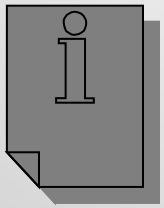
Non-Sterile Products

- Inspector‘s essentials in GMP-inspection -

Dr. Rainer Gnibl

Rainer Gnibl, PhD
Government of Upper Bavaria
Department 53.2 Pharmacy
Maximilianstr. 39
80534 Munich
Germany

Phone +49 89 2176-2877
Fax +49 89 2176-402877
Mail rainer.gnibl@reg-ob.bayern.de



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Overview

1. Essential topics in inspection - Overview
2. Which Systems are critical?
3. Do‘s & Don‘ts in inspection

Overview

1. Essential topics in inspection - Overview
2. Which Systems are critical?
3. Do‘s & Don‘ts in inspection

1. Essential Topics in inspection

Why essential ?

- Some areas are more important than others
  - Focus: Product quality, safety & efficacy
  - (Cross-)Contamination & mix-up
  - Credibility for inspectors ► „*Integrity*“ of provided data
- Important areas create major- or critical findings
- Critical findings result in immediate regulatory action

  acc. Compilation of Union Procedures on Inspections and Exchange of Information Compilation (CoUP)
  - *Compliance management* CoUP - *Procedure on compliance management*
  - Product recalls CoUP - *Procedure for managing rapid alerts arising from* quality defects risk assessment
  - (Partial-)withdrawal of MIA & GMP-certificate CoUP - *Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal healt*h
  - Withdrawal of MA Marketing Authorisation

Essential EU-GMP requirements … from EudraLex Vol. 4

- Pharmaceutical Quality System
  - (*Management Review*) ► i.c.of findings due to ressource-constraints
    - Focus: Idependency to decide about ressources at site?
  - *Product Quality Review*
    - Focus: Linking & accordance to PQS-elements which should reflect problems rel. to *state of control* (= validated state)
  - Essential PQS-elements see also presentation chap. 2
    - *Quality Risk Management*
    - *Deviation Management & CAPA-System*
    - *Change Management*
  - QP's batch-certification management
    - Focus: Integrity of provided data & independency of decision

Essence off all: *Knowledge Management* for *Continual Improvement*
see presentation chap. 2

- Premises & Equipment
  - Zone-concept of premises Separation, dedication, access
  - Design of facilities, utilities & equipment incl. HVAC-system
  - On-site: Structural conditions
  - On-site: Cleanliness of product contact surfaces
  - Decision on *dedicated* or *shared* facilities

    see EU-GMP Part I, chap. 3.6 for decision making and

    see EMA "*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"* for toxicological evaluation

Focus: (Cross-)Contamination & mix-up

see also EU-GMP Part I, chap. 5 - "Prevention of cross-contamination" & chap. 5.21 "Technical measures"

  - Qualification & non-preventive maintenance of equipment/utilities
    - i.c. of Repetitiv break-downs esp. during production or testing
    - Documentation of break-downs & related maintenance for traceability in batch manufacturing- or testing record (BMR, BTR)

Original data (source data):
„*First capture or record of data and data processed, filtered or sorted from them.*“

- **Documentation**
  see also presentation chap. 2
  - Batch records
    - Traceability of correction, alteration or changes of original data
    - Documentation & traceability of events (e.g. incidents, deviations & non-conformances)
  - Batch certification by QP & batch release
    - Traceability of QP-delegation of tasks acc. Annex 16, chap. 1.7
    - Imported products: All activities acc. Annex 16, chap. 1.6 & 1.7 under EU-MIA on EU-territory
  - Data management acc. EMA Q&A-paper „*Data Integrity*“
    - *Data Governance* document (e.g. policy or master plan) Q&A-paper, question 12
    - ALCOA-principles applied throughout data-lifecycle Q&A-paper, question 13

see next page

Focus: Traceability & integrity of data in all types of record/reports

13. How are the data integrity expectations (ALCOA) for the pharmaceutical industry prescribed in the existing EU GMP relating to active substances and dosage forms published in Eudralex volume 4?

