# Current Global GMP Status and Trends With Focus on EU & PIC/S

***JPMA Annual Meeting, Tokyo & Osaka, September 2012***

***Dr.-Ing. Stephan Rönninger***

*Pharma Medicines Technical Operations Global Quality & Compliance, F. Hoffmann-La Roche Ltd*

## GMP in PIC/S and the European Union

## Trend in GMP Inspections

## Good Distribution Practice

## Conclusion

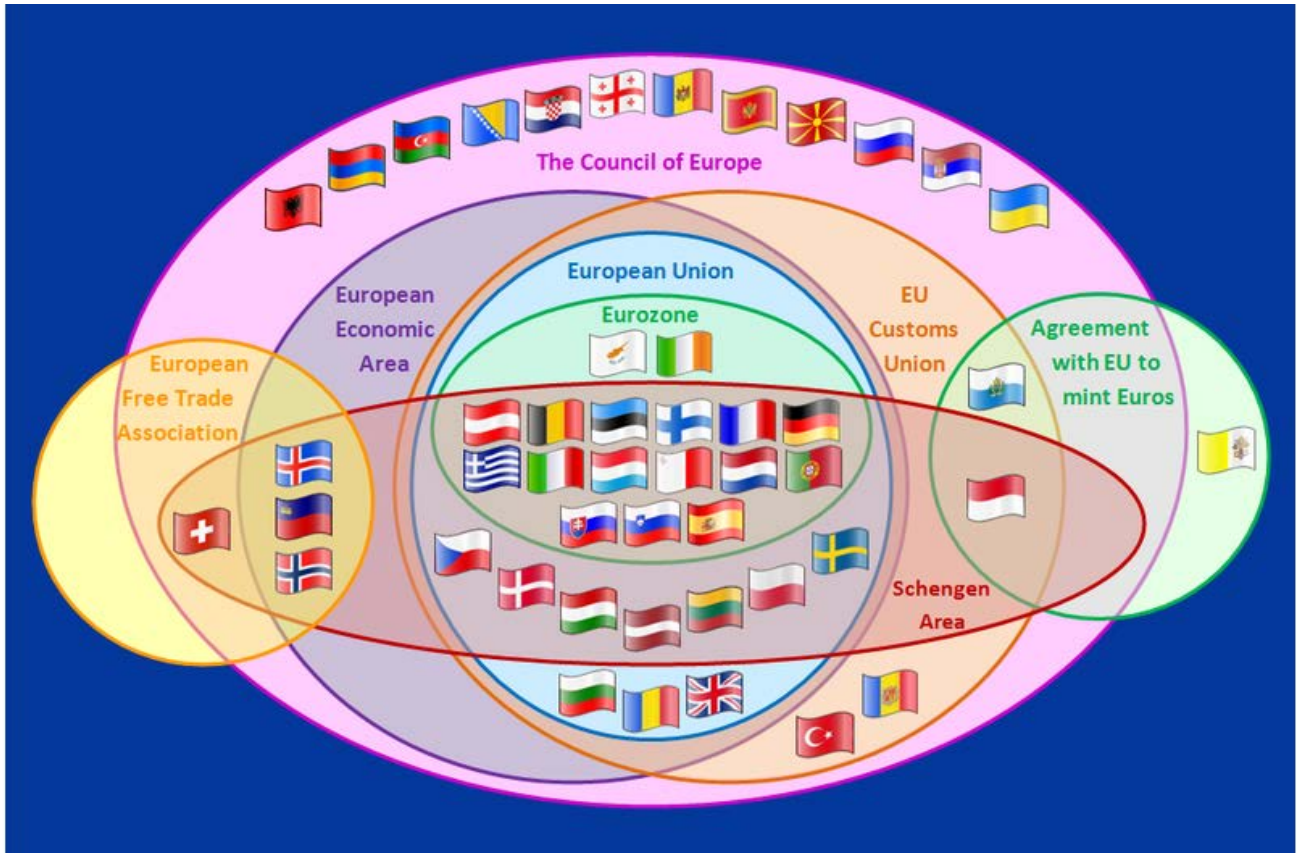
# GMP in PIC/S and the European Union

## Trend in GMP Inspections

## Good Distribution Practice

## Conclusion

# *EU is Not A Synonym for a 'Union'*




© http://en.wikipedia.org/wiki/File:Supranational_European_Bodies.png

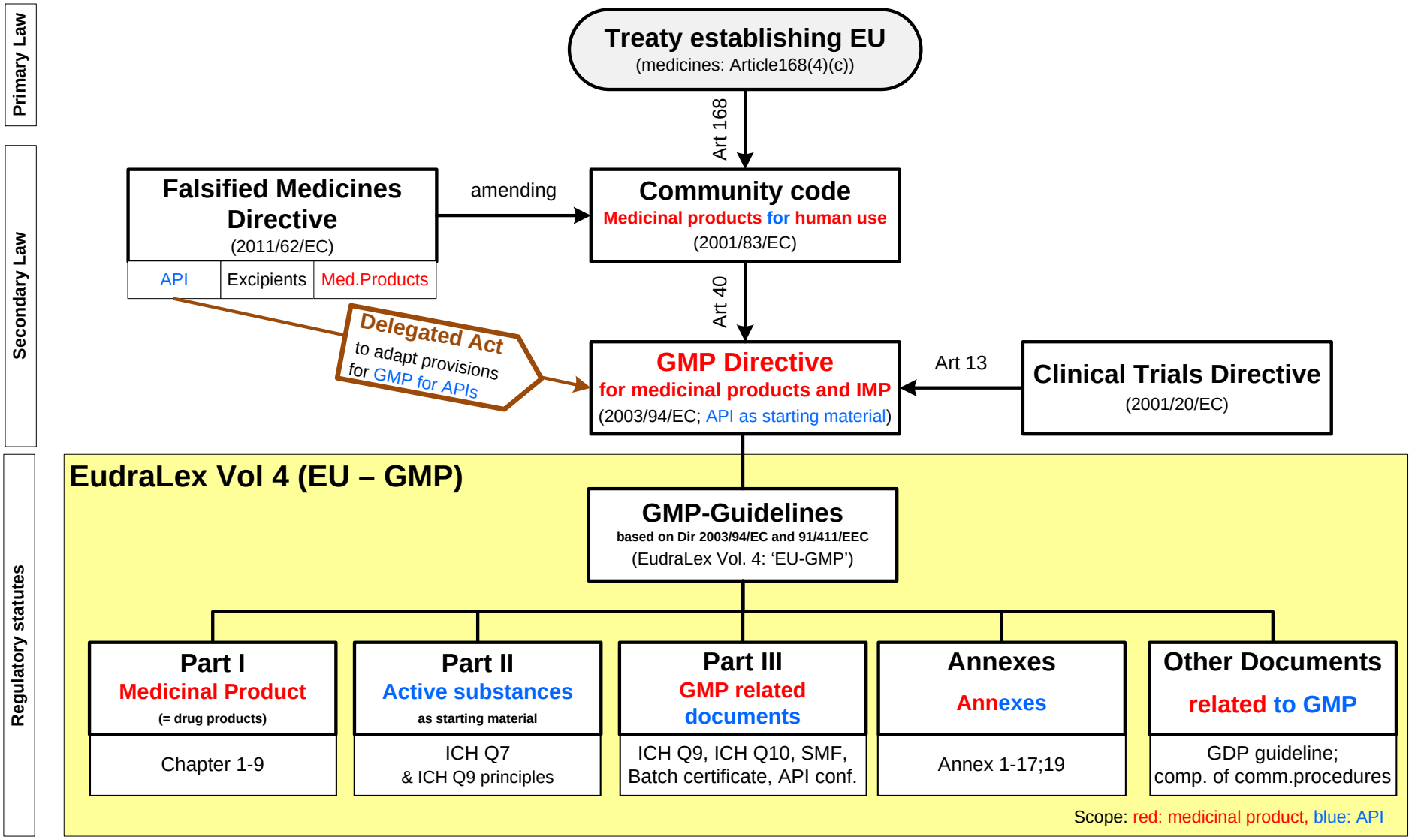
**Policy Making**

**Facilitators**

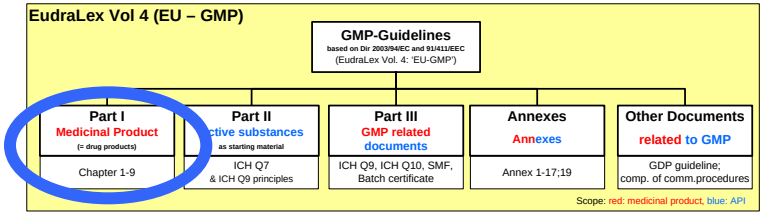
**Decision Makers**

**Advisory Bodies**

# The Legal Basis of the GMPs in Europe



# *EudraLex Vol. 4: EU-GMP Part I*




## Basic Requirements for Medicinal Products

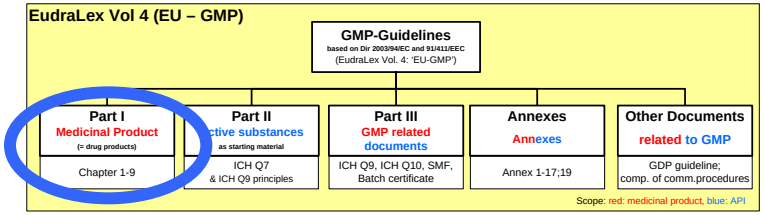
- Chapter 1 *Pharmaceutical* Quality System
- Chapter 2 Personnel
- Chapter 3 Premise and Equipment
- Chapter 4 Documentation
- Chapter 5 Production
- Chapter 6 Quality Control
- Chapter 7 Outsourced Activities *(former Contract Manufacture and Analysis)*
- Chapter 8 Complaints and Product Recall
- Chapter 9 Self Inspection

***General:***
Implementation of the principles of ICH Q8/11,9,10 in the GMPs

***Specific:***
*- QRM principles (Ch 1)*
*- Dedicated facilities (Ch 3/5)*
*- Contract manufacturing (Ch 5)*
*- QbD & QRM (Ch 5)*
*- Transfer Analytical methods (Ch. 6)*
*- Supplier auditing (Ch 9)*

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

