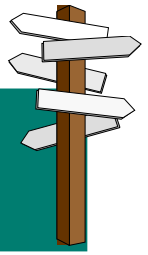
General Introduction to GMP, History, ICH, PIC/S, EU, FDA

LAW: REGULATORY BODIES

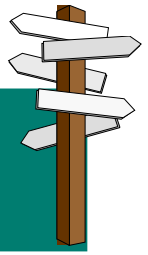


A regulatory body is like a professional body but it is not a membership organisation and its primary activity is to protect the public. Unlike professional bodies, it is established on the basis of legal mandate.

Regulatory bodies exercise a regulatory function, that is: imposing requirements, restrictions and conditions, setting standards in relation to any activity, and securing compliance, or enforcement

Examples:
ANVISA: Brazilian
IGZ: Dutch
NRA's (National Regulatory Angencies)
US-FDA: United States of America
EU: Guidelines and Directives to be implemented by individual memberstates.

WHY BY LAW?



Effect of Medicines:

- Administered to (already) sick persons
- User has no capability to determine quality, effectiveness or safety
- Neither does the prescriber
- Molecules not part of regular metabolic system.
- Globally distributed (scale)

Risks have increased:

- < 1800:
  - Natural medicines
  - “Home made” Herbs etc
- 1800 - 1900:
  - Physics / Small Scale
- > 1900:
  - Medicinal Production
    - Local > National
    - European > Globally
- Existing Situation:
  - Complex Distribution System

EU LEGISLATION

- Assurance of Quality (Medicinal Products)
  - Registration
  - GMP
  - Release by Company (QP vs RP)
- Tracebility of Medicinal Products
  - Across the Entire Supply Chain
- Preventing introduction into the Supply Chain of non-approved Medicinal Products:
  - Counterfeit
  - Over due's and/or Recall

PURPOSE OF LAW

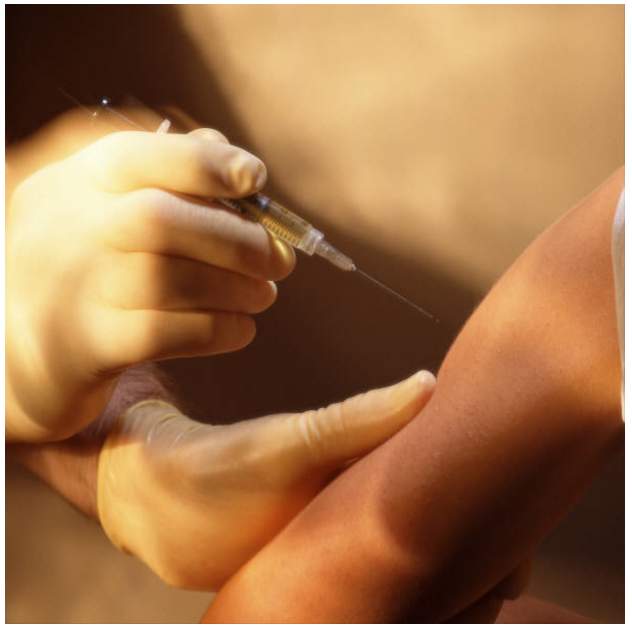
Fit for their intended use,

Comply with the requirements of the dossier

Do not place patients at risk due to inadequate:

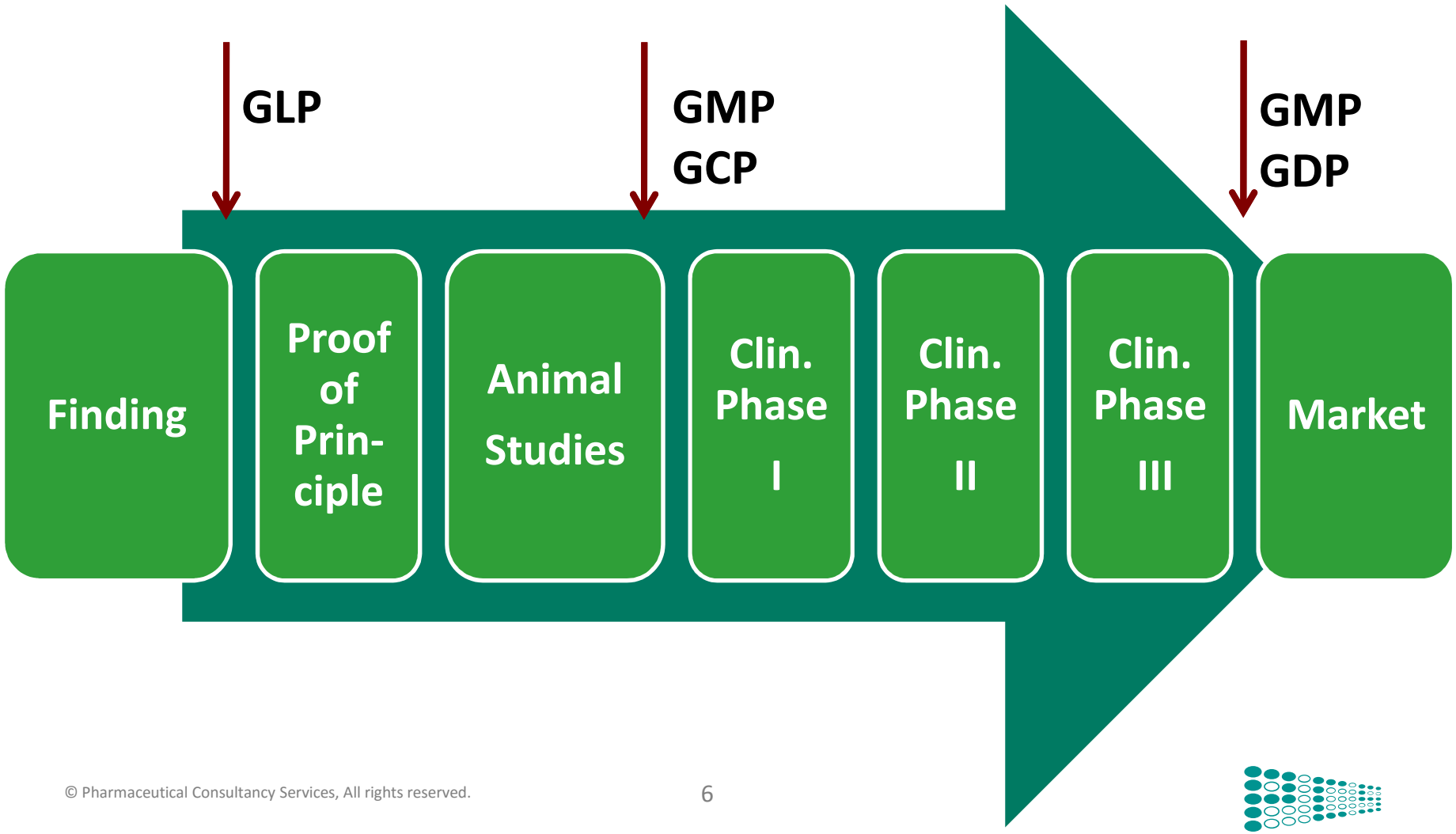
- safety,
- quality
- efficacy.