The main regulatory expectation for data integrity is to comply with the requirement of ALCOA principles. The table below provide for each ALCOA principle the link to EU GMP references (Part I, Part II and Annex 11):

	Basic Requirements for Medicinal Products (Part I): Chapter 4[1] / Chapter 6[2]	**Basic Requirements for Active Substances used as Starting Materials (Part II) : Chapter 5[3] / Chapter 6[4]**	**Annex 11 (Computerised System)**
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[2]Chapter 6 (Part I): Quality control
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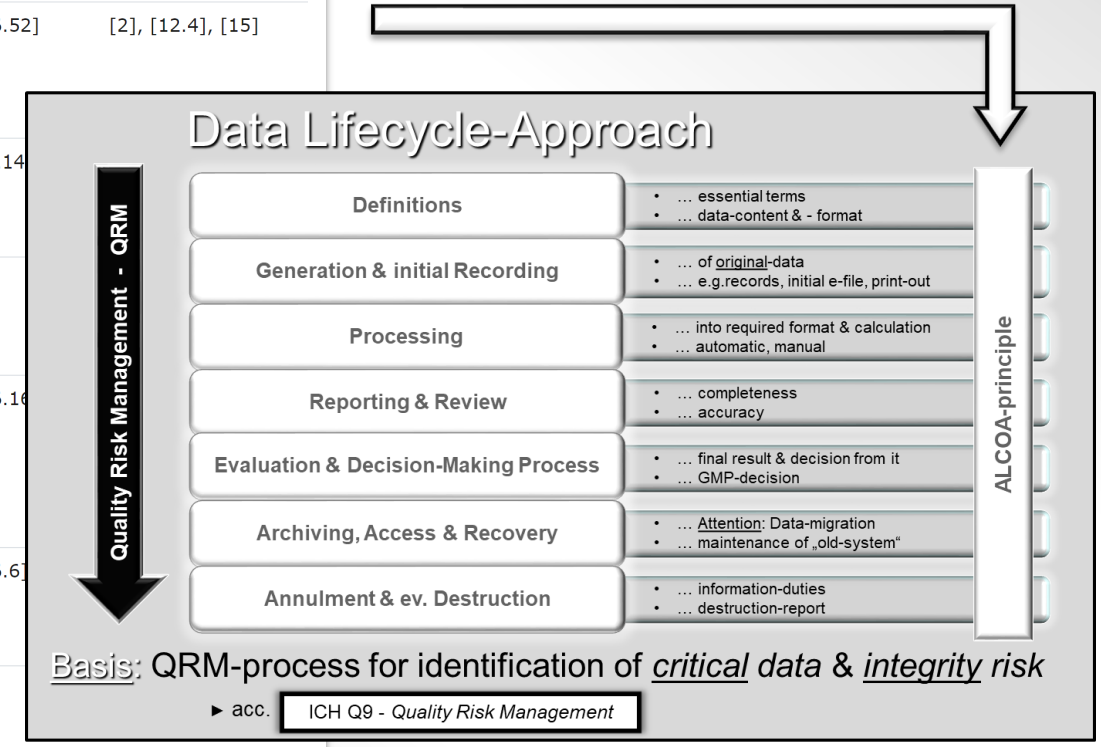

- Production
  - Process-design
    - Personell- & material flow
    - Handling of materials
    - Generation & removal of dust
  - Cleaning validation & -verification
    - Focus: MACO-calculation with PDE from toxicological evaluation

      acc. EMA "*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"*
    - "Old" acceptance-criteria (10ppm or dose-criteria) only possible if more stringent than "new" criteria

Focus: (Cross-)Contamination & mix-up

see also EU-GMP Part I, chap. 5 - "Prevention of cross-contamination" & chap. 5.21, "Organisational measures"

  - Process-validation (PV) & *Ongoing Process Verification* (OPV)
    - Scientific justification for CPPs, CMAs & CQAs from R&D-phase
    - CPPs, CMAs & CQAs reflected in control-strategy
    - Essential: 3 consecutive successfull batches for initial PV

- OPV considers all batches since initial validation (not only batches from current period like PQR)
- Clear criteria for negativ trend in OPV

- Reprocessing of rejected/returned product acc. EU-GMP Part I, chap. 5.67-5.70

Focus: Reliability & robustness of process for ongoing *state of control*

… no processing into compliance or trial-and-error approach

- Quality control
  - Manual integration
    - Original data (prior manual integration) archived
    - No manual integration (of automatically integrated/calculated OOS-result) into compliance
    - Manual integration traceable in Batch Testing Record (BTR) or part of BTR
    - Clear procedure who, when, why & how to manually integrate
  - Manual run-abortions
    - Abortion-rate
    - Manual abortion despite automatic abortion by system (would system also automatically abort?)
    - No manual abortion despite auto-sampler for injection
    - Scientific justification for abortion documented & traceable
    - No manual abortion post sample-injection
    - Clear procedure who, when, why & how to manually abort
  - OOS-management … incl. OOT- & OOL-results
    - No incident- or unusual-event system prior OOS-system (… to pre-sort or pre-filter (pot.) OOS-results out)

