GMP update on Single Use Systems (Part 1)

Contents

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

The European Union (EU)

- A political union of 27 countries of Europe
  - Austria - Belgium - Bulgaria
  - Croatia - Cyprus - Czechia
  - Denmark - Estonia - Finland
  - France - Germany - Greece
  - Hungary - Ireland - Italy
  - Latvia - Lithuania - Luxembourg
  - Malta - Netherlands - Poland
  - Portugal - Romania - Slovakia
  - Slovenia - Spain - Sweden
- The United Kingdom left the EU in January 2020
  - Still works to the requirements of EU GMP

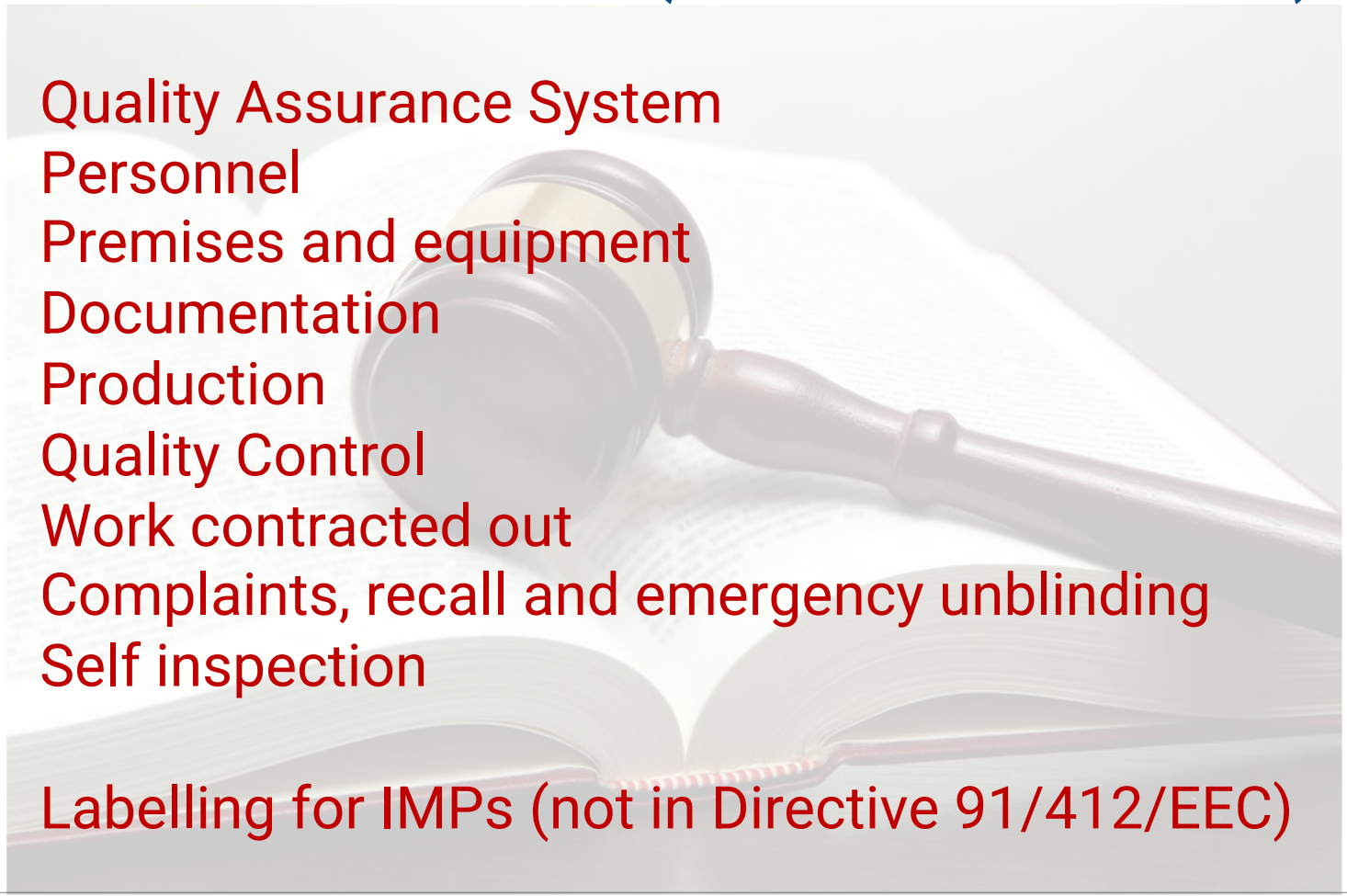
EU Law for GMP

- Two principle Directives
  - **Directive 2003/94/EC** for Human Medicines
  - **Directive 91/412 /EEC** for Veterinary Medicines
- Directive 2003/ 94/ EC (May 2004)
  - Replaced 91/356/EEC
  - Amended to mainly include additional requirements for Investigational Medicinal Products (IMPs)

Directive 2003/94/EC (human medicines)

- Articles 1 – 2: Administrative
- Article 3: Requirement for GMP inspections
- Article 4: Requirement to work to EU GMP
- Article 5: Requirement to make products that comply with their Marketing Authorisation (Product Licence)

Directive 2003/94/EC (human medicines)



- Article 6: Quality Assurance System
- Article 7: Personnel
- Article 8: Premises and equipment
- Article 9: Documentation
- Article 10: Production
- Article 11: Quality Control
- Article 12: Work contracted out
- Article 13: Complaints, recall and emergency unblinding
- Article 14: Self inspection