during the entire period being in the Supply Chain



Protected against Falsification/Counterfeit

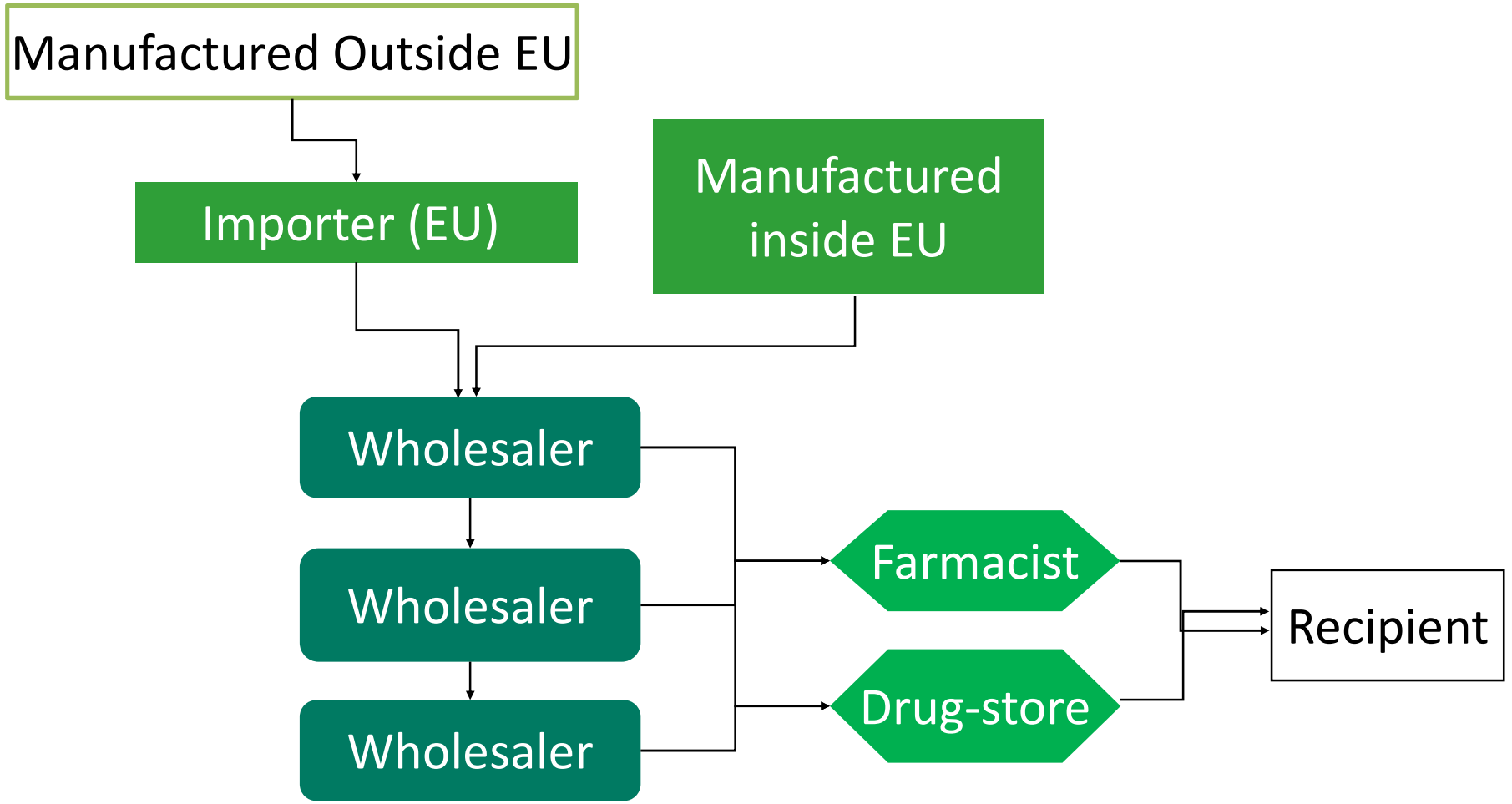
DEVELOPMENT OF MEDICINES



EU “LAW”

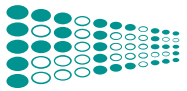
- **DIRECTIVES** for Medicinal Products
- Formerly: 65/65/EEC, 75/319/EEC, 75/318/EEC
  - Combined in: 2001/83/EC
- Counterfeit Directive: 2011/62/EU
- GMP: 2003/94/EC
- GDP: 2013/C 68/01

PRINCIPLE OF LICENCED SUPPLY CHAIN SYSTEM



GDP-GUIDELINES (2013/C 68/01)

- Wholesale distribution
  - Control of the Distribution Chain (maintaining Quality)
  - Prevent entering Falsified Medicines into the chain.
- Current Insights (compared with 1994 version)
  - Quality Systems
  - Risk Management
  - Warehouse-facilities
  - Qualification and Validation
  - Outsourcing
  - Falsified Medicines



GDP VERSUS GMP CHAPTERS (EUDRALEX VOL 4)

