



your partner in compliance

EU and US GMP/GDP: Similarities and Differences

Nov 2016

We are passionate about putting safe and effective products in the hands of patients.

We are an award winning pharmaceutical consultancy that combines industry leading quality and technical insight with robust product development and commercialisation expertise.

This enables you to maximise innovation and product quality by implementing smarter, practical solutions that allow you to focus on what matters – ensuring your patients receive safe and effective treatment.

MPI's lifecycle services

Business Strategy Management

- Competency Assessments
- Due Diligence
- Post M&A Operations Integration
- Business Transformation and Organisational Development
- Enterprise IT Implementation
- ROI Analysis
- New Product Development and Commercialisation (NPDC)
 - Process Mapping
 - Process Development

Pharmaceutical Systems Quality Services

- Virtual Quality Assurance
- Regulatory Affairs
- QMS Design, Development and Remediation
- Quality Metrics

Development

- New Product Development and Commercialisation (NPDC)
 - Process Mapping
 - Process Development
- GLP Support
- Clinical Trial Strategy & Management
- Regulatory Strategy
- QP Services
- IMP management incl. Complaints, Defects & Recalls Handling

Tech Transfer

- Facility Design and Build
- Tech Transfer
- Scale-up

Approval

- Product Authorisation Support
- Inspection Readiness
- Inspection Remediation Activities

Manufacture

- Permanent Inspection Readiness
- QP Services
- Continuous Process Verification
- Facility Redesign and Upgrade
- IMP Management

Distribution

- Inspection Readiness
- QP Services
- RP Services
- De-Risking Supply Chain (SC)
 - SC Mapping
 - SC Risk Assessment

Post Market

- Inspection Readiness
- QPPV Services
- Pharmacovigilance Services
- MA Holder Compliance
- Complaints Defects and Recalls Management
- Promotion and Advertising
- New Product / Market Introduction

Discontinuation

- RP Services
- QP Services
- Regulatory Affairs
- Complaints Defects and Recalls Management
- Tech Support

Product Lifecycle Services

- Regulatory Strategy
- Regulatory Affairs
- Validation
- Error Risk Reduction
- Tech Support / Help Desk
- Knowledge Management
- Change Management
- Labelling and Packaging
- Supply Chain Management
- Risk Management
- Data Integrity
- Vendor Management
- Audit and Gap Analysis
- IT Implementation
- Training

What we do

MPI's services cover all product types across the entire product lifecycle

- Large and small molecules/biotech and non-biotech
- Steriles and non-steriles
- Active Pharmaceutical Ingredients (API)
- All dosage forms
- Medical device and device combinations
- Traditional Herbal Medicines
- Cosmetics



- GLP
Good Laboratory Practice
- GCP
Good Clinical Practice
- GMP
Good Manufacturing Practice
including Good Practice for Tissues and Cells (GP)
and Good Engineering Practice (GEP)
- GDP
Good Distribution Practice
- MAH
Market Authorisation Holder compliance
- GPvP
Good Pharmacovigilance Practice
- GBP
Good Behavioural Practice
- GPP
Good Pharmacy Practice

Some of our client partners...



Content

Key Differences in the Regulatory Framework (EU vs US)



