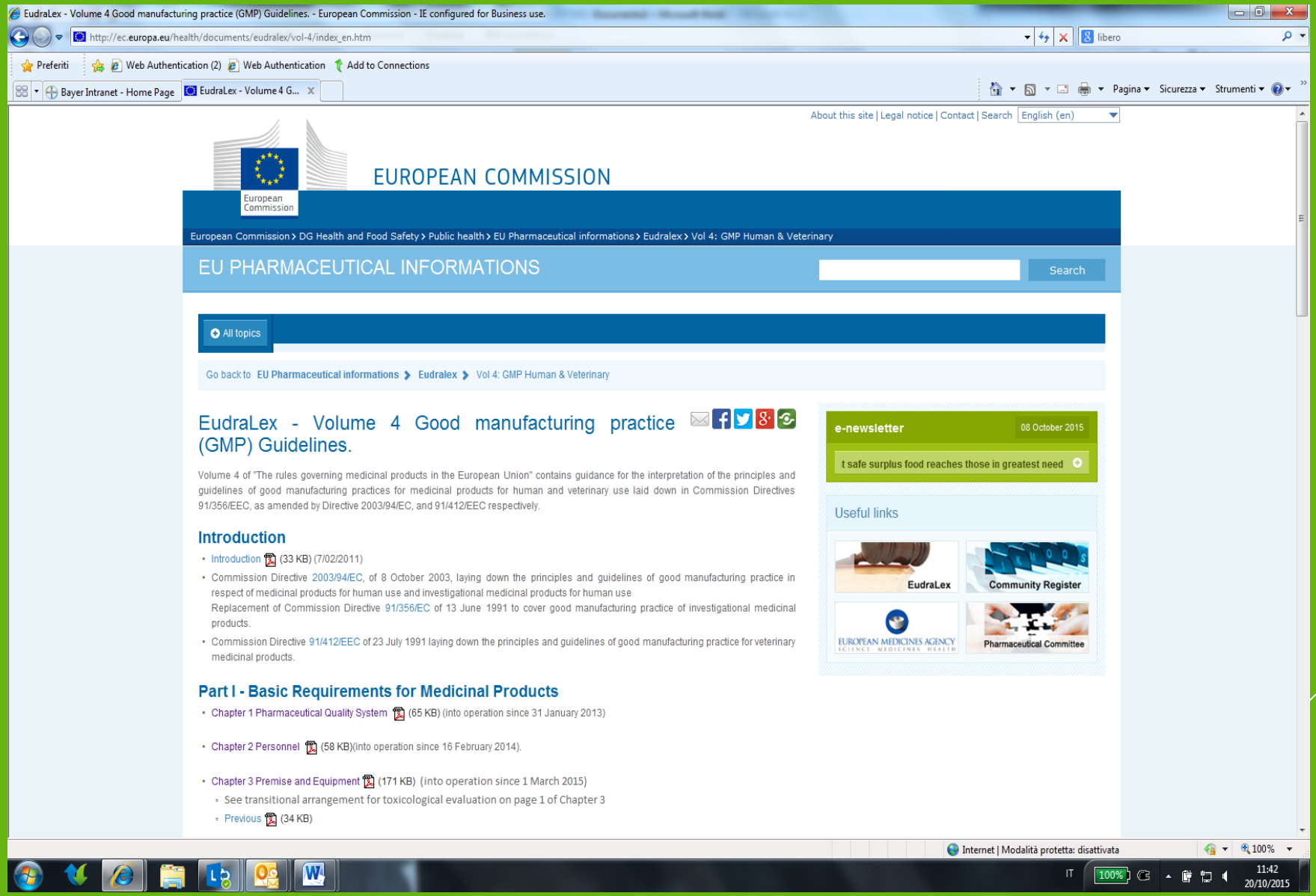

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EU GMP

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*

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EU GMP – Parte I – Capitolo 1 (2013)

Pharmaceutical Quality System (1)

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.***

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EU GMP – Parte I – Capitolo 1 (2013)

Pharmaceutical Quality System (2)

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****. ……..*

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EU GMP – Parte I – Capitolo 1 (2013)

Pharmaceutical Quality System (3)

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

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EU GMP – Parte I – Capitolo 2 (2014)

Personnel (1)

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.*

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EU GMP – Parte I – Capitolo 2 (2014)

Personnel (2)

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

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EU GMP – Parte I – Capitolo 3 (2014)

Premises and Equipment (1)

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**.*

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EU GMP – Parte I – Capitolo 3 (2014)

Premises and Equipment (2)

- ***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)

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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****.*

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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***

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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***

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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)

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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.*

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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)

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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)

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Complaints, Quality Defects and Product Recall (1)

Principle

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 (2)

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**.
…….

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Complaints, Quality Defects and Product Recall (3)

- ***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***

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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*

EU GMP – Parte II (2014)

Basic Requirements for Active Substances used as Starting Materials (2)

- *Production and In-Process Controls*
- *Packaging and Identification Labelling*
- *Storage and Distribution*
- *Laboratory Controls*
- *Validation*
- *Change Control*
- *Rejection and Reuse of Materials*

EU GMP – Parte II (2014)

Basic Requirements for Active Substances used as Starting Materials (3)

- *Complaints and Recalls*
- *Contract Manufacturers (including Laboratories)*
- *Agents, Brokers, Traders, Distributors, Repackers and Relabellers*
- *Specific Guidance for APIs Manufactured by Cell Culture/Fermentation*
- *APIs for Use in Clinical Trials*
- *Glossary*

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EU GMP – Parte III (2010)

GMP related documents (1)

- *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)

GMP related documents (2)

- *Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*
- *Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use*
- *Content of the Batch Certificate for Investigational Medicinal Products*
- *Template for IMP batch release*

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EU GMP – Parte III (2010)

Pharmaceutical Quality System (ICH Q10) (2008)

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

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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 (1)

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- *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 (2)

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- *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)

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1. ***Manufacture of Sterile Medicinal Products (2009) (in revisione)***
2. ***Manufacture of Biological active substances and Medicinal Products for Human Use (2018)***
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 (2)

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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)*

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EU GMP – Annexes (3)

15. *Qualification and validation (2015)*
16. *Certification by a Qualified Person and Batch Release (2015)*
17. *Real Time Release Testing and Parametric Release (2018)*
19. *Reference and Retention Samples (2006)*

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Grazie !

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