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GMP update on Single Use Systems (Part 1)

1

Contents

- Current GMP regulations (European Union)
- FDA requirements
- Technical guidance
- Regulatory expectations

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EU and USA GMP

- There are many different versions of GMP for different parts of the world
- The aim is always the same:
  - To protect the end user from poor quality medicines

3

European Union (EU) GMP

- GMP is harmonised in the EU
- All member states work to EU GMP

4

The legal side of GMP

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The legal side of GMP

- EU GMP began in 1991
- GMP Directives
  - **Directive 91 / 356/ EEC** (Human Medicines)
  - **Directive 91 / 412 / EEC** (Veterinary Medicines)
- Both Directives were quite similar
- Manufacturing sites must work to one of these Directives

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The Human GMP Directive

- Directive 91 / 356/ EEC
  - Updated in May 2004
  - Clinical Trials Directive
    - Amended to mainly include additional requirements for Investigational Medicinal Products (IMPs)
- Directive 2003/ 94/ EC
  - Updated version of human Directive
  - For commercial and IMP medicines

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The Human GMP Directive

- Directive 2003/ 94/ EC
  - Updated again (2022)
  - Splitting out the requirements for commercial and IMP medicines
  - Replace with two new Directives
    - One for commercial medicines
    - One for Investigational Medicinal Products

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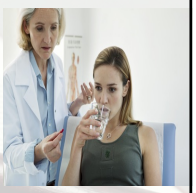
The Human GMP Directive

- Directive 2003/ 94/ EC
- Replaced with:



- Directive 2017/1569 (IMPs)
- Directive 2017/1572 (Commercial)

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PREVIOUS Directive 2003/ 94/ EC

1. Scope
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Quality assurance system
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Work contracted out
13. Complaints, product recall and emergency unblinding
14. Self inspection
15. Labelling (for IMPs)

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NEW Directive 2017/1572 (Commercial)

1. Subject matter
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Pharmaceutical quality system
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Outsourced operations
13. Complaints and product recall
14. Self inspection

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NEW Directive 2017/1572 (Commercial)

1. Subject matter *(name change)*
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Pharmaceutical quality system *(slight name change)*
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Outsourced operations *(slight name change)*
13. Complaints and product recall *(emergency unblinding removed)*
14. Self inspection
~~15. Labelling (for IMPs)~~ *(whole article removed)*

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Any questions?

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NEW Directive 2017/1569 (IMPs)

1. Subject matter *(name change)*
2. Definitions
3. ~~Inspections~~ *(moved to later in the document)*
3. Conformity with good manufacturing practice
4. Compliance with clinical trial authorisation *(name change)*
5. Pharmaceutical quality system
6. Personnel
7. Premises and equipment
8. Documentation
9. Production
10. Quality Control
11. Retention of samples used for quality control *(new)*
12. Responsibilities of the qualified person *(new)*
13. Outsourced operations *(slight name change)*
14. Complaints, product recall and emergency unblinding

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NEW Directive 2017/1569 (IMPs)

15. Self inspection by the manufacturer *(slight name change)*
16. Advanced therapy investigational medicinal *products (new)*
17. Supervision by inspection *(new)*
18. Cooperation and coordination of inspections *(new)*
19. Recognition of inspection conclusions *(new)*
20. Empowerments of the inspectors *(new)*
21. Competence and obligations of the inspectors *(new)*
22. Quality system (of the inspectors) *(new)*
23. Impartiality of inspectors *(new)*
24. Access to premises *(new)*
25. Suspension or revocation of manufacturing authorisation *(new)*

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Any questions?

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Directive 2017/1572 (Commercial)

1. Subject matter
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Pharmaceutical quality system
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Outsourced operations
13. Complaints and product recall
14. Self inspection

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Directive 2017/1572 (Commercial)

1. Subject matter
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Pharmaceutical quality system
7. Personnel
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9. Documentation
10. Production
11. Quality Control
12. Outsourced operations
13. Complaints and product recall
14. Self inspection

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Directive 2017/1572 (Commercial)

1. Subject matter
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Pharmaceutical quality system
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Outsourced operations
13. Complaints and product recall
14. Self inspection

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Directive 2017/1572 (Commercial)

1. Subject matter
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. **Pharmaceutical quality system**
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Outsourced operations
13. Complaints and product recall
14. Self inspection

"The manufacturer shall establish, implement and maintain an effective pharmaceutical quality system, involving the active participation of the senior management and the personnel of the different departments"

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Directive 2017/1572 (Commercial)