GDP Chapters (Other Documents)	GMP Chapters (Part I)
1. Quality Management	1. Pharmaceutical Quality System
2. Personnel	2. Personnel
3. Premises and Equipment	3. Premise and Equipment
4. Documentation	4. Documentation
5. Operations	5. Production
6. Complaints, Returns, Suspected Falsified Medicinal Products and Medicinal Product Recalls	6. Quality Control
7. Outsourced Activities	7. Outsourced Activities
8. Self-Inspections	8. Complaints and Recall
9. Transportation	9. Self Inspection
10. Specific Provisions for Brokers	

EU GMP-GUIDELINE CONTENT

Annexes: (1-19) amongst others:

1-Manufacture of Sterile Medicinal Products

2-Manufacture of Biological active substances and Medicinal Products for Human Use

3-Manufacture of Radiopharmaceuticals

4-Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products

6-Manufacture of Medicinal Gases

9-Manufacture of Liquids, Creams and Ointments

11-Computerised Systems

15-Qualification and Validation

17-Parametric Release

19-Reference and Retention Samples

EU GMP-GUIDELINE CONTENT

- **Part II: Basic Requirements for Active Substances used as Starting Materials**

Text of old Annex 18

EU GMP-GUIDELINE CONTENT

- **Part III - GMP related documents**
- Amongst others;

Site Master File

Q9 Quality Risk Management

Q10 Guidance on Pharmaceutical Quality System

MRA Batch Certificate

U.S. FDA

US-FDA OFFICES

Strategic locations around the world, including China, Europe, India and Latin America.

Work closely with foreign governments, industry, and other stakeholders

US-FDA 21CFR'S

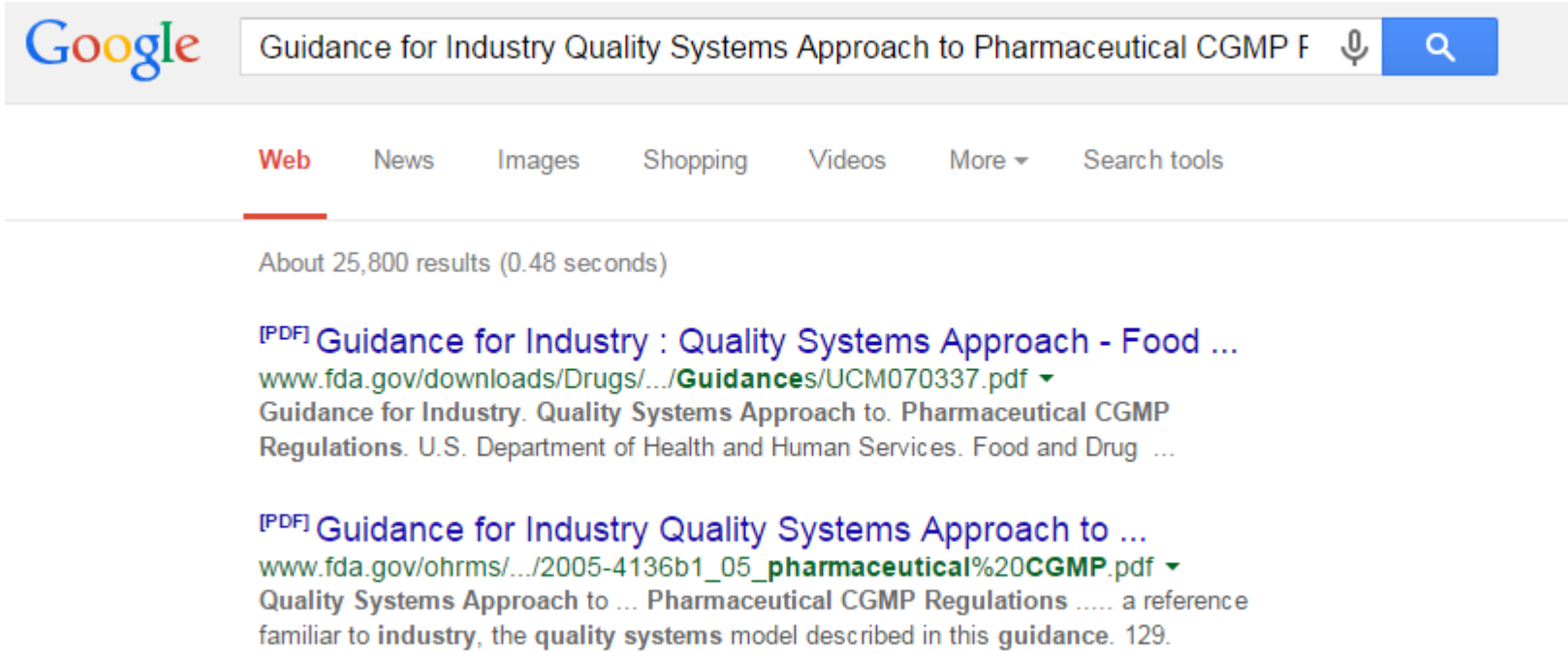
US FDA Title 21 CFR Parts

- Part 11 - regulations on electronic records and electronic signatures
- Part 210 – **CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL**

  Part 211 - **CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS**
- Part 600 - Biological Products:General
  Part 601 - Licensing Biologics
  Part 610 - General Biological Products Standards

MODERNIZATION OF FDA

This guidance is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the FDA`s current good manufacturing practice (CGMP) regulations (2l CFR parts 210 and 211).



http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf

MODERNIZATION OF FDA

October 2014 Guidance (US) for Industry: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144) was signed into law. Section 707 of FDASIA adds 501(j) to the Food, Drug, and Cosmetic Act (FD&C Act) to deem adulterated a drug that "has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection." Section 707(b) of FDASIA requires the Food and Drug Administration (FDA) to issue guidance that defines the circumstances that would constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection, for purposes of section 501(j).

