

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)



1) Get ready for an EDQM Inspection & 2) Typical Deficiencies observed

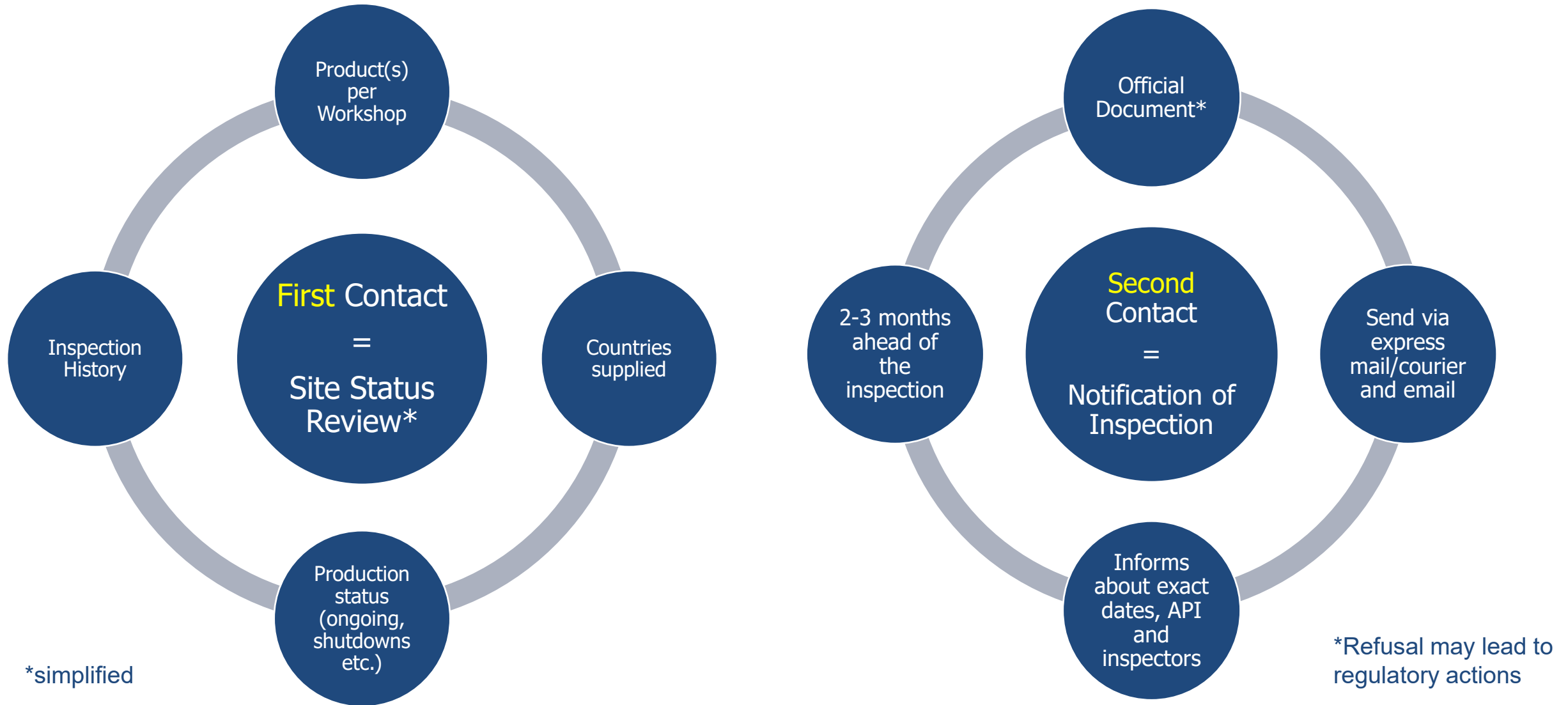
EDQM Training Webinars

13 December 2024

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So it begins ...



BEFORE: the company should

Prepare and provide requested documents (e.g. SMF, PQRs)

Send Invitation Letters

Provide support in Hotel booking

Appoint skilled Interpreters (if needed)

Pay Travel Expenses & Inspection Fees

Organise transfers (hotel, airport, factory)

Organise lunch during the inspection

BEFORE: the company should **not**

Notify undeclared changes in the CEP dossier

Interrupt Production

Paint premises and equipment

Create, rewrite, manipulate documents

Perform unscheduled maintenance activities

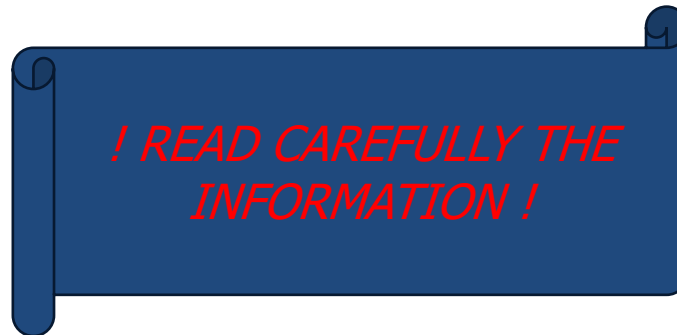
Draft new or update procedures (Unless if already foreseen)

Hire new staff members (Unless already foreseen)

BEFORE: not over yet....