Decision for manual integration before knowledge about OOS-result

Hold-time study for sample-preparation required to argue with instability

- Invalidation of OOS-results
  - Invalidation-rate
  - Scientific based, traceable & documented justification for invalidation
  - Documented evidence needed
  - Retention of initial/original sample preparation within hold-time
  - *Hypothesis-Testing* only with initial/original sample preparation
  - *Hypothesis-Testing* for root-cause analysis, not for invalidation of OOS-result
  - Clear batch disposition procedure i.c. of valid OOS-result

Focus: Integrity & traceability of data esp. i.c. of invalidated non-conformance result

Stability-OOS most often reason for recalls

- Ongoing-stability programme
  - Representative for all batches in market (OOS triggers recall of all batches in market, not only of OOS-batch)
  - Relase of batche close to specification-limit should take future stability-OOS into consideration esp. if recurrent
  - Attention: Inspectors will link recurrent stability-OOS to process-validity

- Recurrent batch-release close to specification-limit and/or repetitive OOS should trigger
  a) Investigation, process change, ev. new validation &
  b) MA-variation depending on change

Wrong quality culture:
Just playing down recurrent stability-OOS to on-off-events and ignoring real root-cause

- Method-validation
  - Focus: *State of control* (validated state)
  - Attention: Inspectors will link frequent incidents, deviations or invalidation of OOS-result to method-validity

Complaints & quality defects

Focus: Investigation of real root-cause for *Continual Improvement*

- Inspector´s view:

Value of complaint … if entitled

- Direct response from patient / market
- Direct link to quality, safety & efficacy
- Direct related to product quality („*quality defect*“)

Complaint-handling direct feedback-tool to improve quality !

► Long-term-effect: Costs

Presupposition:

- Objective
- Comprehensive
- Outcome-open

complaint handling !

Right intension … & inspector‘s focus

- Registration of all quality-defects
  - No pre-sorting & -exclusion in systems prior complaint-management
  - No exclusion in „(external-) call-centers“

  Only complete data enables objective complaint-management
- Harmonization of classification & investigation
  - Between individual defect-investigators
  - Between sites (Attention: Global-systems)

  Variabilities influence data-basis & -objectivity
- Overall & full root-cause investigation
  - Primary- & secondary level … *„underlaying system“*

  Only real (initial) root cause triggers adequate & effective CAPA
- Meaningful trending

  Only from trends you identify system-failures

- „Clustering“ of complaints
  - Enables overlapping trending

  Clustering reveals hidden trends & system-failures

- Intelligent „clustering“ ► grouping, overlapping, correlating …
  - by dosage form
  - by equipment / rooms
  - by shift
  - by manufacturing-site …

  Treding not only & always rel. to individual batch or product

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2. Which systems are critical ?

Questions:

- Which results/events are critical?
- Which systems are worth to be compromised?
- On which systems would you focus ? … if you would have the intention

Event due to system-failure

Results from systems with neg. impact on QP`s batch-release

Events from systems you could personally be blamed for

Results from systems with neg. impact on QP-declaration

Sytems which generate costs (e.g. batch-rejection, complaint, recall, market-shortage, variation)

Summary: Everything which „*went wrong*“ rel. to quality & GMP

Systems managing „*non-conformances*“

„*Non-Conformance*“ Systems … in GMP-environment

- Deviation Management
  … incl. „*Incidents-, events, abnormal results, other non-conformances …*“
- Non-preventive Maintenance
  Focus: „*Equipment break down*“ & resp. run/-sequence abortions
- Change Management … esp. with CMOs or external laboratories
  Focus: MA-relevant changes (variations) on e.g. process, method, materials, supply chain
- OOL, OOT & OOS
  Focus: Final product- & stability testing, media momnitoring (incl. HVAC)
- Quality Defect-, Complaint- & Recall Management

Indirect via „*Non-Conformance*“ Systems:

- OPV Ongoing Process Verification, PQR Product Quality Review, Management Review ► Focus: „*State of control*“
- Self inspections, audits & authority inspections

„*Non-Conformance*“ Systems essential for „*Knowledge Management*“ & „*continual improvement*“ … because you can learn from failure-knowledge