MODERNIZATION OF FDA

BACKGROUND AND PURPOSE

- August 2002, the FDA announced the Pharmaceutical CGMPs for the 21st Century Initiative
- Intent to integrate *quality systems* and *risk management* approaches

GOAL OF THE GUIDANCE

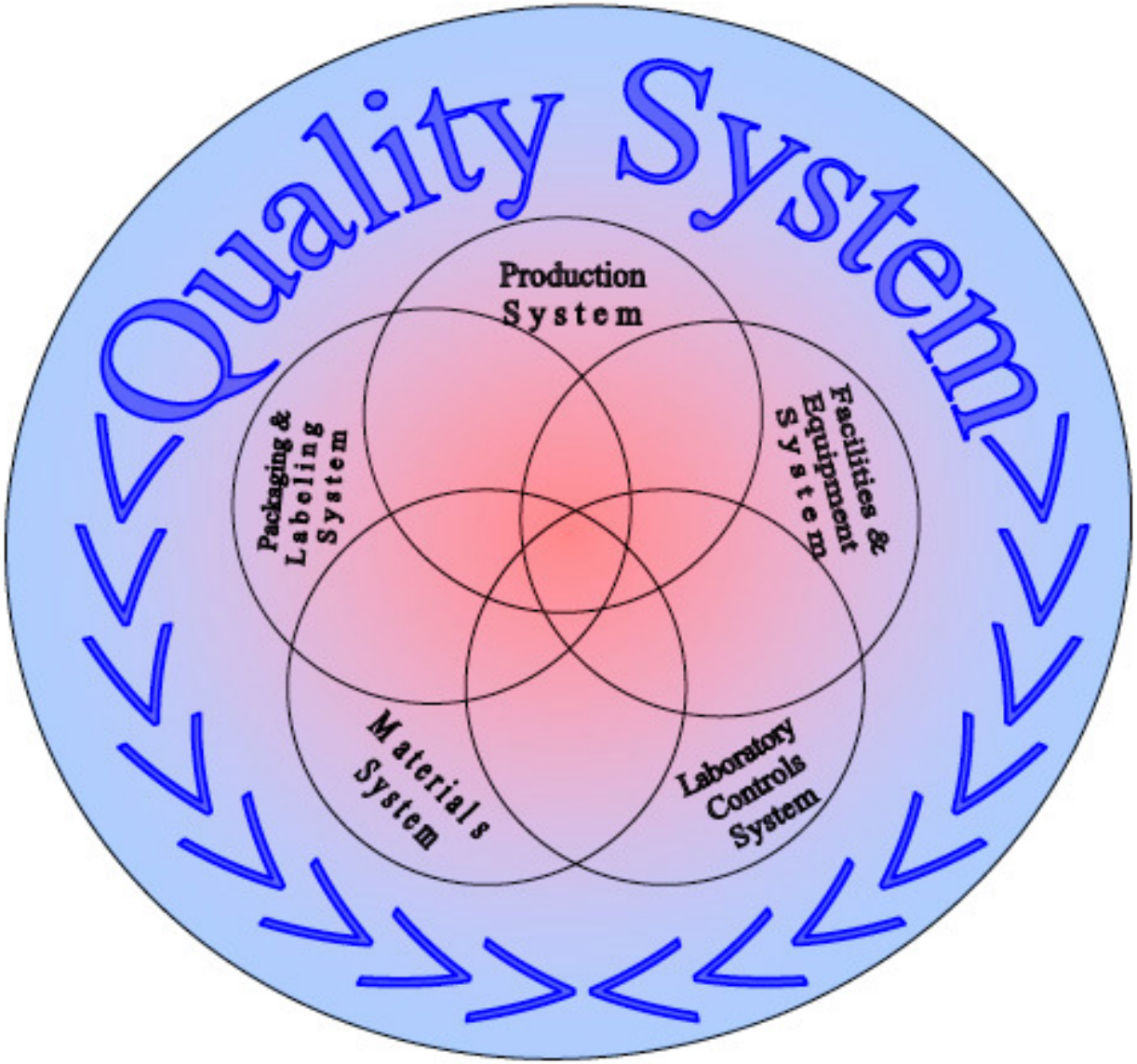
- Describes a comprehensive quality systems model
- Demonstrates how/where the elements of this comprehensive model can fit within the requirements of the CGMP regulations
- Bridge between the 1978 regulations and current understanding of quality systems

SCOPE OF THE GUIDANCE

- ***NOT*** intended to create new requirements for pharmaceutical manufacturing
- ***NOT*** intended to be a guide for the conduct of FDA inspections
- Explains how implementing comprehensive quality systems can help manufacturers achieve compliance with 21 CFR parts 210 and 211

ORGANIZATION OF THE GUIDANCE

- Major sections:Management Responsibilities, Resources, Man. Operations & Evaluation Activities



WHAT IS 483

An FDA 483 is a form used by an FDA investigator following an inspection of your plant. It lists deficiencies in your quality system and potential non-compliance issues with GMP's. **These observations are based on the investigators interpretation of the GMP regulations as they apply to your specific situation.** During the investigator's closing meeting with management, you may be given a Form 483. The Form 483 is officially known as the "Notice of Inspection Observations."

WHAT IS 483

The content of a 483 may be handwritten, typed, completed in a PDF file and printed, or completed via the FDA's computer system called Turbo EIR

- Header information
- Observations
    - Annotation
- Signatures
- Converse side
- Addenda/amendments

USP

USP

USP Chapters

General chapters numbered above <1000> in USP–NF typically are **informational and contain no mandatory requirements**, unless specifically referenced in a monograph

General chapters designated as below <1000> contain tests and procedures that are intended to apply to items recognized in *USP* or *NF* when called out in a monograph

Example: **General Chapter <1116>** *Microbiological Control and Monitoring of Aseptic Processing Environments*

USP

- <1229> ***Sterilization of Compendial Articles***
- <1229.1> ***Steam Sterilization by Direct Contact***
- <1229.2> ***Moist Heat Sterilization of Aqueous Liquids***
- <1229.3> ***Monitoring of Bioburden***
- <1229.4> ***Sterilizing Filtration of Liquids***
- <1229.5> ***Biological Indicators for Sterilization***
- <1229.6> ***Liquid Phase Sterilization***
- <1229.7> ***Gaseous Sterilization***
- <1229.8> ***Dry Heat Sterilization***
- <1229.9> ***Physicochemical Integrators and Indicators for Sterilization***
- <1229.10> ***Radiation Sterilization***
- <1229.11> ***Vapor Phase Sterilization***

WHO (WORLD HEALTH ORGANIZATION)