# *EudraLex Vol. 4: EU-GMP Part I*



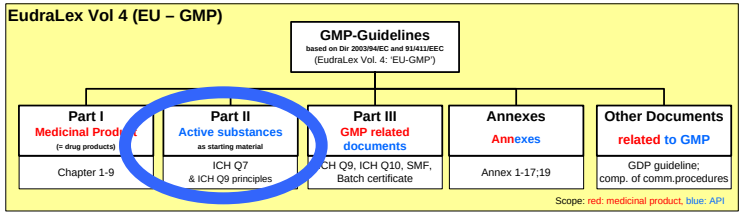

## Chapter 1: Pharmaceutical Quality System *(effective 31. Jan 2013)*

- **Changes are to align with ICH Q10 and implement QRM principles**
- **PQS facilitator to manage GMP**
  - Appropriately qualified and trained personnel
  - Adequate premises and space
  - Suitable equipment and services
  - Correct materials
  - Containers and labels
  - Approved procedures and instructions
  - Suitable storage and transport
  - Quality Control
  - Product Quality Review
- **More than Q10**

## ICH Q10: Pharmaceutical Quality System

- **Management Responsibility**
- **Continual Improvement of process performance and product quality**
- **Pharmaceutical Quality System Elements**
  - Process Performance and Product Quality Monitoring System
  - Corrective Action and Preventive Action (CAPA) System
  - Change Management System
  - Management Review of Process Performance and Product Quality
- **Continual Improvement of the PQS**

# *EudraLex Vol. 4: EU-GMP Part II*

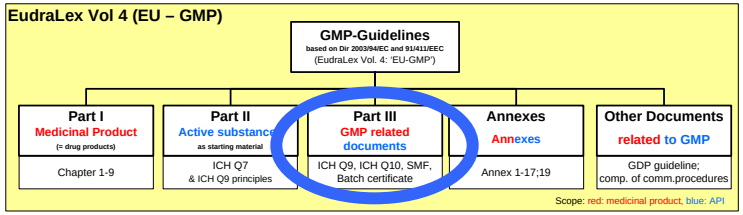



## Basic Requirements for Active Substances used as Starting Materials

= ICH Q7 & ICH Q9 principles (added as chapter 2.2)

- ***Other ICH documents related to APIs***
  - *ICH Q 9: APIs in scope*
  - *ICH Q10: Refers to ICH Q7 as a foundation*
  - *ICH Q8(R2): Part II of ICH Q8 describes the development principles*
  - *ICH Q11: Selection of 'API starting material' and source materials (Chapter 5.1): approved regulatory filing defines when to start GMP*
  - *Q&A on Q7: Under discussion in ICH*