Problem: Wrong *Quality Culture* ► Non-objective data management („*data integrity*“)

Knowledge management:

Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Pharmaceutical Quality System

- Aim: *Continual Improvement* by *Knowledge Management*

PQS actively indicate need for GMP- or regulatory change on QRM-basis

via **Knowledge Management Elements** over product-/process lifecycle

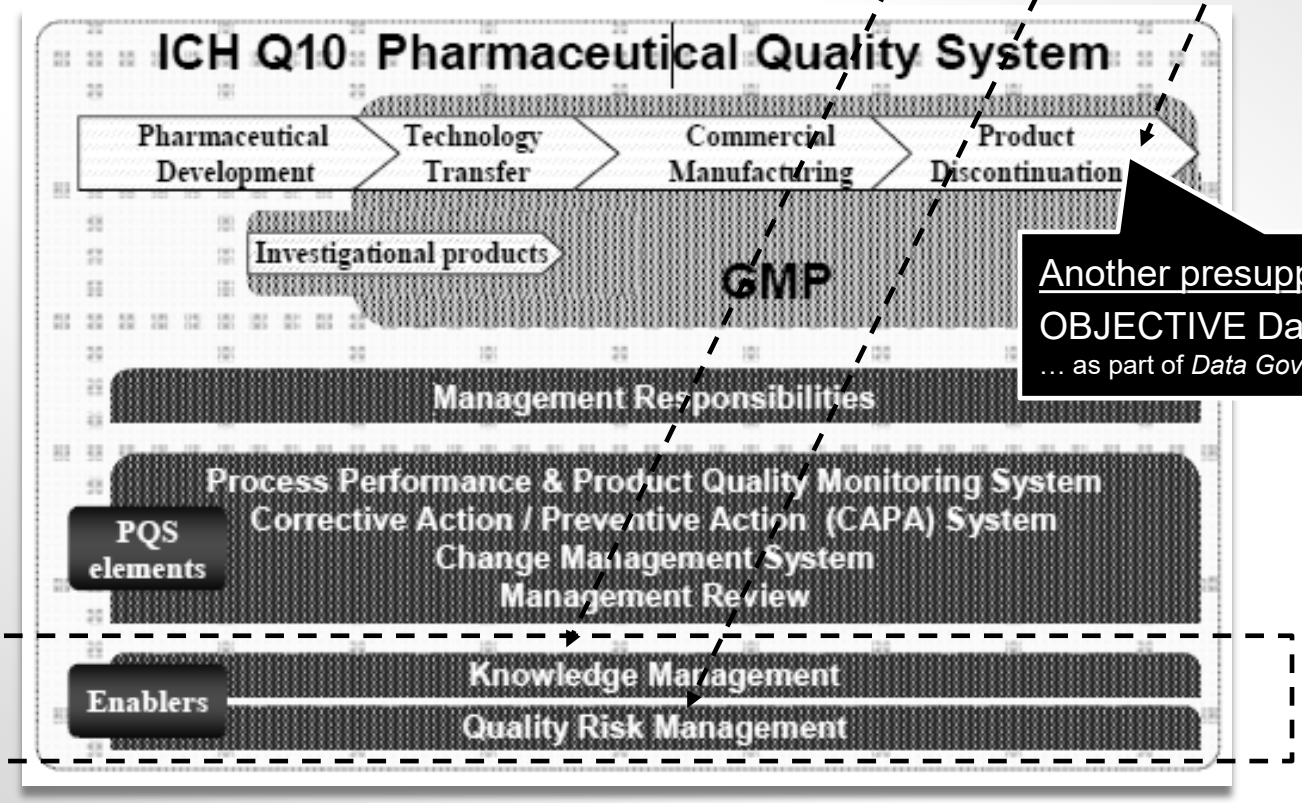


Diagram of the ICH Q10 Pharmaceutical Quality System Model

Another presupposition:
OBJECTIVE Data Management
… as part of *Data Governance* Policy

Pharmaceutical Quality System

- **Knowledge Management Elements** from PQS linked to product

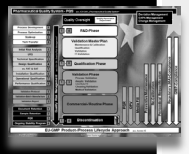
Enabler: ICH Q9 - *Quality Risk Management*

- Essential data systems:

Non-Conformance Management
incl. Investigation, root cause analysis & recall
Incidents & deviations
Quality defects & complaints
OOT-results
OOS-results