Key Differences between US and EU – Focus GMP/GDP



Process Key Differences between Annex 1 and CFR's Sterile Manufacture






FDA vs EU GMP Inspections - Differences in Approach and Style

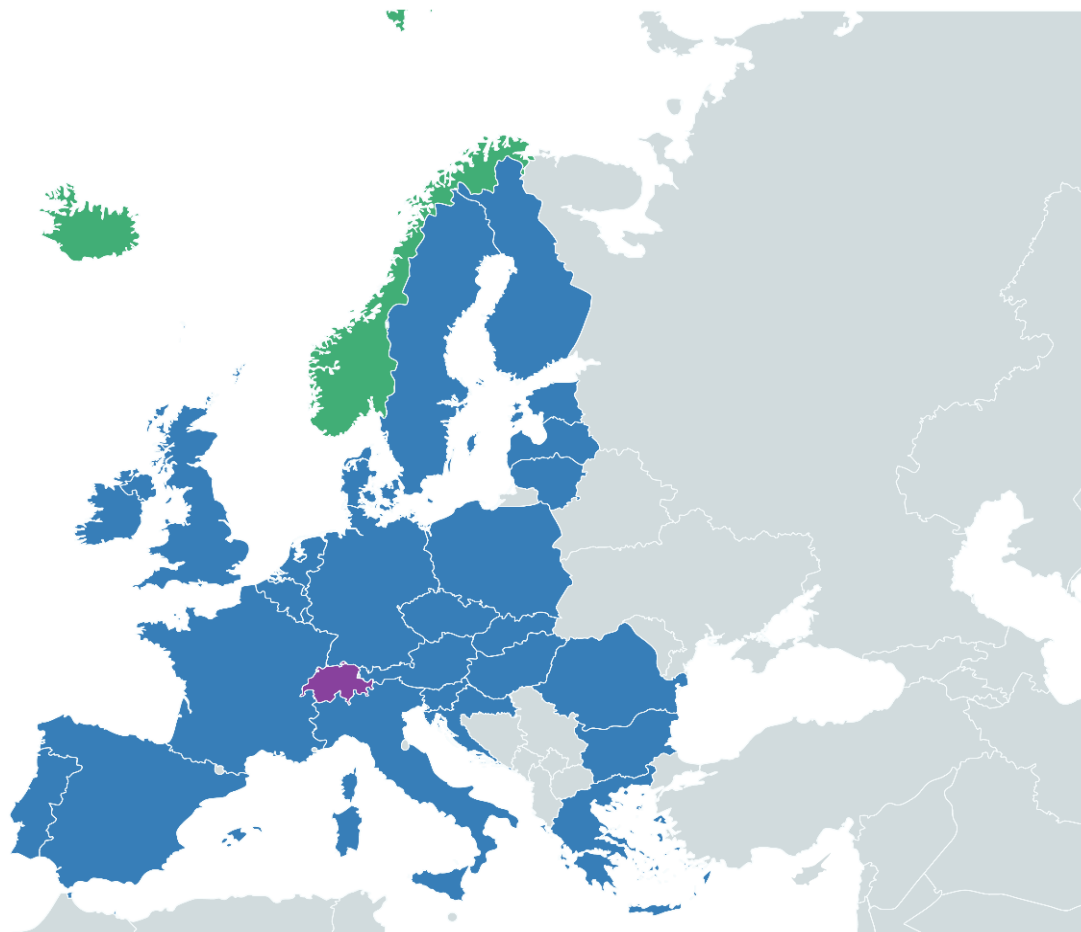