# *EudraLex Vol. 4: EU-GMP Part III*

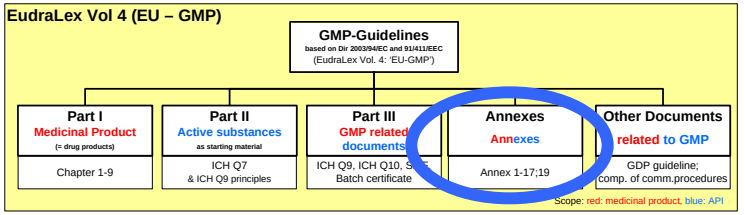



## GMP related documents

- Site Master File (SMF)
- ICH Q9 Quality Risk Management
- ICH Q10 Note for Guidance on Pharmaceutical Quality System
- Internationally harmonised requirements for batch (‘MRA Batch Certificate’)
- Template for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use

# *EudraLex Vol. 4: EU-GMP*

## *Annexes with Human Medicines in scope*

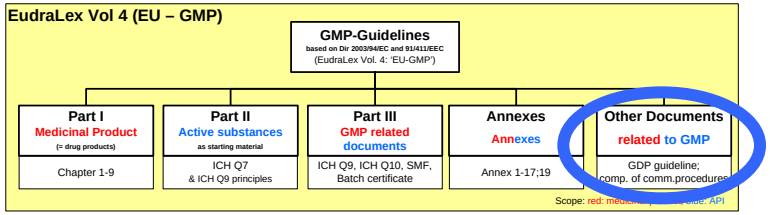



- Annex 1 Manufacture of Sterile Medicinal Products
- Annex 2 Manufacture of Biological Medicinal Products for Human Use
- Annex 3 Manufacture of Radiopharmaceuticals
- Annex 7 Manufacture of Herbal Medicinal Products
- Annex 8 Sampling of Starting and Packaging Materials
- Annex 9 Manufacture of Liquids, Creams and Ointments
- Annex 10 Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation
- Annex 11 Computerised Systems
- Annex 12 Use of Ionising Radiation in the Manufacture of Medicinal Products
- Annex 13 Manufacture of Investigational Medicinal Products
- Annex 14 Manufacture of Products derived from Human Blood or Human Plasma
- Annex 15 Qualification and validation
- Annex 16 Certification by a Qualified person and Batch Release
- Annex 17 Parametric Release
- Annex 19 Reference and Retention Samples
- ~~Annex 20 Quality Risk Management~~

In PIC/S GMPs

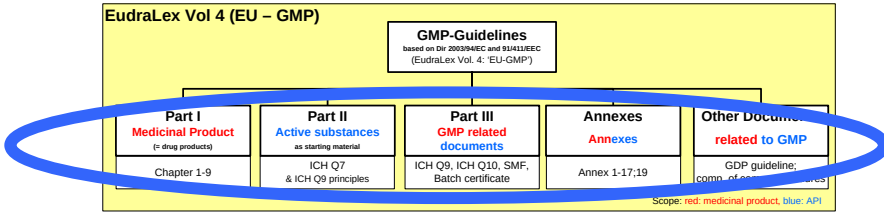
*Implementation of the principles of ICH Q8/11,9,10 in the GMPs e.g. CPV(15), RTRT (17), PAT (19)*

# *EudraLex Vol. 4: EU-GMP*
# *Other Documents Related to GMP*




- **Compilation of Community Procedures** on Inspections and Exchange of Information updated to include new EU formats and procedures
  - A collection of GMP/GDP inspection-related procedures
    - GMP & GDP Inspections
    - Rapid Alert system: Quality defects, Recalls, Suspected defects
    - Exchange of information among inspectorates
    - Quality systems within the inspectorates themselves
    - Format of inspection reports
    - Follow up on quality defects
- **Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)**

# *Harmonisation of GMPs*




# EU GMPs = PIC/S GMP

## without Annex 16 (batch release) & GDPs

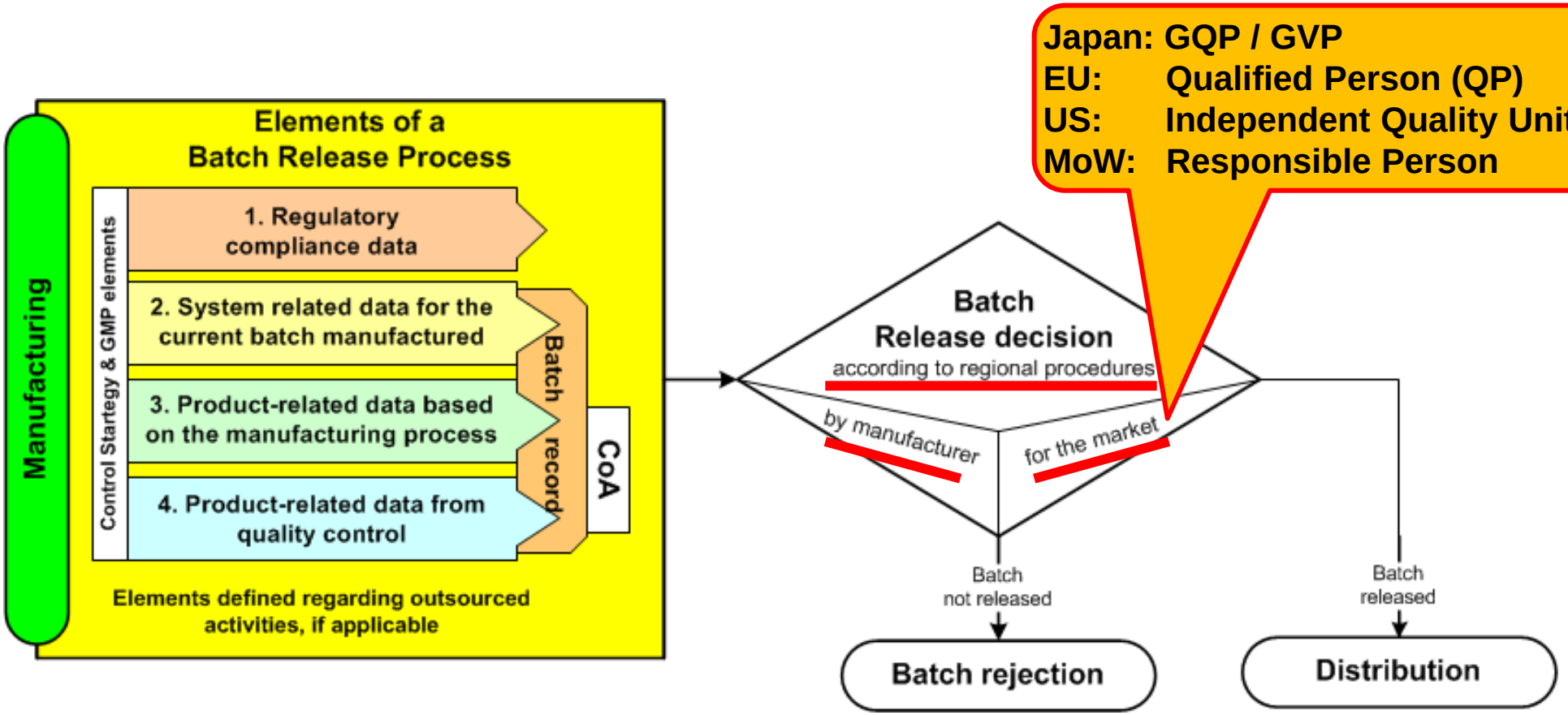
- **Reason for excluding batch release**
  - Regulated by domestic laws and differences in implementation
- **Reason for excluding GDPs**
  - Legal differences in responsibilities by some EU countries