Quality Reviews
Management Review
Product Quality Review - PQR

Product- & Process Lifecycle Management
ev. R&D
Validation
Master Batch Record
Manufacture, packaging, testing
Ongoing Process Verification - OPV



Stability programme

- Essential tools:

Change Management

CAPA-System

Regulatory Compliance Management
incl. Variation management

Additional or new PQS-elements for *Knowledge Management* & *Continual Improvement* not needed, but OBJECTIVE DATA MANAGEMENT within systems

ICH Q9 - Quality Risk Management

Initiate
Quality Risk Management Process

Risk Communication … between conc. parties

Risk assessment
- Hasard identification
- Risk analysis
- Risk evaluation

unacceptable

Re-evaluation

acceptable

unacceptable

Risk Management

Risk control
- Define mitigating measures

Risk-acceptance

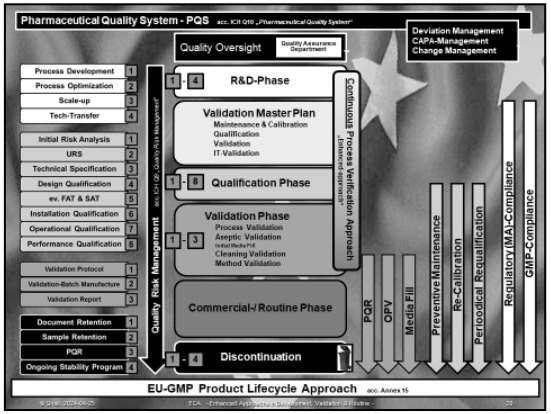
unacceptable

Result: Risk mitigation-strategy

Risk review of events
- Deviations, changes
- OOS, OOT
- … other events

Totality of all risk-mitigating measures:
Control strategy

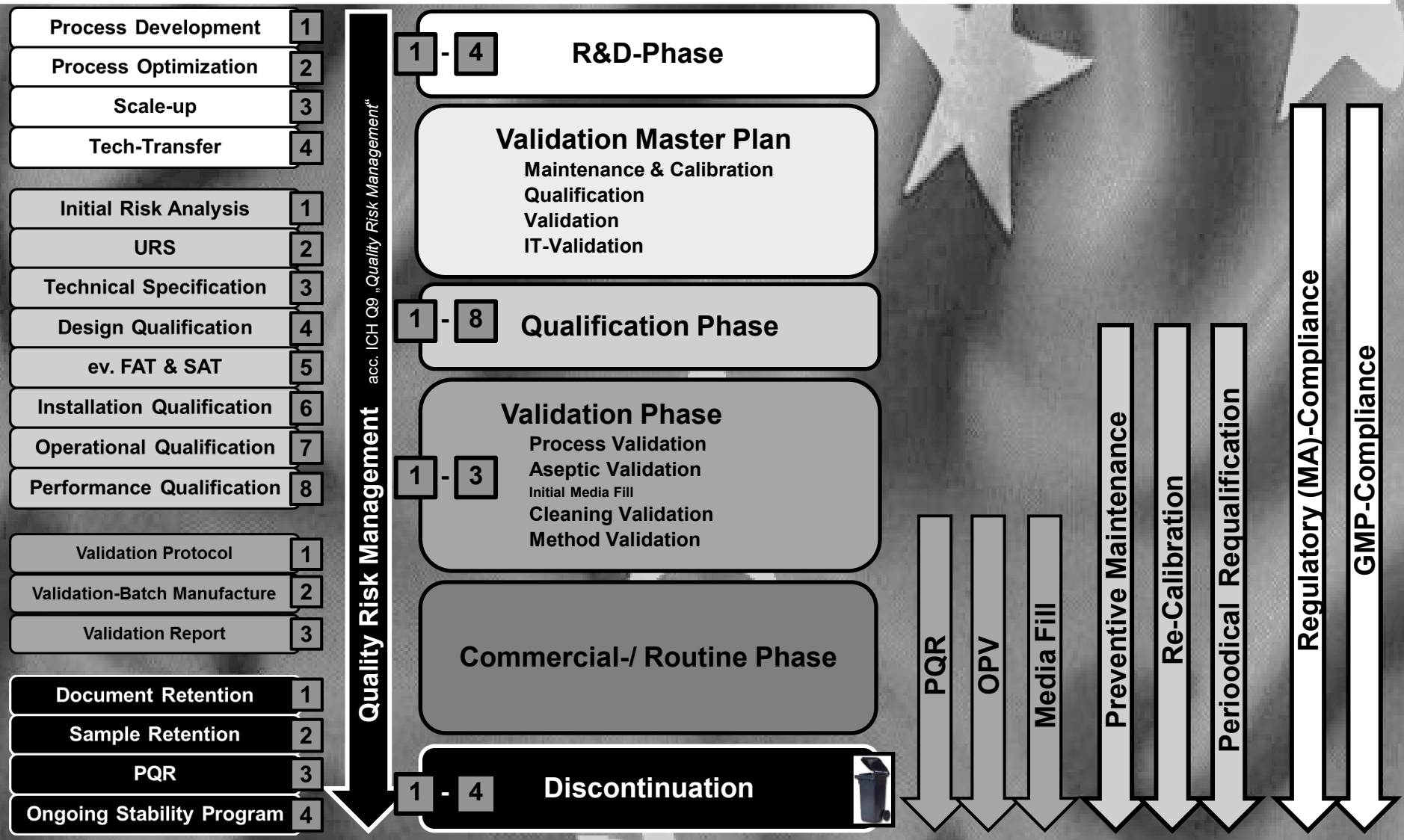
QRM basis for product lifecycle



Risk-mitigating measures e.g.
- Facility-/equipment design
- Qualification tests
- Identification of CMAs, CQAs
- Identification of CPPs
- Process-/method design
- Control strategy
- Process-/method variability & -capability
- Statistical methods
- Trending