- Article 15: Labelling for IMPs (not in Directive 91/412/EEC)

Directive 2003/94/EC (human medicines)

- Article 6: Quality Assurance system

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

EU GMP: Chapters

- Chapter 1: Pharmaceutical Quality System
- Chapter 2: Personnel
- Chapter 3: Premises and equipment
- Chapter 4: Documentation
- Chapter 5: Production
- Chapter 6: Quality Control
- Chapter 7: Outsourced activities
- Chapter 8: Complaints, quality defects & product recalls
- Chapter 9: Self inspection

EU GMP: Annexes (1)

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 & ointments
10. Metered dose inhalers

EU GMP: Annexes (2)

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

EU GMP: Annexes (1)

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 & ointments
10. Metered dose inhalers

EU GMP – Four parts

- EU GMP is now in FOUR 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
  - Site Master Files
  - Quality Risk Management (ICH Q9)
  - Quality Management Systems (ICH Q10)
- Part 4: ATMPs (Advanced Therapy Medicinal Products)

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".* *(EU GMP Introduction)*

- *This has ramifications for auditors, as organisations can do things "differently"*
- *GMP auditors therefore need to be pragmatic*
- *Organisations need to keep up-to-date with new ideas and technology*

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)

PICS 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

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

GMP in the USA

- The Code of Federal Regulations contains all the legal requirements of US Government departments

- 21 CFR Part 211: Current GMP for finished pharmaceuticals (1976) is the legal requirement for medicinal (drug) manufacture

GMP in the USA: 21CFR 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

GMP in the USA: Other sources of info

- Instead of regularly updating the CFR, the FDA publish a number of other sources of information which collectively contribute to make up “Current” GMP (or CGMP)

- The Federal Register
  - Daily publication from Congress
  - Becomes law on 1st April the following year

- Warning letters
  - Not easy to fully interpret

GMP in the USA: Other sources of info

- Instead of regularly updating the CFR, the FDA publish a number of other sources of information which collectively contribute to make up “Current” GMP (or CGMP)

- Guidance documents, examples:
  - Out Of Specification (OOS) results
  - **Aseptic manufacturing**
  - Process validation
  - Quality Systems

Regulatory expectations for Single Use Systems (SUS)

- EU GMP Annex 1: Sterile Products (1 March 2009)
  - No specific mention of SUS

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)

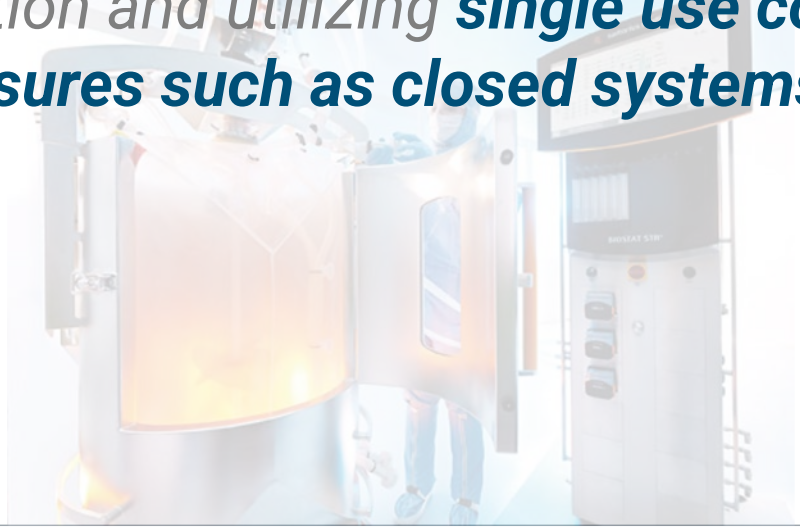
Regulatory expectations for Single Use Systems (SUS)

- 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 …*

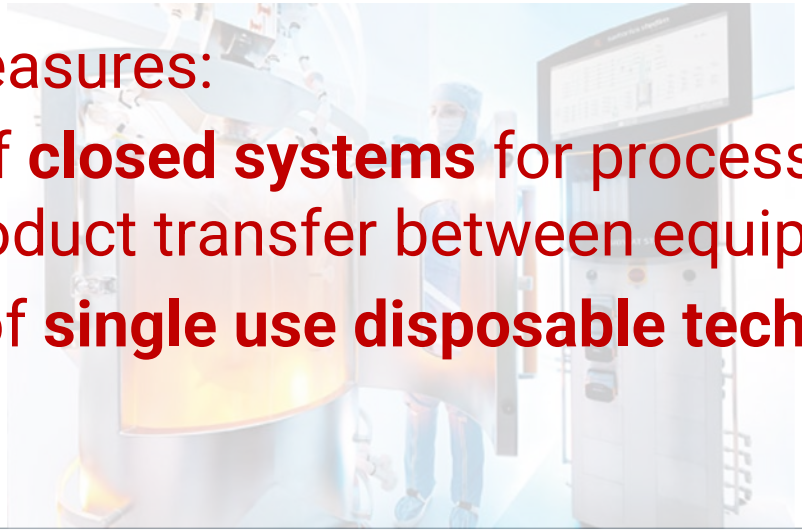
Regulatory expectations for Single Use Systems (SUS)

- 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***.



Regulatory expectations for Single Use Systems (SUS)

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



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

Technical guidelines

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

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