**Conclusion**

- Implementing equivalent GMPs by inspectorates is possible

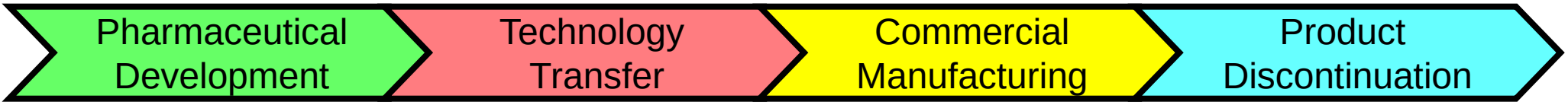
# *Harmonisation of GMPs*
# *Batch Release*

- **Concepts are equivalent - Responsibilities are different**

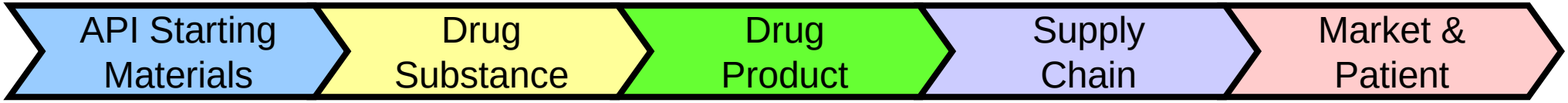


# *Use the Right Terminology When Talking on Concepts*

- **Life Cycle** *(e.g. Q10)*




- **End-to-End Quality** *(e.g. business set up / regulations)*



GMP in PIC/S and the European Union

**Trend in GMP Inspections**

Good Distribution Practice

Conclusion

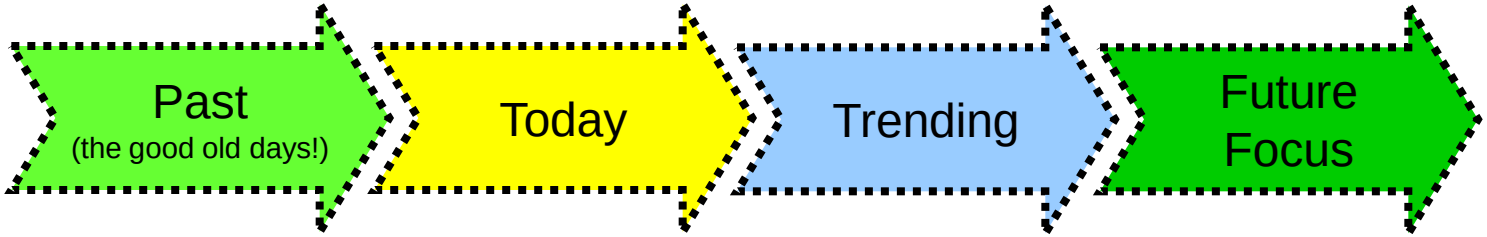
# *Aim of the Inspections*
# *Make a 'CASE'*

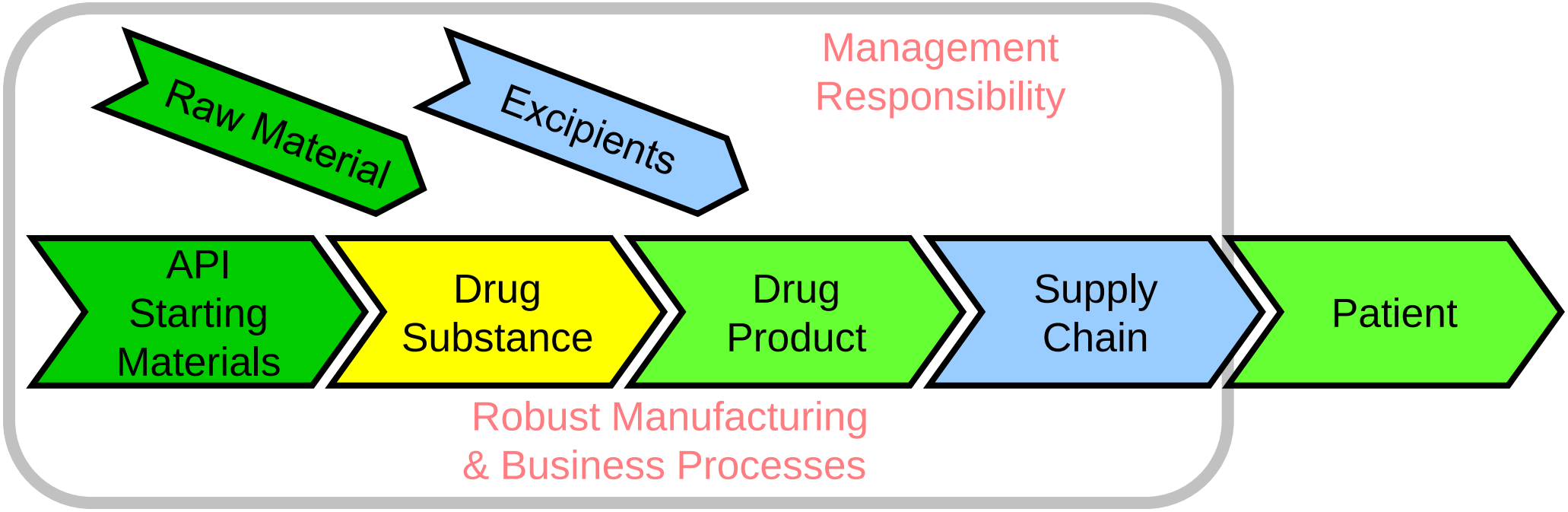

- **Inspections are essential to evaluate**
  - **C**apability,
  - **A**dequacy of production and control procedures,
  - **S**uitability of equipment and facilities, and
  - **E**ffectiveness of the quality management system