Key Differences in the Regulatory Framework EU vs US

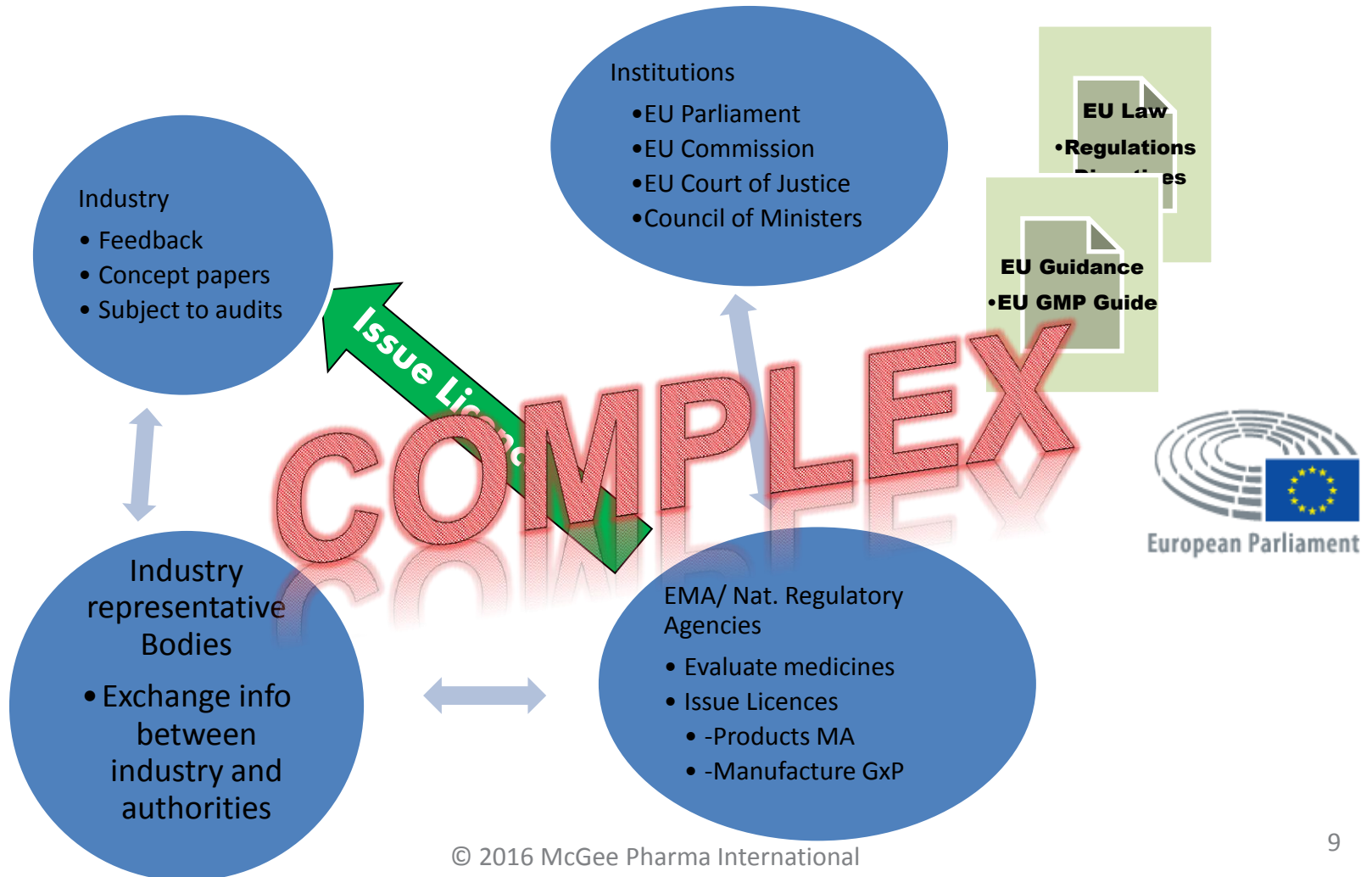


Countries in Europe

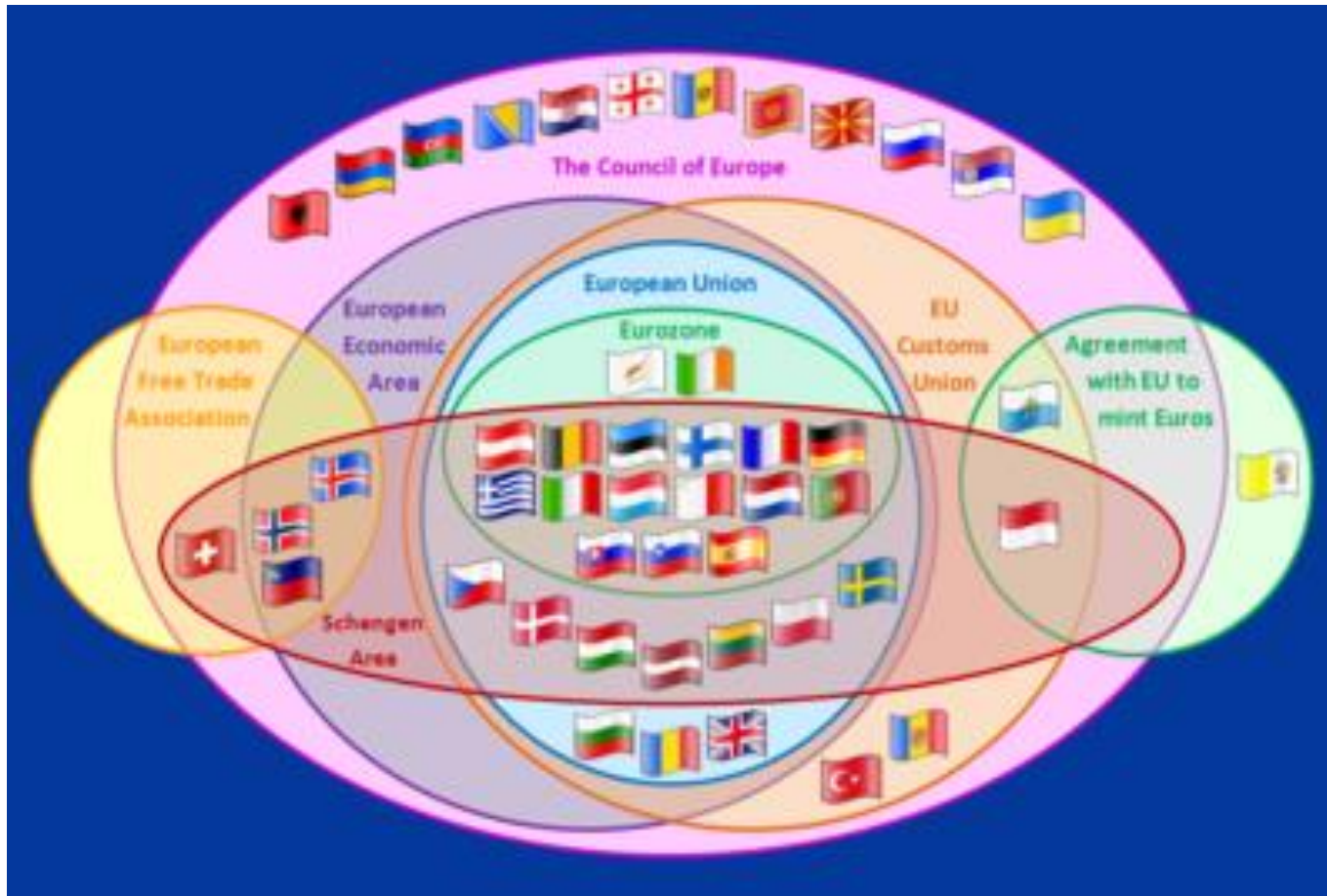
-  European Union
-  European Economic Area
-  Single Market (neither EU nor EEA)