1. Subject matter
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Pharmaceutical quality system
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Outsourced operations
13. Complaints and product recall
14. Self inspection

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The EU Guide to GMP - Chapters

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 recalls
9. Self inspection

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• GMP Directive	• Guide to GMP
6. Pharmaceutical quality system	1. Pharmaceutical Quality System
7. Personnel	2. Personnel
8. Premises and equipment	3. Premises and equipment
9. Documentation	4. Documentation
10. Production	5. Production
11. Quality Control	6. Quality Control
12. Outsourced operations	7. Outsourced activities
13. Complaints and product recall	8. Complaints, defects and recalls
14. Self inspection	9. Self inspection
Law	Guidelines

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The EU Guide to GMP - Annexes

1. Sterile manufacturing
2. Biological products
3. Radiopharmaceuticals
4. Veterinary medicinal products
5. Immunological veterinary products
6. Medicinal gases
7. Herbal medicinal products
8. Sampling of starting materials
9. Liquids, creams and ointments
10. Metered dose inhalers

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The EU Guide to GMP - Annexes

11. Computerised systems
12. Use of ionizing radiation
13. Investigational medicinal products (IMPs)
14. Products derived from blood
15. Qualification and validation
16. Certification by a QP and batch release
17. Parametric release
19. Reference samples
21. Importation of products (into the EU)

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EU GMP Introductory statement

- *"It is recognised that there are acceptable methods, other than those described in the Guide, which are capable of achieving the principles of Quality Assurance. The guide is not intended to place any restraint upon the development of any new concepts or technologies which have been validated and which provide a level of Quality Assurance at least equivalent to those set out in this guide"*

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Any questions?

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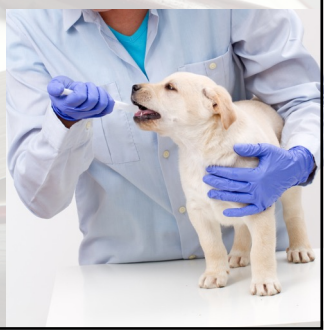
The Veterinary GMP Directive

- Veterinary Directive 91 / 412 / EEC
  - Has not been updated
  - Content is still roughly the same as the human Directive for commercial products
  - No mention of IMPs



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Directive 91 / 412 / EEC (Vet)

1. Scope
2. Definitions
3. Inspections
4. Conformity with good manufacturing practice
5. Compliance with marketing authorisation
6. Quality Management
7. Personnel
8. Premises and equipment
9. Documentation
10. Production
11. Quality Control
12. Work contracted out
13. Complaints and product recall
14. Self inspection

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Any questions?

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EU GMP 4 Parts

- **Part 1:** Finished Product GMP
- **Part 2:** Active Pharmaceutical Ingredients (API) GMP
- **The Annexes** (relevant to Parts 1 & 2)
- **Part 3:** GMP related documents
- **Part 4:** Advanced Therapy Medicinal Products (ATMPs)

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PART 3: GMP related documents

- Includes additional guidance documents, such as:
  - Quality Risk Management (ICH Q9)
  - Quality Management Systems (ICH Q10)
  - Site Master Files

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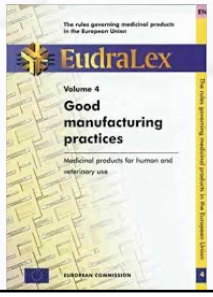
EUDRALEX

- The European Union Drug Regulatory Authorities Lexicon
- Contains many parts concerning the approval of medicines and sites of manufacture



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EUDRALEX

Vol. 1 Pharmaceutical legislation

Vol. 2 Notice to applicants

Vol. 3 Scientific guidelines for medicinal products

Vol. 4 Good Manufacturing Practices

Vol. 5 Pharmaceutical legislation (veterinary)

Vol. 6 Notice to applicants (vet)

Vol. 7 Scientific guidelines for medicinal products (vet)

Vol. 8 Maximum residue limits (vet)

Vol. 9 Pharmacovigilance

Vol. 10 Guidelines for clinical trials

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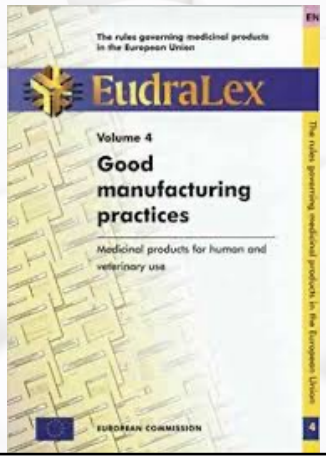
EUDRALEX

- Get EU GMP from EUDRALEX
  - https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en



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Any questions?