  **in assuring the overall state of control**
- **Evaluation of authenticity of submitted data and link to the registration dossier (Pre-approval inspections)**

ICH Q-IWG enhanced training, 2011

# *Evolution of Inspection Focus Areas*



# *Inspection Trends by PIC/S*
# *An Inspectors Benchmark*

- **A questionnaire was sent 1st quarter 2012 to all PIC/S Participating Authorities and applicants to offer data**

- **The questionnaire seek information on:**
  1. **Most frequently cited categories of GMP deficiencies**
  2. **Most severe GMP deficiencies (critical and/or major)**

# *Inspection Trends by PIC/S*
# *Most Frequent vs. Most Severe Deficiencies*

| Most frequently cited deficiencies | | Most severe deficiencies | |
|---|---|---|---|
| Production | 24% | Production | 27% |
| Quality system | 20% | Quality system | 20% |
| Quality control | 14% | Premises + equipment | 17% |
| Premises + equipment | 14% | Validation | 14% |
| Validation | 12% | Quality control | 9% |
| Personnel issues | 8% | Regulatory issues | 6% |
| Materials management | 7% | Materials management | 5% |
| Regulatory issues | 1% | Personnel issues | 3% |

See details: Hans Smallenbroek , Boon Meow Hoe, *Top GMP Deficiencies*, **Pharm. Tech. Europe**, May, **2012**, 42-44

# *Inspection Trends by PIC/S*
# *Most Frequent vs. Most Severe Deficiencies*

- **Similarities**
  - There are no significant differences among regions
  - There is a correlation between the most frequent GMP Deficiencies Classes and the most severe GMP Deficiencies Classes
- **Inspectors should communicate more effectively and efficiently to the industry on the weaknesses**
  - Some of the most frequently cited GMP deficiencies may due to easy detection as part of the inspection process e.g. Documentation – manufacturing
  - The design and maintenance of premises may relate to aged buildings or saving on maintenance budget (ranked 2nd in the list of critical findings in inspections performed by PIC/S inspectorates)
- **PIC/S may develop a common GMP deficiencies classification model**
  - Define what are 'critical', 'major', 'minor' observations

# *Manage Expectations in Inspections*

- **Inspectors like to see …**
  - All processes running, all effected areas and equipment
  - Quality management system practices are in place (training, maintenance, monitoring, cleaning validation...)
  - Deviations and changes
- **Companies like to show…**
  - Routine processes and level of work performance
  - Improvements and developments, established standards and innovations
  - System design by presentations (QA, QC, Manufacturing)

# *What companies have?*
# *What inspectors looking for?*

- **A Site Master File**
  - Yes, very useful – stay with the table of content
- **A Quality Manual**
  - ISO 9001 type seems to be a good structure
- **A 'Quality Management System'**
  - Whatever it is called 'QMS' is a network
  - It's expected to implement the chosen 'QMS' (including definitions)
  - Obligation of common language between industry and National Competent Authorities (NCA)
  - Distinguish executive / global / domestic levels

# *Avoid Deficiencies in Inspections*
# *Quality Management System (QMS)*

- **In an inspection industry should demonstrate**
  - Commitment and willingness in the ‘QMS’ from all functions and people involved
  - Ownership of the ‘QMS’
  - Senior management involvement
  - Local and global ‘QMS’ should be defined and explained including their interphases and status of implementation
  - Robustness processes and systems described in the ‘QMS’
  - Monitoring, consistency and  effectiveness of the ‘QMS

# *Avoid Deficiencies in Inspections*
## *Root Cause Analysis and Corrective Actions*

- **Root cause**
  - Define the scope and any impact on other processes and batches
  - Investigate potential factors and supported by data/trends where possible
  - Confirm the root cause where possible
- **Corrective actions**
  - Implement interim measures, if necessary
  - Evaluate unintended consequences and impact on adjacent areas
  - Set and follow realistic timelines
- **How to work on?**
  - Create working team with different knowledge and skills
  - Active follow up with clear responsibilities including an efficacy check
  - Communicate experiences and leanings

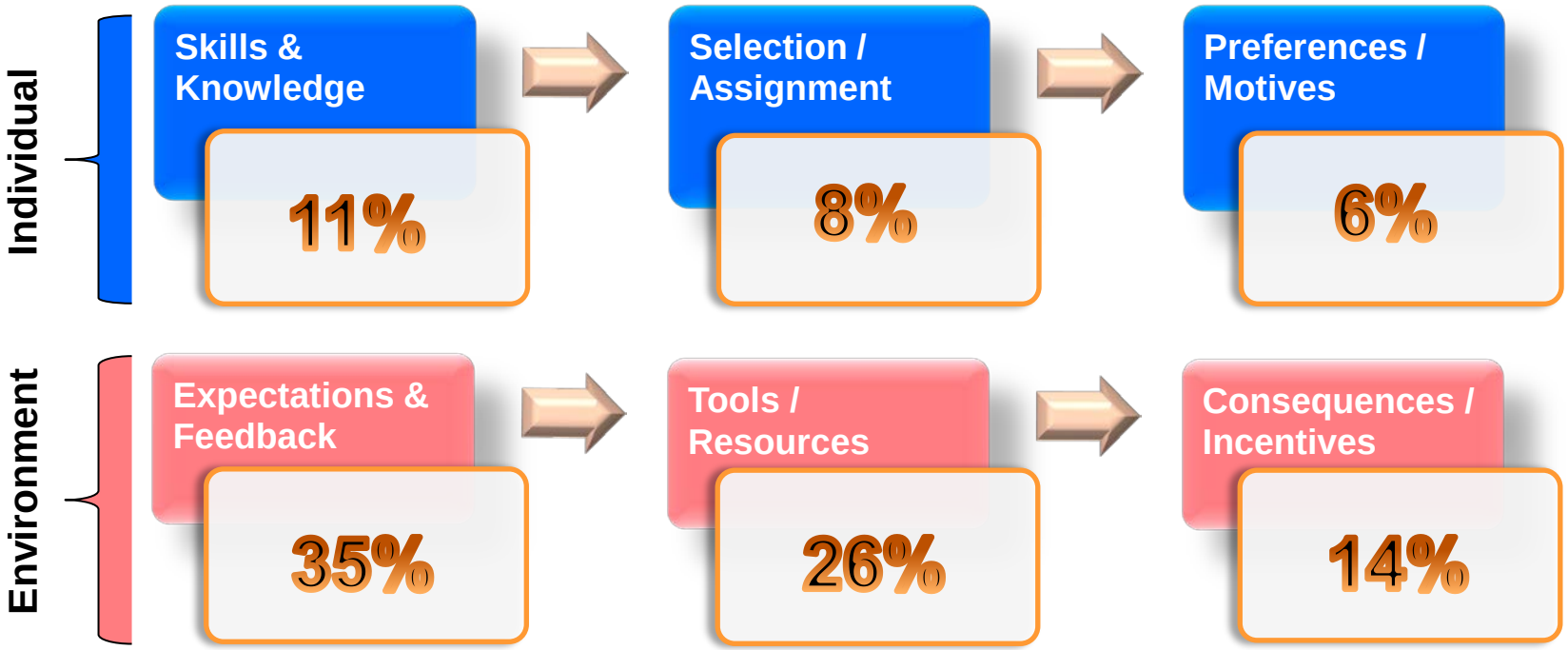
# *Avoid Deficiencies in Inspections*
## *Personal / Training*