WHO GUIDELINES FOR VACCINES

The World Health Organization brings together international experts in specific fields through its biological standardization programme to develop and revise specific recommendations for the production and quality control of vaccines of major international public health importance

http://www.who.int/biologicals/vaccines/en/

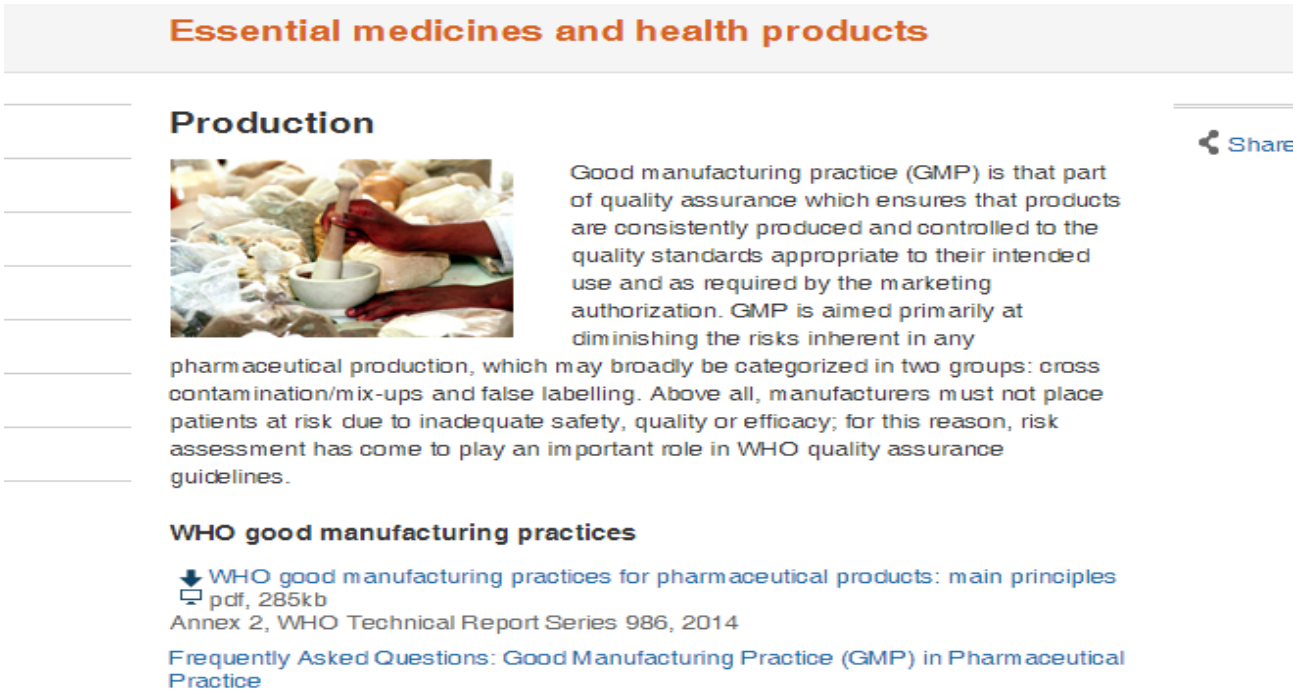
TRS 822, Annex 1 Biological products, GMP;

General topics and regulatory guidance

- Biotechnology and related topics
- Cell substrates
- WHO reference cell banks (RCBs)
- Clinical evaluation of vaccines
- Good Manufacturing Practices (GMP)
- Lot Release of Vaccines
- Non-clinical evaluation of vaccines
- Regulation of post approval changes to vaccines
- Regulation and quality control of vaccines
- Stability of vaccines and reference preparations
- Sterility testing
- Thiomersal
- Transmissible Spongioform Encephalities (TSE)

WHO GENERAL GMP GUIDELINES

TRS 986, Annex 2 WHO good manufacturing practices for pharmaceutical products: main principles



Essential medicines and health products

Production

Share

Good manufacturing practice (GMP) is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP is aimed primarily at diminishing the risks inherent in any pharmaceutical production, which may broadly be categorized in two groups: cross contamination/mix-ups and false labelling. Above all, manufacturers must not place patients at risk due to inadequate safety, quality or efficacy; for this reason, risk assessment has come to play an important role in WHO quality assurance guidelines.

WHO good manufacturing practices

WHO good manufacturing practices for pharmaceutical products: main principles
pdf, 285kb
Annex 2, WHO Technical Report Series 986, 2014

Frequently Asked Questions: Good Manufacturing Practice (GMP) in Pharmaceutical Practice

http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/

WHO GENERAL GMP GUIDELINES

TRS 961 - Forty-fifth Report (Geneva, 18–22 October 2010)
WHO Expert Committee on Specifications for Pharmaceutical Preparations

WHO Expert Committee on Specifications for Pharmaceutical Preparations - WHO Technical Report Series, No. 961 - Forty-fifth Report (Geneva, 18–22 October 2010)
(2011; 440 pages)

Abstract

Annex 1: Release procedure of International Chemical Reference Substances;

Annex 2: WHO good practices for pharmaceutical microbiology laboratories;

Annex 3: WHO good manufacturing practices: main principles for pharmaceutical Products;

Annex 4: WHO good manufacturing practices for blood establishments (jointly with the Expert Committee on Biological Standardization);

Annex 5: WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms;