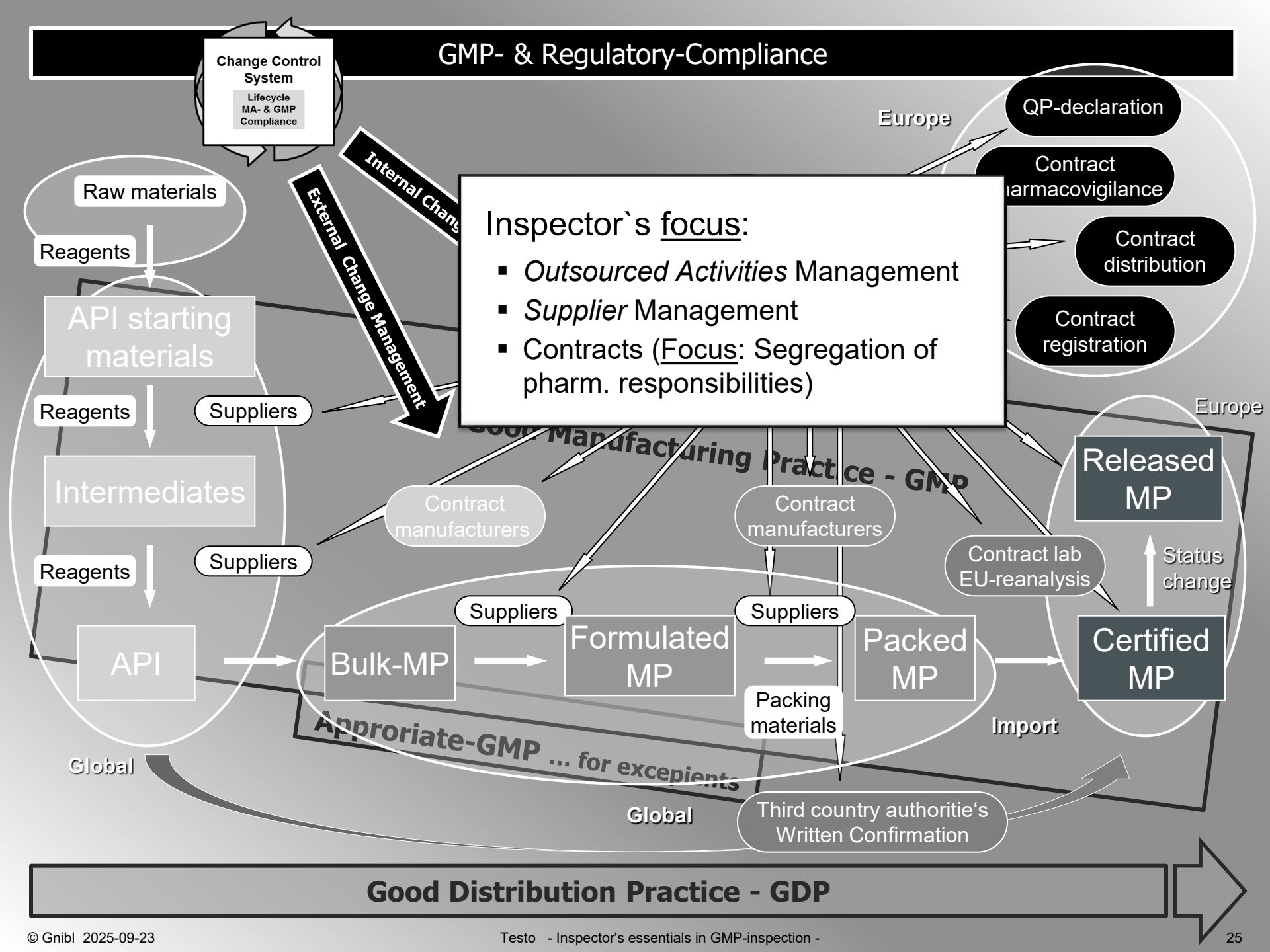
... among others

Knowledge Management Elements



EU-GMP Product-/Process Lifecycle Approach acc. Annex 15

GMP- & Regulatory-Compliance



… remember …

Attributable (data can be assigned to the individual performing the task)

Legible (data can be read by eye or electronically and retained in a permanent format)

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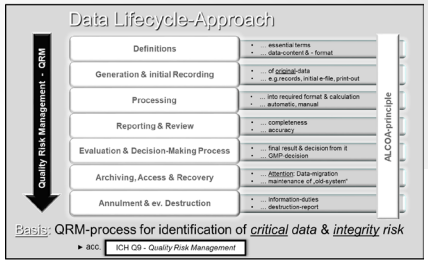
Objective Data Management

Definition „*Data Integrity*“



a. What is “data integrity”?

For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).[5]

Data integrity is critical throughout the CGMP data life cycle, including in the creation, modification, processing, maintenance, archival, retrieval, transmission, and disposition of data after the record’s retention period ends.[6] System design and controls should enable easy detection of errors, omissions, and aberrant results throughout the data’s life cycle.

Source: Data Integrity and compliance with drug CGMP, Questions and answers, Guidance for Industry, US-FDA, December 2018

Adherence of ALCOA-principle over total data-lifecycle

… remember …

2. Which Systems are critical?
   - Objective Data Management


EUROPEAN MEDICINES AGENCY
European Medicines Agency - Science, medicines, health

Questions and answers: Good manufacturing practice

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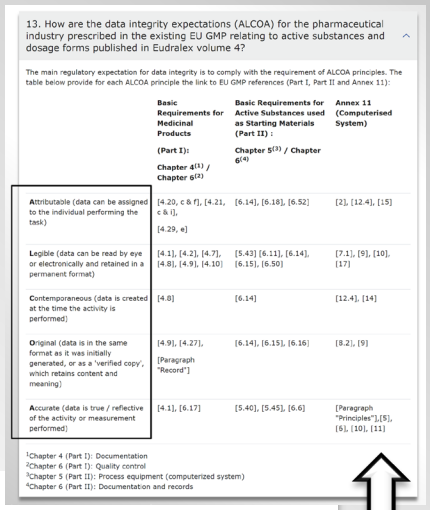
Further questions and answers are published as the need arises. Individual questions and answers may be removed when the relevant GMP guidelines are updated.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EMA Q&A-Paper: "*Data integrity*"

- Question Nr. 13:

  *How are the data integrity expectations (**ALCOA**) for the pharmaceutical industry prescribed in the existing EU GMP relating to active substances and dosage forms published in Eudralex volume 4*?

- Answer Nr. 13:

  *The table below provide for each **ALCOA principle** the link to EU GMP references (Part I, Part II and Annex 11)*

EU-requirements related to data integrity: ALCOA-principle

Wrong data management

Which data have to be documented & archived ?

All data, created because of GMP-requirements !

Original data (source data):
„First capture or record of data … .“

- Original-data,
- Meta-data &
- all data processed, filtered, sorted … from them.

“FDA requires complete data in laboratory records, which includes raw data, graphs, charts and spectra from laboratory instruments”

Quelle: Data Integrity and compliance with drug CGMP, Questions and answers, Guidance for Industry, US-FDA, December 2018

When do I have an integrity problem?

If I ask myself, whether I should document THIS!

If I need to escalate THIS prior to documentation!

If THIS is not documented at the end!