- **Manage expectations**
  - Train task related and link to GMP requirements
  - Use qualified trainers; include a variety of techniques to train
  - Verify effectiveness of a training
  - Assess training on continuous basis e.g. frequency
  - Maintain Records
- **In case of a human error**
  - Find the ‘true root cause’ and gaps
  - Don’t default to ‘training inadequate’
  - A corrective measure is not just ‘changed SOP and retrained staff’

# *Avoid Deficiencies in Inspections*

## *Personal / Training*

- **Consider to study performance gaps**
- **Potential contributors**




**For 70 - 80% of the people these are cause of why they do not perform better**

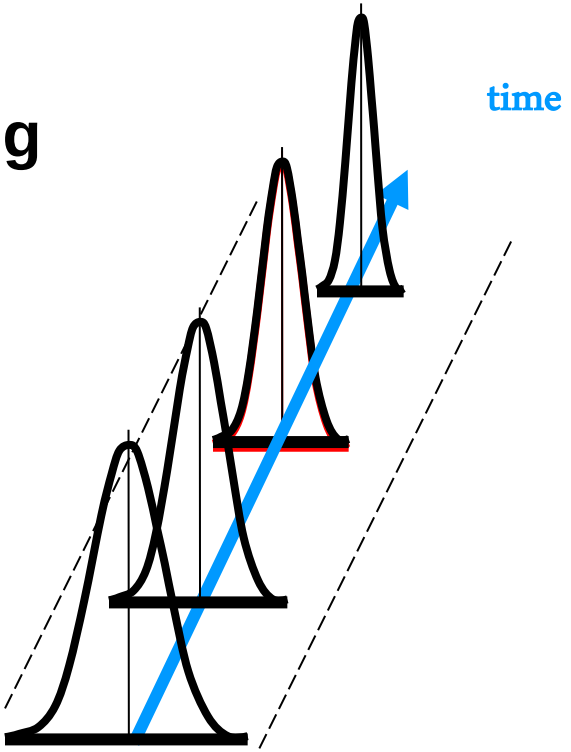


Source: H. Stolovich. 2004 Training Ain't Performance

# *Avoid Deficiencies in Inspections*
# *Documentation and Batch Release Decision*

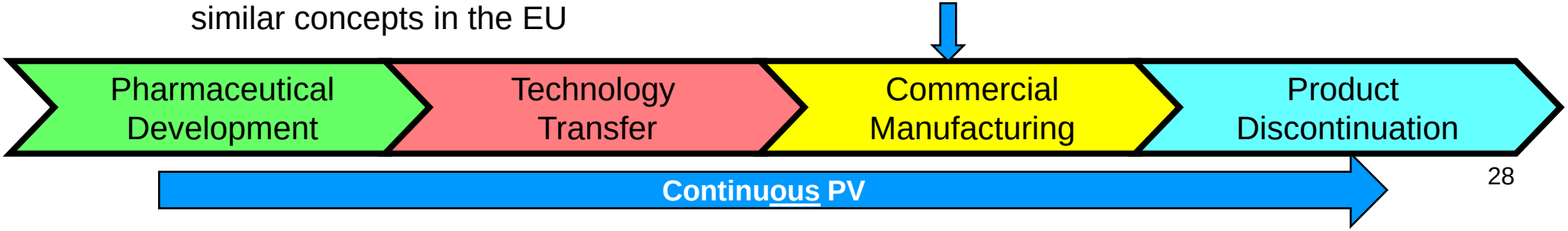
- **Documentation on Manufacturing**
  - Executing according to procedures, SOPs, templates
  - Executing QMS elements e.g. monitoring, QC testing, deviation, environmental monitoring data, related alarm handling
  - Real time documentation of mashine parameters
- **Quality Control and Release**
  - Batch release in case of imported products
  - Handling of manual data versus LIMS system entries in a batch record
  - Make information to be available for the Batch Release decision
  - Specifity of batch release procedure in case of manufacture in other country
- **Regulatory compliance data**
  - Deficiencies between text of the filing available at the site versus regulatory submissions

# *Avoid Misunderstanding*
# *Process Validation*




- **Process design yields a product meeting its pre-defined quality criteria**
- **Demonstrate the robustness of a process or analytical method**
- **Continuous Process Verification (CPV)**
  - An approach for the legal obligation of ‘process validation’
  - A concept (defined by ICH)

‘Continu*ed* process verification’ used by FDA as ‘stage 3’ (commercial manufacturing); similar concepts in the EU



# *About Process Validation*

## Traditional Process Validation

**Outcome:**
Repetition possible

**Achieved by:**
+ Usually 3 validation batches
+ Additional sampling

## Continuous Process Verification

**Outcome:**
A robust process is functioning

**Achieved by:**
+ Ongoing monitoring
+ Risk control actions, if applicable

**Fulfill the legal responsibility of 'Process Validation'**

# *Validation and QRM*

- **QRM principles should be used**

**1. To identify the scope, extent and focus of the validation**

A) Decide on parameters (e.g. Risk ranking filtering / Fishbone diagram / FMEA)