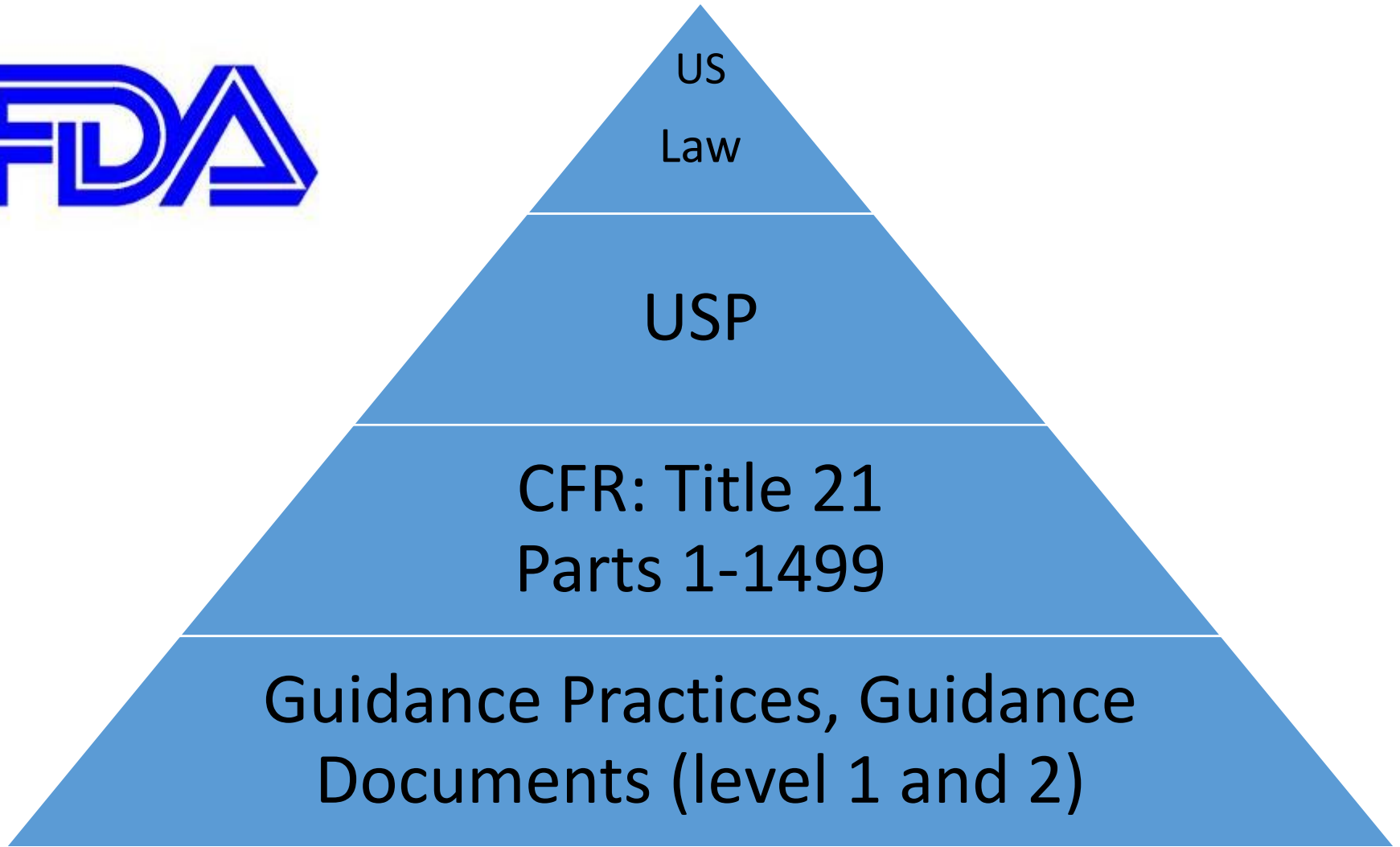


How Things Work in the EU/EEA



How things work in the EU





Differences in Regulatory Framework: EU vs US

US GMP requirements detailed in Title 21 CFR

- Code of Federal Regulations has legal binding force

EU GMP requirements – Regulations, Directives & Guides e.g.

- **Regulations** have binding legal force in every Member State (MS) and enter into force on a set date in all the MSs.
- **Directives** lay down outcomes that must be achieved; each MS may interpret when transposing into national laws
- Eudralex, Volume IV: Rules governing medicinal products in the EU
 - **Guidance** on GMPs

EMA and NCA agencies

European Commission authorises medicines on the recommendation of the European Medicines Agency (EMA)

EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU

EMA is only responsible for medicines that are managed through the centralised authorisation procedure

EMA works closely with the 28 Member States as well as the European Economic Area countries (Norway, Iceland and Liechtenstein)

National Competent Authorities (NCA) are responsible for the authorisation of medicines available at a national level

Collaboration Initiatives

Mutual Recognition Agreement (MRA) not in place between the US and EU

Sharing of information but FDA policy prevents sharing of 'Trade Secret' information in Field Inspection Reports

Collaboration Initiatives

EU-US Mutual Reliance Initiative (MRI)

- Launched 2014- strategic collaboration between FDA & EU MSs
- Confidence building through exchange of information & engagement on respective systems for supervision of manufacturers
- To date, EU has visited several FDA's district offices & evaluated work; FDA has observed a number of inspections in individual Member States & will continue to do so in 2017

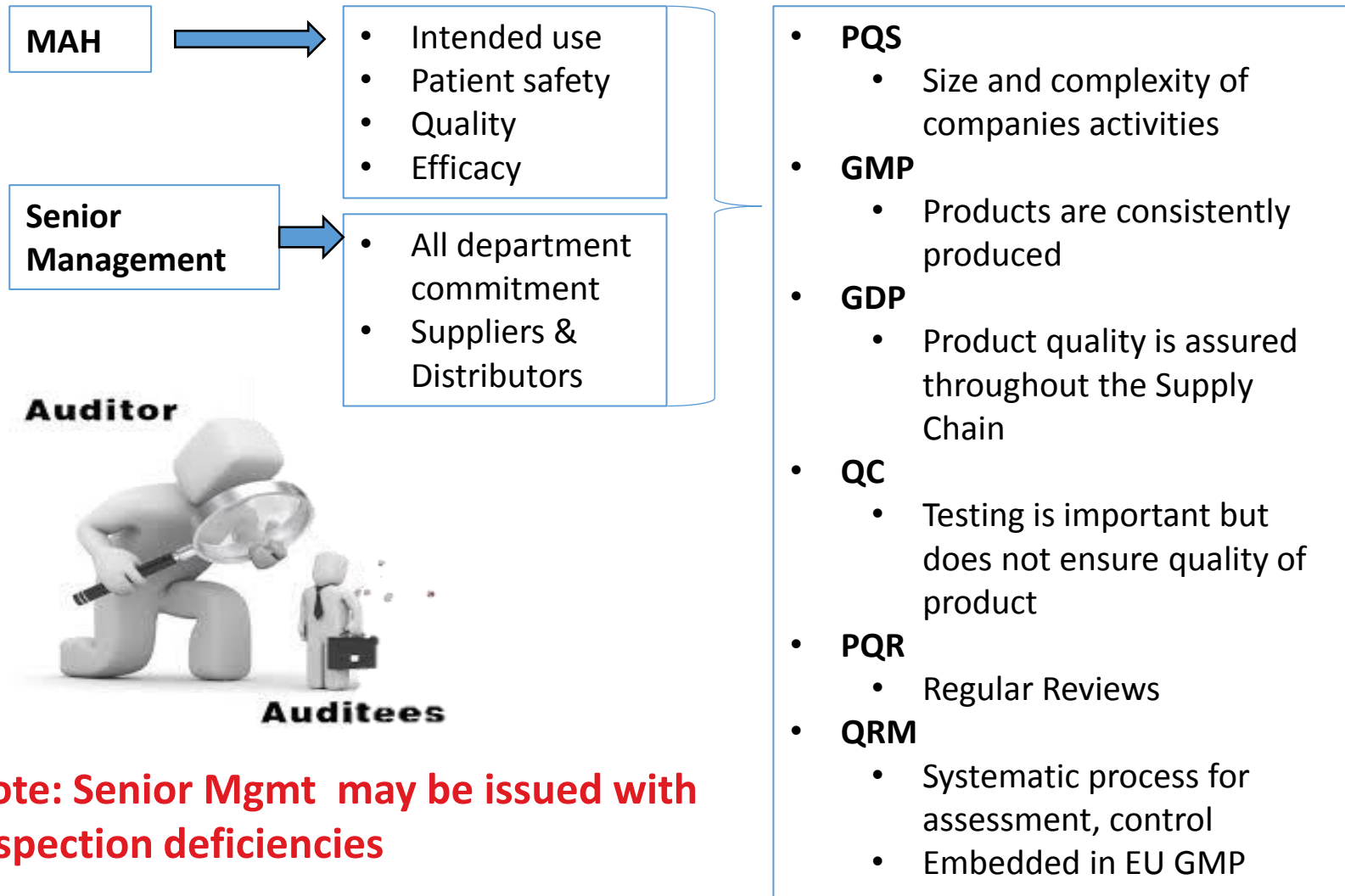
EU proposal tabled for discussion Apr 2016 ahead of Transatlantic Trade & Investment Partnership (TTIP) negotiations between EU & US