http://apps.who.int/medicinedocs/en/d/Js18652en/

(ICH) INTERNATIONAL CONFERENCE ON HARMONIZATION

ICH

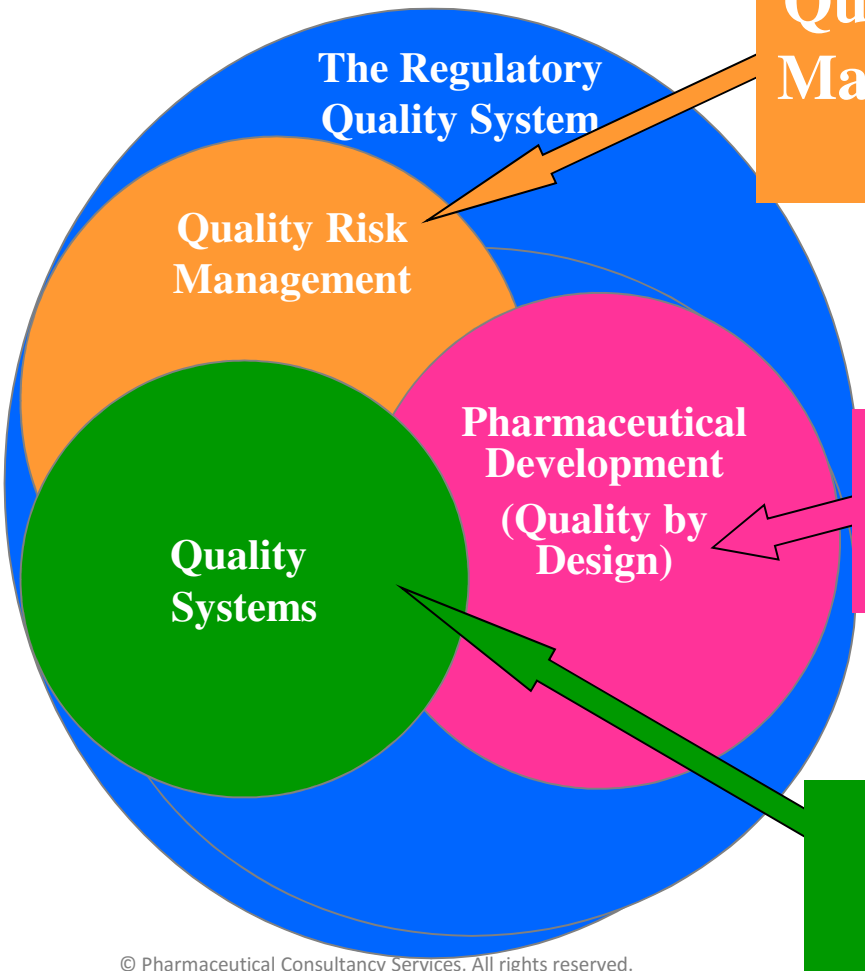
- ICH – International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
- Pioneered by EU in 1980s to facilitate the move towards single market for Pharmaceuticals
- Bilateral discussions between Europe, Japan and USA on possibility of harmonisation
- WHO Conference 1989 in Paris, agreement was reached to initiate a joint regulatory-industry initiative for international harmonisation
- ICH was borne in April 1990 (Brussels)

ICH

ICH Work Products (Quality Section)

- Stability – Q1 A – Q1 F
- Analytical Validation – Q2 A – Q2B
- Impurities – Q3 A – Q3 C
- Pharmacopoeias – Q4 – Q4 B
- Quality of Biotechnological Products – Q5 A – Q5 E
- Specifications – Q6 A – Q6
- Good Manufacturing Practice (APIs) – Q7 A
- Pharmaceutical Development – Q8
- Risk Assessment – Q9
- Pharmaceutical Quality Systems – Q10
- Development and Manufacturing –drug substances–Q11 (draft)

BRUSSELS 2003 (ICH)



Quality Risk Management (Q9)

Pharmaceutical Development (Q8)

Quality Systems (Q10)

For companies with :

1. **Good design and control strategies**
2. **Good Risk Management strategies**
3. **Good Quality Systems**

Reduced intensity of Regulatory Oversight:

1. **Reduction of submissions on changes/variations**
2. **Inspection of quality systems**

ICH

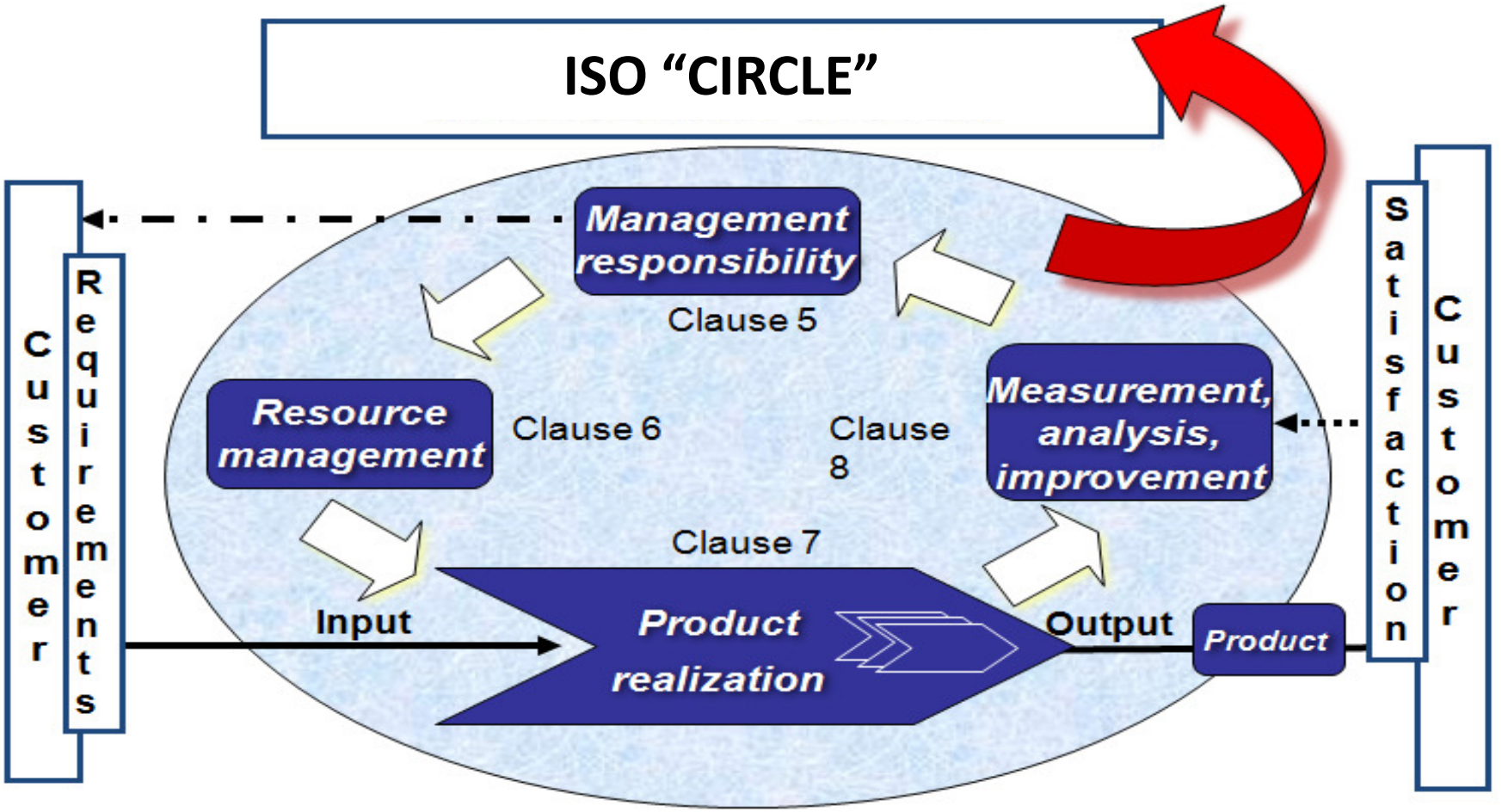
International Harmonisation on Legislatory Quality Vision:

Develop a *harmonized* pharmaceutical quality system applicable across the *life cycle* of the product emphasizing an integrated approach to quality *risk management* and *science* (ICH Brussels 2003)

ISO

Top management shall provide evidence of its commitment to the development and implementation of the quality management system and continually improve its effectiveness (ISO9000-2008)

ISO “CIRCLE”



Clauses are references to the ISO-chapters

Q10; PQS

STANDARD QMS (QUALITY MANAGEMENT SYSTEM) ELEMENTS

Change Control/Management	Training
Deviation/NC	Distribution
CAPA	Artwork
Complaints/Incidents	Audit System (Internal/External)
PQR/APR	Documentation
Recall	CMC maintenance
Destruction	Technical Transfer
Vendor Management	Pharmacovigilance
Quality Control	Clinical Studies
On-going Stability	Marketing Material
Enquiries	Regulatory Affairs
Validation/Verification/Qualification	Data Management
External Inspections	Investigations
Facilities / Utilities / Equipment	Development Studies

Q10; QUALITY MANAGEMENT

Q10: Pharmaceutical Quality System (PQS)

- ISO
- GMP
- ICH-Q8 and ICH-Q9

Concept of Q10 is broader than GMP

Q10 objectives

- Achieve product realization
- Establish and maintain a state of control
- Facilitate continual improvement

Life-cycle approach

Q10; QUALITY MANAGEMENT

Based on (enablers)

- Knowledge

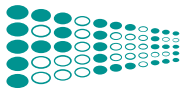
  Subject Matter Experts –SME introduced by ASTM2500-

- Risk Management

  Based on ICH-Q9

A more science based approach as underlying theme.

MANAGEMENT IS HELD RESPONSIBLE



Q10; QUALITY MANAGEMENT

Controls (1)

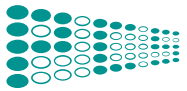
- Process Performance
- Product Quality Monitoring

Controls (2)

- Change Management
- CAPA
    - *Correction (direct related to specific batch/event)*
    - *Corrective Action (broader concept to avoid re-occurrence)*
    - *Preventative Action (concept of avoiding –future- risks)*

Controls (3)

- **MANAGEMENT REVIEW**



Q10; QUALITY MANAGEMENT

Management Review

- Senior Management should be responsible for:
  - *Pharmaceutical Quality System Governance*
  - *PQS, to be suitable and effective*
  - *Assessing the Conclusions on periodic review;*
    1. *process/product*
    2. *Pharmaceutical Quality System (PQS)*

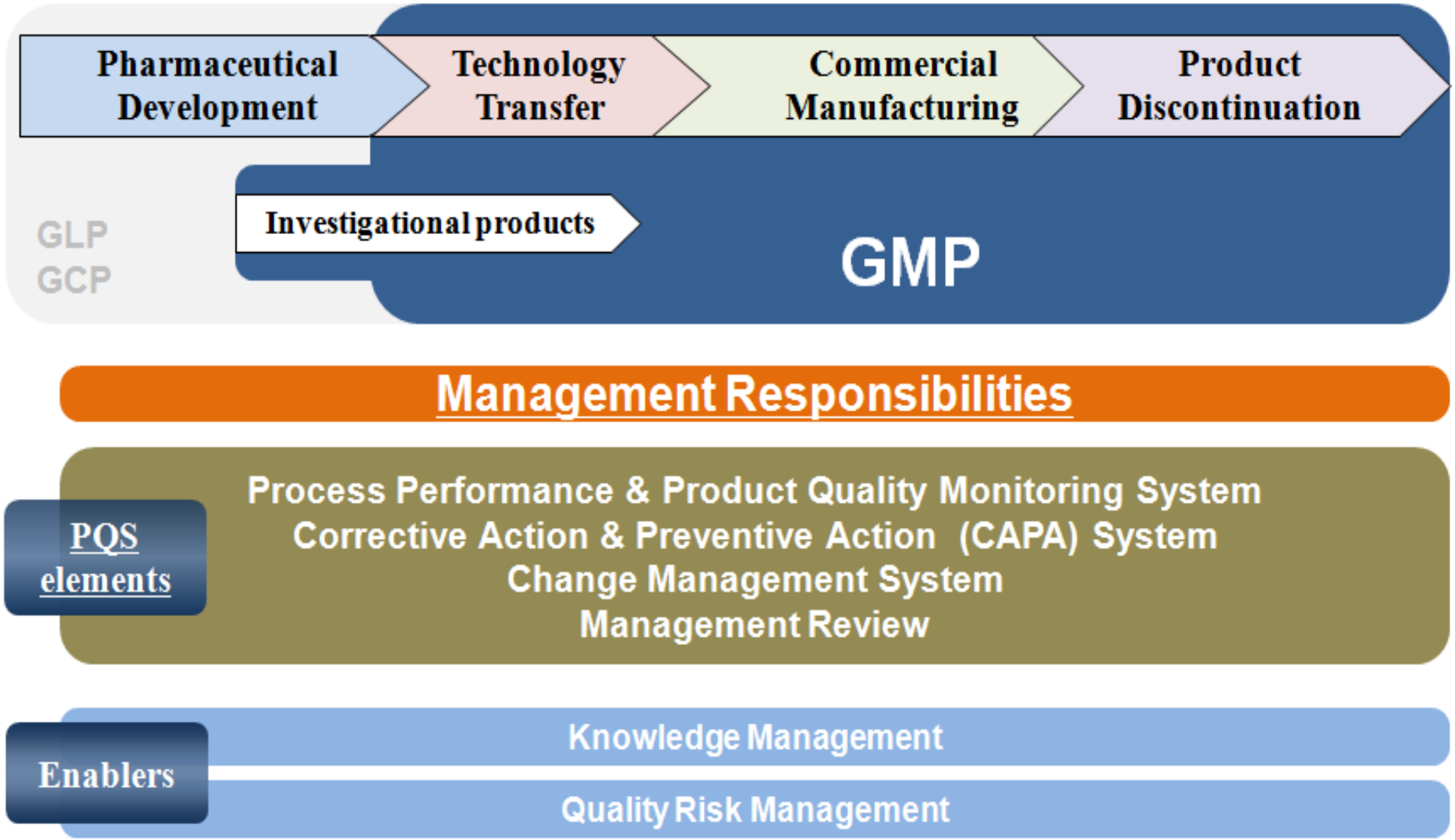
Compared with GMP Part 1 - Old Chapter 2 section 3