B) Decide on ranges (e.g. Modeling / Design of Experiments (DoE))

**System approach**

**2. To support continuous process verification**

A) Retrospective testing & trending using the traditional approach (e.g. X-bar charts, histograms)

B) Prospective monitoring the process performance (e.g. process capability assessments or Exponential Waited Moving Average (EWMA), Cumulative sum (CuSum) charts)

**Product approach**

# *Avoid of Deficiencies*
# *QRM Implementation*

- **Manage uncertainties**
  - Complete knowledge about a process
  - Expected or unexpected variability
  - Risk scoring systems which are highly subjective
- **Achieve a shared understanding among different stakeholders**
  - Nature of the scoring method used to estimate the risk
  - Each stakeholder might perceive different potential harms
  - Different probability on each harm occurring
  - Consider how risks are perceived by different people
- **Scientific rational available**
  - Product contact utilities are always ‘critical’
  - Controls and activities relating to risk-based equipment qualification
  - If identified as ‘critical’, equipment components need to be qualified, calibrated or monitored

# *Inspection Practice*
## *Summary*

- **Global companies receive inspections by multiple inspectorates at one manufacturing site (up to 32, EFPIA data)**
- **Most inspection runs along the product flow:**
  - *30% of inspection time used for "plant tour"*
  - *30% of inspection time covers Quality Management topics*
  - *20% of inspection time covers Quality Control topic*
  - 20% of inspection time is used for clarification e.g. Presenting filing and country specific documentation and processes (e.g. batch release, contracts)
- **During *80 %* of inspection time redundant GMP topics are inspected by foreign inspectorates**

# *Inspection Practice*

## *Detect Potential Focus of Inspections*

- **Domestic environment of the inspector**
  - Governmental discussions
    *e.g. Transparency initiative, Drug shortage, Counterfeits*
  - Pending decisions on formal collaboration
    *e.g. Mutual Recognition Agreements (MRA)*
  - Specific domestic regulations and expectations
    *e.g. Particles, Stability (Climatic zones III/IV)*
  - Specific circumstances
    *e.g. Power supply, security, theft, trespassing*
- **Look what regulators concern themselves with**
  - Upcoming updates on regulations and guidelines
  - Announced internal trainings
  - Personal experience

# *How We Can Manage Discrepancies Raised During Inspections?*

- **Mutual understanding is key**
  - Identify different regulation between countries
  - Define differences on interpretation of findings in one company and by other regulatory agency
  - Analyse inconsistency interpretation between inspectors within agency or between agencies
  - Translation issues
- **Implementing risk-based decisions**
  - What is the risk?
  - Risk related to which area? (ICH Q9 links to risk to patient)
- **Discuss in an open dialogue and compromise**