- Aim to further harmonise pharmaceutical regulations between the EMA & US FDA
- Could speed new drug approvals & manufacturing inspections in both regions

Key Similarities & Differences between EU and US GMP/GDP



Pharmaceutical Quality System (PQS) -EU



Note: Senior Mgmt may be issued with inspection deficiencies

APR (US) Vs PQR (EU)

Objectives: Annual Product Review (APR)

- The FDA “Annual product review” is intended to confirm that every batch of product released during the review period complied with the registered process and specification.

Objectives: Product Quality Review (PQR)

- The EU PQR concentrates on the quality system and process to show that they continue to produce consistently good quality product.
- EU Inspectors expect discussion & evaluation of the data presented and ID of appropriate process improvements as required*

EU Inspectors are now requesting PQRs in advance of inspections!

Tracking & Trending of Key Process Indicators (KPIs) – EU GMP Chapter 1

Chapter 1 updated to align with ICH Q10 PQS

- Use of QRM in establishing a **control** strategy for process performance & product quality
- Use of tools for **measurement & analysis** of process performance & product quality
- Demonstration of a **state of control**
- Identification of opportunities for potential **continuous improvement**

Review by management on a periodic basis:

- Measurement against PQS objectives - leading & lagging metrics
- Monitor effectiveness of processes & plan for improvements, using outputs from e.g.
 - APQRs
 - Complaints, Deviation, CAPA, Change Management processes
 - Feedback on outsourced activities
 - Self-assessment processes including risk-assessments & trending
 - External audits such as regulatory inspections & customer audits

Quality Metrics and KPI's

FDA Metric-based Surveillance (Janet Woodcock, PDA Conf. Washington, Sep 2013):

- Pharmaceutical Industry: Lack of commitment to Quality
- Drug recalls often not GMP failures but failures of quality by design
- Intrinsic quality: To continually recognise, improve and solve problems and not just to please regulators
- Using metrics and assessments of the quality culture is where we need to be through metric-based surveillance
- FDA wants to shift to 'Performance-based Regulation' proposal setting up 'Metric-based Surveillance'
- Adopting commitment to high quality medicines v meeting regulatory standards being minimal expectations
- Quality Push: 'Beyond compliance and moving to a quality culture of the whole ecosystem including regulators'

FDA proposed metrics - 2015

Aim of Quality Metrics program:

- Support risk based inspection scheduling
- Predict & potentially mitigate drug shortages

Metrics to be calculated by FDA for each product/establishment

- Lot Acceptance Rate
- Product Quality Complaint Rate
- Invalidated OOS Rate
- APR/PQR On-Time Rate

Optional – for public comment

- Senior Management engagement – who reviews and approves A/PQR?
- CAPA effectiveness based on re-training?
- Process capability measured for each CQA – Y/N indicators



ISPE Quality Metrics Initiative: Pilot Program (Wave 2) – June 2016

ISPE is supportive of starting with 3 of the proposed metrics

- Lot Acceptance Rate (report by site, differentiated by product)
- Product Quality Complaints (report by product only)
- Invalidated OOS (report by site)

ISPE recommends to defer as potential future metrics or data points

- APR on Time Rate and Optional Metrics
- “lots pending disposition for over 30 days”

Start with reporting consistent with current industry practice

- May reduce burden for start up of program

Preliminary results from ISPE Pilot Wave 2 included in Response to FDA

Anticipated costs for firms to comply with FDA requests

Quality Metrics

“As we know, there are known knows; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns—the ones we don’t know we don’t know.”⁹

US Defense Secretary, Donald Rumsfeld, Feb 2002

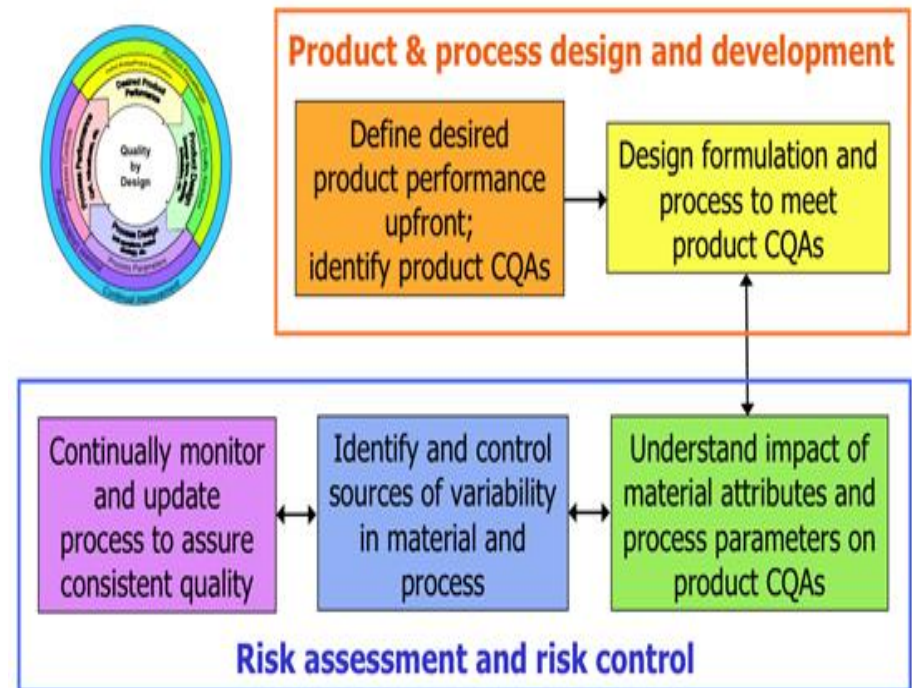
- Need to consider product lifecycle if we are to measure quality culture
- Need to avoid creating confusion through different methodologies to prepare metrics
- Need to avoid driving inappropriate behaviours
- Xavier University research