Key Personnel includes the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the authorised person(s) designated for the purpose. Normally key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other

EUDRALEX VOL. 4 CH. 1 - PQS

- 1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.

- 1.6 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.



Q9; QRM

Q9; QUALITY RISK MANAGEMENT

Risk (ICH-Q9 definition)

- Probability of occurrence of harm
- Severity of that harm

Prime importance: protection of the patient

Note: included within term "patient" is: the to be vaccinated recipient.

Systematics:

- Formal / Informal
- Multi-disciplinary
- Examples in Q9: at least works as agenda(s)

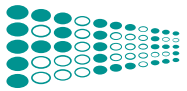
Q9; QUALITY RISK MANAGEMENT

Integrated throughout Quality Management System:

- Documentation
- Training and education
- Quality defects
- Auditing / Inspection
- Periodic review
- Change management / change control
- Continual improvement
- ……

Inspectorates / PIC/S:

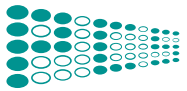
- Develop training programme on QRM for inspectors
- Develop guidance for assessment of QRM implementation in industry
- Update PIC/S Site Master File format with QRM



Q9; QUALITY RISK MANAGEMENT

Concept includes (not limited)

- Risk:
  - Identification
  - Analysis
  - Evaluation
  - Control
- FMEA – studies (as an example)
- Impact Assessments
  - Change Management
  - Deviations / NCMR
  - CAPA
- DATA gathering



Q9; QUALITY RISK MANAGEMENT

Notes:

- Risk to quality is just one component of the overall risk!
- Product quality should be maintained throughout the product life cycle
- Risk management in pharma industry means protection of the patients by managing the risk to quality

(PIC/S) PHARMACEUTICAL INSPECTION CONVENTION

PIC/S

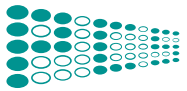
PIC (Pharmaceutical Inspection Convention) was founded in October 1970 by EFTA (**European** Free Trade Association) under the title of “The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products”.

Started with 10 members (European), followed by others (8), including Australia, until 1993.

PIC Scheme (Cooperation) was formed on 2 November 1995. PIC and the PIC Scheme, which operate together in parallel, are jointly referred to as **PIC/S**. **USA is a member since 2011**

PIC/S

- PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products
- 46 Countries
- EMA, WHO and UNICEF are Partnering with PIC/s



PIC/S

The need to form the PIC Scheme became necessary when it was realised that an incompatibility between PIC and European law did not permit individual EU countries that were members of PIC to sign agreements with other countries seeking to join PIC.

PIC/S provides an active and constructive co-operation in the field of GMP (Good Manufacturing Practice). The purpose of PIC/S is to facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of GMP inspectors.

Interesting publications:

- PI 032-2
- PI 012-3
- PI 007-6
- PI 014-3

Where to find them!

http://www.picscheme.org/publication.php

PIC/S GUIDANCE

PDA

OVERVIEW PDA TR`S 2013/2014/2015

2013:

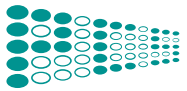
- TR 60 – 64
- TR 54 – 3, TR 54 – 2
- Review TR 43, TR 33, TR 3

2014:

- TR 65 – 68
- TR 54 – 4
- Review TR 13

2015:

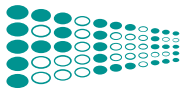
- Points to consider for Aseptic Processing Task Force; Part 1: January



OVERVIEW PDA TR`S 2013/2014/2015

2013:

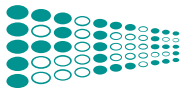
- TR 60 – Process Validation: A lifecycle approach
- TR 61 – Steam in place
- TR 62 – Recommended practices for manual aseptic processes
- TR 63 – Quality requirements for the extemporaneous preparation of clinical trial materials
- TR 64 – Active temperature-controlled systems
- TR 54 – 2 (Annex 1), TR 54 – 3 (Annex 2)
- Review TR 43, TR 33, TR 3



OVERVIEW PDA TR`S 2013/2014/2015

2014/15:

- TR 65 – Technology Transfer
- TR 66 – Application of Single-Use Systems in pharmaceutical manufacturing
- TR 67 – Exclusion of objectionable microorganisms from nonsterile pharmaceuticals, medical devices and cosmetics
- TR 68 – Risk-Based approach for prevention and management of drug shortage
- TR 69 - Bioburden and Biofilm Management in Pharmaceutical Drug Substance Manufacturing (very recent)
- TR 54 – 4 (Annex 3)
- Review TR 13 - Fundamentals of an Environmental Monitoring Program



TESTING

BY HAND RAISING

Senior Management responsibilities were in the past NOT clearly defined/emphasized:

OPTIONS:

1. TRUE
2. NOT-TRUE
3. DON'T KNOW

BY HAND RAISING

ICH guidelines, are only mandatory once incorporated into "local" laws/guidelines:

OPTIONS:

1. TRUE
2. NOT-TRUE
3. DON'T KNOW

BY HAND RAISING

PIC/s and PDA are NOT regulatory bodies:

OPTIONS:

1. TRUE
2. NOT-TRUE
3. DON'T KNOW

THANK YOU FOR YOUR ATTENTION

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