Wort-Cluster *„Data Intergrity“*

- ***Bad** Documentation Practice*
  - Repetitive unintentionally or systematically
- ***Non**-Traceability*
  - Who, what, when, where, how, why …
- ***Pre**-Assessment*
  - Pre-evaluation, -consultation prior initial recording (*pre-capture*)
  - Pre QC-testing
- **Positive-selection** - Negative filtration
  - Partial, sketchy initial recording (*data-gaps)*
  - Filtering for processing, reporting & reviewing
- **Manipulation**
  - Retrospective change, addition or deletion
- **Destruction**, **deletion** & **intended new recording**

Attention: Deliberatelly oral false statements … acc. inspector`s expectation

- Loss in credibility & trust

Essential PQS-element for OBJECTIVE Data Managment

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Q 12: Is it required by the EU GMP to implement a specific procedure for data integrity?

A: There is no requirement for a specific procedure, however it may be beneficial to provide a summary document which outlines the organisations total approach to data governance.

(EMA Q&A-paper on data integrity, 08/2016)

Data Governance Policy (Masterplan)

Pharmaceutical Quality System

Attention: DRAFT

EU-GMP Guide Part I (chap. 4) - *Documentation*

Section Number

1. Principle
2. Scope
3. Data governance systems
4. Generally required GMP documentation (by type)
5. Master Documents (not exhaustive list)
6. Generation and Control of Documentation
7. Good documentation practice
8. Retention of documents
9. Data Integrity in documentation
10. Hybrid Systems
11. Glossary

NEW sections:

- *Data Governance System*
- *GDocP & Data Integrity*
- *Hybrid Systems*
- *Glossary*

… and new order of sections & arrangement of requirements within sections

Real Problem:

Wrong *Quality Culture* caused by senior management's pure focus only on business aspects … in case of non-conformance

1. Priority: Business - 2. Priority: Continuous Supply - 3. Priority: Quality

- "*Non-Conformances"* documented only after consultation
- Pressure on operator´s to "*not document*"
- „*Keep non-conformances isolated, un-critical on-off events*"
- "*Do not bring non-conformances on global level*"
- De-escalation of events by so called "*management-escalation-procedure*"
- "*System-failures*" not desired

First other mind-set of Senior Management needed !

Overview

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3. Do´s & Don´ts in inspection

What is desired?

- Open & technical based discussions
- Mutual respect
  - Technical based, professional level
- Result-open discussions
  - Focus: *Continual Improvement* (no minimization of findings)
- Open dealing with findings
  - Company: Admitting findings
  - Inspektor: ev. Taking back findings
- Clear answers on clear questions
  - … even if answer leads to finding
- Asking in anything is unclear

- Note …
  - ....why requested document is not correct one & reference relevant document
- Non-existence of documents or gaps
  - ... acknowledge gaps immediately or promptly
- Activities realistic according to routine
  - No special behavior due to "inspection situation"

What should be avoided !

- Delay inspection
  - Documents not provided promptly
  - Repeatedly & deliberately submitting false documents
  - Staff difficult to reach
- Refuse direct access to rooms
  - Rooms not inspected cannot be assessed ► No inspection result
- Vague answers
  - ... verbal information repeatedly deviates from content of documents
  - ... not substantiated & later refuted ► Loss of trust
  - ... according to estimated expectations of inspector
- Equipment & activities regularly "at-rest" during tour
  - ... or only cleaning activities

- "Omniscient" QA department
  - Other departments not represented at all
  - Too late involvement of other departments (delay)
- Unreflective "defense" of defects
  - ... even if associated with *Continual Improvement*
  - … only to reduce no. of defects ↓
  - ... out of dogmatism
- Immediate correction of findings
- Renewed discussion of defects in final meeting
  - ... even if already exhaustively discussed during inspection
  - ... or conclusively determined in daily wrap-up
- End of inspection
  - "Pushing" at end of day
  - Wanting to "clearly" determine end already at beginning of day

- Request for defect grouping
  - ... only to reduce no. of defects for global QA
- Internal disagreement (dispute) reg.
  - Responsibility for response or
  - Technical content of response
- "Mouthing off“
  - ... in response to report "*everything was completely different*", "*misunderstood during inspection*" or "*all a big misunderstanding*”
- Make inspector personally responsible for regulatory requirements
- Answer to report (CAPA-plan) ...
  - ... send "giga byte“
  - ... corrected documents without highlighting changes
  - ... identical argumentation, which was already rejected during the inspection


That´s it from the
dark side !!!