Process Validation - Revised Annex 15 to align with US PV Guideline 2011

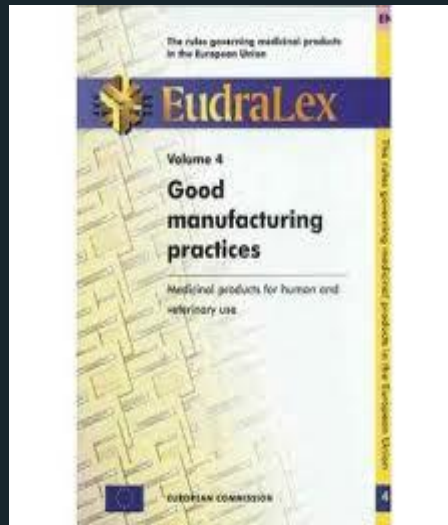
Options for Process Validation have been extended to:

- **Traditional Approach**
- **Continuous Process Validation** as described in ICH Q8
- **Hybrid Approach** (hybrid of the Traditional and Continuous Process Validation)

As part of "ongoing process verification", product quality should be monitored during the product life cycle to show that the "state of control" is fulfilled and that trends are assessed. "Ongoing process verification" should be based on and reported according to a protocol or equivalent documents



Some EU Specifics



Contamination Control – EU Hot Topic!

Updates to Chapters 3 and 5

- Documented **Contamination Control Strategy** required
- QRM principles should be used to assess & control the risks of contamination & cross contamination
- Risk Assessment should include a toxicological evaluation of the products being manufactured
- Dedicated facilities are required when:
 - the risks cannot be adequately controlled by operational &/ or technical measures
 - scientific data does not support threshold values or
 - threshold values are below required levels of detection



Chapter 5: Dedicated Facilities/Toxicology

Prevention of cross-contamination and the need for toxicological assessment:

- Specific attention to design of the premises and equipment (link to Chapter 3)

Challenges:

- Need to be read in conjunction with the EMA guideline on setting health based exposure limits for use in risk identification
 - Ref: EMA/CHMP/CVMP/SWP169430/2012; effective 01 June 2015
- Use of toxicologist specifically required to evaluate allowable limits of carryover
- Tighter limits required? – potential requirement for dedicated equipment and facilities



Chapter 5 – Production Updates (EU)

Supply Chain traceability

- Qualification of suppliers to reflect the legal obligations of MAHs
- Manufacturer must ensure that all the starting materials used originate from controlled sources – GMP compliance for API & excipients
- GMP & GDP audits should be carried out at manufacturers and distributors of API – QRM approach
- Clarification and harmonisation of expectations of manufacturers regarding the testing of starting materials (active substances, excipients)

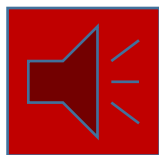
Continuity of Supply

- Guidance on industry notification to Regulatory Agencies of restrictions in supply
- Manufacturer should report to MAH any constraints in manufacturing operations which may result in abnormal restriction in supply

Supply Chain and GDP

Supply Chain Challenges:

- Complexity of supply chain
- Transparency of everybody involved
 - What parties are involved in which activities at each stage of the chain?
 - Who is the original manufacturer- of the API, Excipient, Product?
 - Who has responsibility for each 3rd party? MAH vs WDA vs MIA Holder
- Quality and robustness of Quality Systems across the supply chain
 - QMS and operational SOPs must be very comprehensive and cover all aspects from API to FP
 - SOP on Quality Risk Management
- Maintaining traceable, authentic and complete documentation



Map the Supply Chain end to end!

EU GDPs (2013/C 343/01)- Summary

SUMMARY

- The Wholesaler must maintain an **adequately resourced QMS** - incorporates QRM principles, validation, change control, deviation and corrective and preventive action (CAPA) management
- The Wholesaler must **appoint an RP** - responsible for ensuring that the wholesaler is in compliance with GDP & the conditions of the WDA
- **Premises and equipment must ensure proper storage** and distribution
- **Validation** of critical processes
- **Suppliers and Customers must be qualified**
- **Suspected falsified medicinal product** must be segregated & distributors must inform the relevant competent authority & MAH (**Refer to FMD 2011/62/EU**)

- **Recall** - a system must be in place and this must be challenged periodically
- **Procedures** must be in place for **complaints, returns, falsified medicines and recalls**
- **Outsourced Activities** must be covered by **written contract**
- Must be able **demonstrate products have not been subject to conditions during storage/transport that may compromise quality**. Deviations should be recorded/investigated
- Product - transported to **label claim**
- **Transportation conditions and packaging** should be **validated**
- **Brokers must be registered** with the Competent Authority

GMP for Excipients

Expectation is that Manufacturing Authorisation Holders perform a risk assessment to determine the Excipient Manufacturers' risk profile

A number of steps to be taken to achieve this:

- Classification of risk profile of each Excipient in each formulation- Low/Medium/High
- Determine GMP Controls
- Classification of Manufacturer's risk profile - Low/Medium/High Risk
- Risk Control Strategy

19 considerations include:

- Source - animal/mineral/vegetable/synthetic
- Past history of supply
- Purpose and function of excipient
- Patient risk (e.g. route of administration, volume consumed)
- Source of excipient and supply chain
- Supplier history etc.