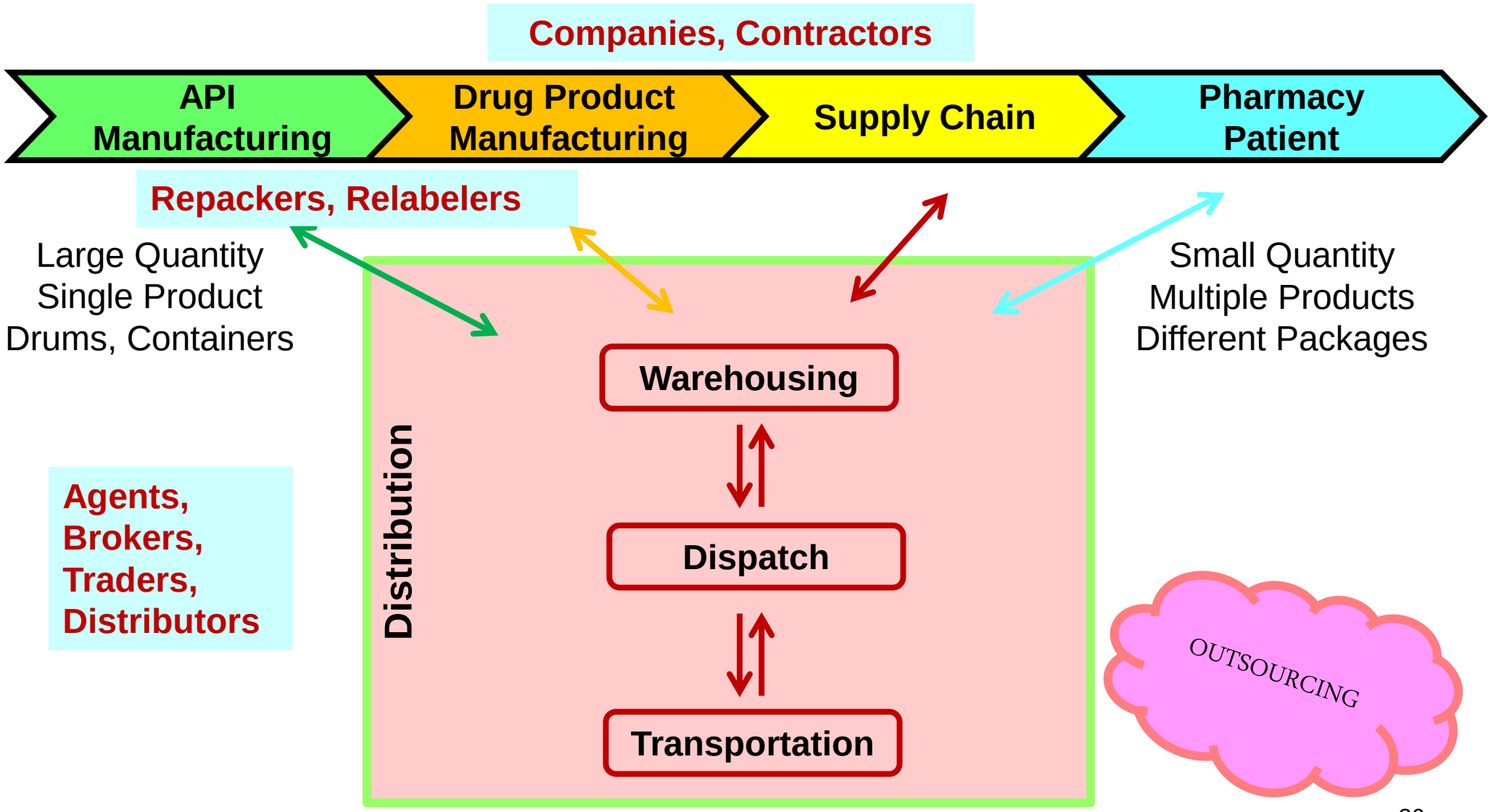
GMP in PIC/S and the European Union

Trend in GMP inspections

**Good Distribution Practice**

Conclusion

# *Good Distribution Practice*



# *Regulatory Framework*
# *Drug Products*

World Health Organization

Guidelines exist since 1999

Inspection of drug distribution channels

Annex 6, WHO Technical Report Series 885, 1999

# *Regulatory Landscape*

World Health Organization

WHO Technical Report Series, No. 957, 2010, Annex 5

## WHO Good Distribution Practices for Pharmaceutical Products

Standard GMP

1. Introduction
2. Scope of the document
3. Glossary
4. General principles
5. Regulation of the distribution
6. Organization and management
7. Personnel
8. Quality System
9. Premises, warehousing and storage
10. Vehicles and equipment
11. Shipment containers and container labelling
12. Dispatch and receipt
13. Transportation and products in transit
14. Documentation
15. Repackaging and relabelling
16. Complaints
17. Recalls
18. Returned products
19. Counterfeit pharmaceutical products
20. Importation
21. Contract activities
22. Self-inspection

References

# *Preventing Counterfeits*

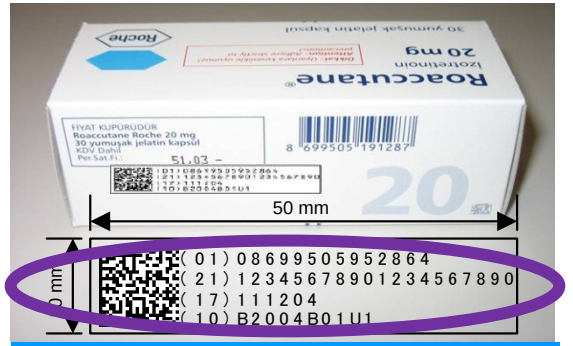
## *Coding / Serialization / Tamper evidence / Aggregation*

**Coding**
primary/secondary pack

Product #
Optionally: Batch# & EXP date


**Serialization**
secondary pack

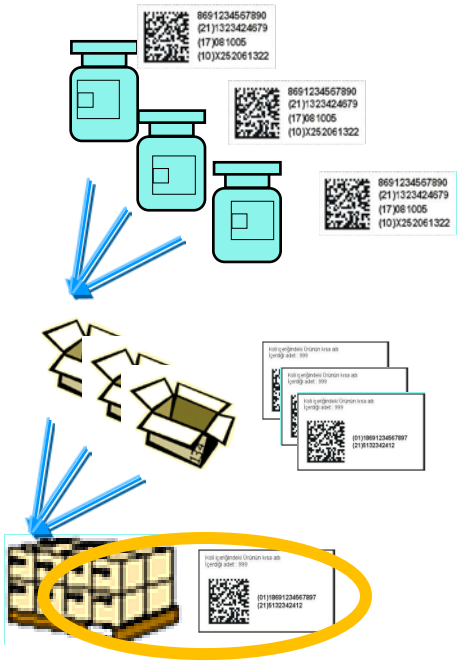
+ Unique identifier on item




**&Tamper evidence**
the secondary pack

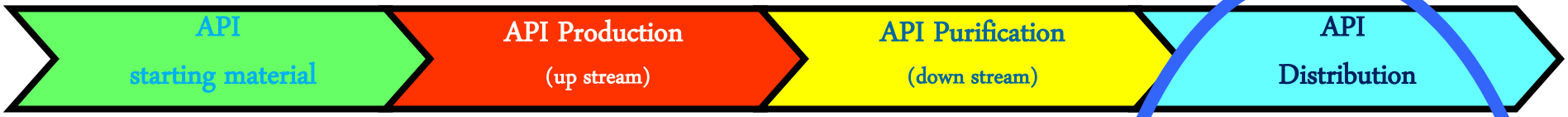
**Aggregation**
shipping unit

+ Unique identifier on bundle / case / pallet



# *Regulatory Framework*

## *e.g. GMP for API's (ICH Q7)*




### API Starting Material

- ICH Q7: Definitions
- ICH Q11: Selection of starting material

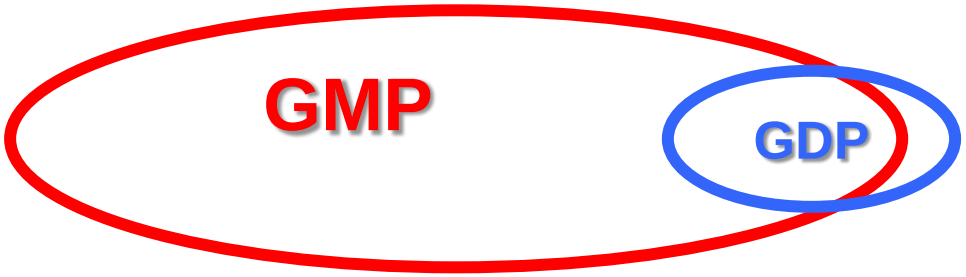
### Manufacturing

- Ch 4: Building and Facilities
- Ch 5: Process and Equipment
- Ch 6: Documentation and Records
- Ch 7: Materials Management
- Ch 8: Production and In Process Controls
- Ch 14: Rejections and Reuse

### Distribution

- Ch 9: Packaging and Identification Labeling
- Ch 10: Storage and Distribution
- Ch 17: Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

# *Summary*




- **Manufacturing Authorisation holder**
  - Manufacture compliant product at a site
- **Marketing Authorisation Holder**
  - Ensure compliance to GMP
  - Owner of the product (see ICH Q10)
  - Legal responsibility for quality and regulatory compliance

GMP in PIC/S and the European Union

Trend in GMP Inspections

Good Distribution Practice

## Conclusion

# *Conclusion*

- **Products and Processes are Fit for the Intended Use**
  - Ensured by implementing harmonised GMPs / GDPs
- **No Surprises**
  - Ensured by implement a '*Quality by Design*' mind set
- **Preventing Emerging Regulations**
  - Ensured by implementing the sprit of existing requirements


*Tor Gråberg, Chairman PIC/S, Geneva, May 2011*


*We Innovate Healthcare*