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United States GMP

- Code of Federal Regulations (CFR)
- Each Government department has its own volume
- Food and Drugs - Volume 21
- Part 211 – United States GMP (21CFR211)

- To protect the end user from poor quality medicines
- FDA - Food and Drug Administration

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Contents of 21 CFR Part 211

- Organization and personnel
- Buildings and facilities
- Equipment
- Control of components and drug product containers and closures
- Production and process controls
- Packaging and labelling control
- Holding and distribution
- Laboratory controls
- Records and reports
- Returned and salvaged drug products

Law | Updates are very difficult to get through the system

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Current GMP (CGMP)

- 21CFR211 plus …
- Federal Register
  - Daily publication from Congress
  - Becomes law on 1st April the following year
- Warning Letters
  - Give an indication of current areas of regulatory focus and problems seen

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Current GMP (CGMP)

- 21CFR211 plus …
- Guidance Documents - examples …
  - Process Validation: General Principles and Practices
  - Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations
  - Sterile Drug Products Produced by Aseptic Processing
  - Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

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BREXIT

- The UK:
  - To continue to work to EU GMP
  - Will have no influence on EU GMP
- Complications:
  - QP release of materials from the UK into the EU (and vice versa)
  - Approval of new medicines in both the EU and the UK
- To be (possibly) agreed:
  - Regulatory inspections between the EU and UK
  - Overseas inspections beyond the EU

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Any questions?

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Other countries of Europe

- There are other European countries that are not part of the European Union
  - For example: Switzerland, Norway and Turkey
- These countries work to EU GMP, even though they are not in the European Union (EU)

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PIC/S GMP

- Pharmaceutical Inspection Co-operation Scheme (PICS)
  - Co-operative framework among regulatory inspecting agencies
- If a country joins PIC/S then they will recognise GMP inspections done by other PIC/S member countries
  - Over 45 countries have signed up to PIC/S
  - Including EU, USA, Japan, South Korea
- PIC/s GMP is more or less the same as EU GMP
  - No mention of the Qualified Person
  - Not updated at the same time

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WHO GMP

- The World Health Organisation (WHO):
  - Primary role is to direct international health
  - Part of the United Nations
- Has a GMP guide
  - The same as PICS GMP
- Used in countries where there is no recognised pharmaceutical inspection system
  - Some parts of Africa, South America and Asia
- Do not “approve” manufacturing sites, but the inspection reports are available to download

World Health Organization

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Any questions?

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Regulatory expectations for Single Use Systems (SUS)

- EU GMP Annex 1: Sterile Products
  - (1 March 2009)
  - No specific mention of SUS
  - Will cover recent update to Annex 1 in next session

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Regulatory expectations for Single Use Systems (SUS)

- EU GMP Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use
  - (26 June 2018)

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Regulatory expectations for Single Use Systems (SUS)

- EU GMP Annex 2
- PREMISES AND EQUIPMENT (Clauses 5 – 18):
  - *Dedicated production areas should be used for the handling of live cells capable of persistence in the manufacturing environment …*

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Regulatory expectations for Single Use Systems (SUS)

- EU GMP Annex 2
- PREMISES AND EQUIPMENT (Clauses 5 – 18):
  - *Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems*

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Regulatory expectations for Single Use Systems (SUS)

- EU GMP Chapter 5: Production
  - (1 March 2015)

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Regulatory expectations for Single Use Systems (SUS)

- EU GMP Chapter 5: Production
- PREVENTION OF CROSS-CONTAMINATION (Clauses 5.17 – 5.22):
  - Technical Measures:
  - 5.21iv: Use of closed systems for processing and materials/product transfer between equipment
  - 5.21vii: Use of single use disposable technologies

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Regulatory expectations for Single Use Systems (SUS)

- FDA: Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing
  - (Sept 2004)
  - No specific mention of SUS

55

Technical guidelines

- Parenteral Drug Association (PDA)
  - Technical Report No. 66 Application of Single-Use Systems in Pharmaceutical Manufacturing (2014)

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References

- EU GMP Directives and Guidelines:
- https://ec.europa.eu/health/documents/eudralex/vol-4_en
- PICS GMP:
- https://www.picscheme.org/en/publications?tri=gmp
- WHO GMP:
- https://www.who.int
- USA GMP – 21CFR 211:
- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm
- USA GMP – Federal Register
- https://www.federalregister.gov/
- USA GMP – FDA Guidance Documents
- https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
- PDA Technical Guidance
- https://www.pda.org/bookstore/home

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