EU GMP Guide, Chapter 7 Outsourced Activities

Overview

- Reflects globalisation of supply chain
- Reflects ICH Q10 - PQS
- Clearly defines expectations regarding quality contracts
- **Key Difference with US:**
Extends to all outsourced activities impacting GMP beyond manufacturing and analysis



The Role of the Qualified Person (QP)

A position recognised under EU pharmaceutical law

“the ultimate responsibility for the performance of an authorised medicinal product over its lifetime; its safety, quality and efficacy lies with the marketing authorisation holder (MAH) ” and “... the responsibility for ensuring that a particular batch has been manufactured in accordance with its marketing authorisation, with EU Good Manufacturing Practice (GMP), or equivalent, ... lies with the QP”.

“No batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations in accordance with annex 16”

Personal responsibility and liability of the QP

QP must be registered or appointed or approved with the competent authority of the relevant EU Member State & named on the Manufacturer’s Licence

Role of the QP – Update in 2016



EU GMP Guide, Annex 16, section 3.5.5

*"The **entire supply chain** of the medicinal product, starting from the manufacturing sites of the starting materials and components, and including all parties involved in any manufacturing and importation activities of the medicinal product, is **documented and available** for the QP."*

Section 2



Where the QP has to rely on GMP assessment by third parties:

- QP should ensure that a written final assessment and approval of third party audit reports has been made in accordance with EU GMP Chapter 7
- QP should be aware of the outcome of an audit with critical impact on the product quality before certifying the relevant batches



Section 3.5.9

*"The **active substances** used in the manufacturing of the finished products have been manufactured in accordance with **GMP** and, where required, imported and distributed in accordance with Good Distribution Practices (**GDP**)....."*



Section 3.5.21

" The appropriate arrangements for distribution and shipment are in place."

Metal Catalyst Guidance

Applies to APIs and Excipients

Permitted Daily Exposure (PDE)

Sources of metal:

Catalysts

Equipment

Piping

Concentration Limit (ppm) = $\text{PDE } (\mu\text{g per day}) / \text{Dose } (\text{g per day})$

Metal Catalyst Guidance contd

Risk Assessment Process Steps –metal impurities

- Identify the potential sources of elemental impurities that are known or suspected, or have the potential to end up in the finished product
- Evaluate the actual or predicted levels of elemental impurities by comparison with the established PDEs
- Summarise and document the risk assessment and determine if the controls built into the process are sufficient to limit elemental impurities in the finished dosage form

Includes recommendation for 24 elements to be considered in the risk assessment and also describes special considerations for biotechnologically derived products

June 2016 – effective date for new MA applications

Dec 2017 – effective date for authorised medicinal products.

**Key Differences between
Annex 1 and 21 CFR's
Sterile Manufacture**

Numerous guidance and regulations addressing different aspects of aseptic processing:

FDA

- 21CFR 210
- 21CFR 211
- 21CFR 600s
- FDA Aseptic Processing guidance document

EU

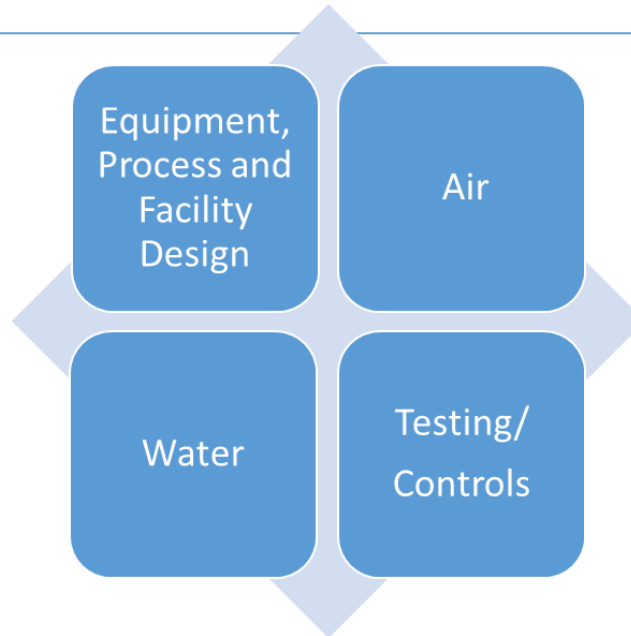
- EU Directives supported by the EU GMP Guide (Eudralex Vol. 4, Annexes 1 and 2)
- EU GMP Guide, Annex 1 Manufacture of Sterile Medicinal Products, 2008
- EU GMP Guide, Annex 2 Biological Manufacture of Biological Active Substances and Medicinal Products for Human use

Chapter 5 – Production

E.U.: Aseptic Manufacture is seen as the last resort. Only the stability of the product is considered as a factor in choosing the sterilisation method (not the container closure system).

U.S.: Aqueous based oral inhalation solutions, ophthalmics and injectables must be sterile. Sterilisation in the final container is the sterilisation method of choice.

Focus on four key factors:



Summary of Differences:

| Factor (topic) | US | EU |
|--|---|--|
| Equipment, Process & Facility Design | <p>Capping Process Does not specify the environmental requirements for capping operations; they should be appropriate and are inspected against that expectation</p> | <p>Capping Process Considers a vial not closed until the seal is in place (potential for contamination exists until that point); interpretation of minimum requirements difficult (<i>revision of Annex 1 is expected in 2016 to provide additional clarity</i>).</p> |
| <p>Equipment, Process & Facility Design - Room Classification / Air Quality</p> | <p>Subtle differences between naming system for area classification used (although same intent) NOTE: may result in some differences in areas of focus during regulatory inspections and interpretation of minimum requirements</p> | |
| | <p>Class 100, etc. (US designation, 3520 particles per ft³ of 0.5µm size)</p> | <p>Grade A, etc. Class A must meet ISO classification of 4.8 for particles of 5µm</p> |
| | <p>Operates to ft³ measurement;</p> | <p>Operates to m³ measurements;</p> |
| <p>Air Quality (Particulates – Type, size, and number/m³)</p> | <p>Particulates at “dynamic” conditions (i.e. in-operation).</p> | <p>Distinction between critical area particulates while “at rest” and “in-operation”</p> |

Summary of Differences:

| Factor (topic) | US | EU |
|--|---|--|
| Air Quality - Air samples | Sample volume: should be sufficient to optimize detection of contaminants | Sample volume: for classification of Grade A, minimum sample volume of 1m ³ |
| Air Quality - HEPA filters (Air exchange rate not specified by either agency) | Provides additional guidance on efficacy, leak and challenge testing; FDA - HEPA filters are leak-tested twice a year and require periodic monitoring | Filter leak testing / monitoring applies equally in the EU - defined by the ISO 14644 standard. |
| Water quality | Accepts reverse osmosis and distillation (per USP) as methods for production of WFI; WFI produced by ultrafiltration (not listed in USP) may also be acceptable. FDA – Constant circulation of WFI at a temperature range of 65°C - 80°C. | WFI to be produced by distillation (reverse osmosis is currently not considered acceptable). Constant circulation of WFI > 70°C <i>NOTE: new draft of EP monograph allows for non-distillation methods for producing WFI but does not define GMP controls for the generation system; this update being coordinated & aligned with a revision to EU GMP Guide Annex 1</i> <i>May 2002 NFG on Water Quality Specifies the grade of water to be used for different stages of API Manufacture</i> |

Summary of Differences:

| Factor (topic) | US | EU |
|---|--|---|
| Testing & Controls (Sample collection requirements) | <ul style="list-style-type: none"> Microbiological samples, limits and method of collection are not harmonized. However, both EU/EMA and FDA require identification of contaminants when positive results are obtained. Agencies in both jurisdictions expect a risk based approach to defining the sampling points in the water distribution systems; EU expects this risk assessment to be formal, documented and reviewed annually. <p>Further details on air, in-process environmental monitoring & simulation sampling, ref: <i>Aseptic Processing – Key differences between EU & US requirements (white paper)</i></p> | |
| Testing & Controls (Media Fill Studies) | Recommended microbiological action limits for Grade A = 1; however, caveat that <i>“samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants”</i> . | Recommended microbiological action limits for Grade A < 1 |

Additional EU requirements:

| Factor (topic) | US | EU |
|--|--|--|
| Steriliser / Autoclave | Expectations are aligned; however, not as specifically defined in regulations or guidance documents. | Autoclave qualification, operation, and load validation looked at in considerable detail (against the detail of the EN 285 & HTM 2010 standards). |
| In-process environmental monitoring samples | <p>Several sampling locations include fingers, facemask, etc.</p> <p>1 cfu/4 hours (Microbiological Settling Plates Action Levels (diam. 90mm))_Caveat that <i>“samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants”</i></p> | <p>5-finger touch plates expected; expectation that the face (typically for forehead), chest and both arms are sampled.</p> <p>Expectation that program includes all sampling methods (active air; contact plates; settle plates; glove prints); FDA more flexible on mix of methods especially use of settle plates.</p> <p><1 cfu/glove or settle plates (diameter 90 mm) cfu/4 hours</p> |

Additional EU requirements:

| Factor (topic) | US | EU |
|--|--|--|
| <p>Room Classification / Air Segregation</p> | <p>No specific classification for the final gowning stage (see Air section below); inspections are risk based, focusing on those operations that require employees to enter the critical areas of the processing line</p> | <p>Gowning requirements are specified for each grade of area A to D. In addition, it is expected that changing rooms are designed as airlocks and that the final stage of the changing room should, in the at rest state, be the same grade as the area into which it leads.</p> <p><i>“the final stage of a change area/room is required to be the same grade as the area into which it leads</i></p> |
| <p>Testing and Controls (EU regulatory inspection focus / expectations)</p> <p>Ref to paragraphs of EU GMP Guide, Annex 1</p> | <p>Paragraphs 77-80: specific expectations for acceptable time intervals between washing & drying; between drying & the sterilization of components, containers & equipment and between sterilization & use (demonstrate appropriate records are available for actual time intervals for routine processing)</p> <p>Paragraph 80: requirement to minimize the time between the start of preparation of a solution and its sterilization or filtration through a micro-organism retaining filter (actual times documented on a batch basis; compliance with process validation in relation to time and critical filtration parameters (e.g. pressure) is evaluated as part of the batch review process)</p> <p>Paragraph 80: bioburden monitoring of the bulk solution before sterilization (expected for every batch & part of batch review process).</p> <p>Paragraph 62: disinfectants and detergents should be monitored routinely for microbial contamination (validation studies to support shelf lives is common among EU & FDA) .</p> | |

FDA vs EU GMP Inspections Differences in Approach and Style

EU Approach to Regulatory Inspection

Typically announced inspections

Duration is defined: typically 3-5 days x2 inspectors for manufacturing sites

Typically, inspectors are recruited from Industry – have direct experience in manufacture/ GMP

Inspections are practical – data driven approach; supported by document review

- Detailed review of systems, processes and facilities - in the manufacturing area
- Aim is to evaluate system design, process control & ability of people to do the job
- Typically interactive – scientific engagement to enable continual improvement
- Observations (CR, MAJ, Other) confirmed at end of inspection
- Report follows in approx 15 days – ALL observations included
- Response to ALL observations expected with timelines for implementation of actions





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Next Steps

- **Are you interested in learning more about current/pending European legislation?**

If so, we would be very happy to sign you up to our e-newsletter, TABS, which we publish three times per year. This publication reviews new and impending legislation and assesses the practical implications for industry providing advice and guidance on requirements for compliance. Simply email jane.lyons@mcgeepharma.com and we will add you to our e-newsletter list.

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