Some further points to be noted:

- EDQM informs the local Inspectorate about the dates and scope of the inspection
- EDQM welcomes the presence of local inspectors as observers
- An inspection schedule with documentation requests and general aspects as well as recommendations is sent to the company about one week before inspection starts



DURING the inspection

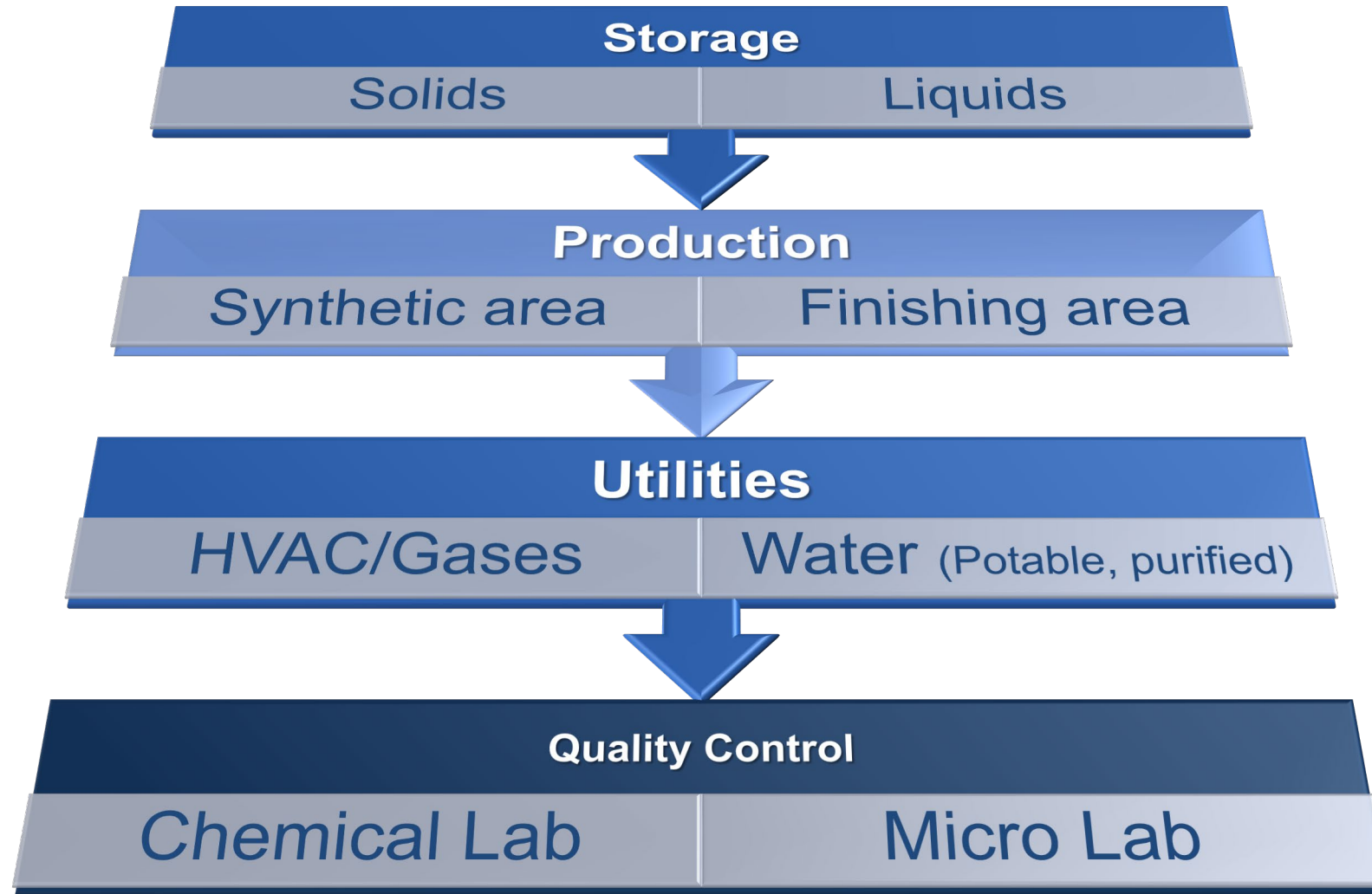
General Points to consider:

- Ensure ability to retrieve any document:

- Documents to be provided as fast as possible
- Ensure that the “Inspection War Room” is close to the meeting room
- Even if requested documents are not embedded in the Company’s quality system, they should be made available to the team as they can provide valuable additional information

- Instruct the staff members to answer to inspectors’ questions straightforwardly, clearly and honestly, in order to maintain trust and confidence

DURING: Plant Tour



DURING: Plant Tour cont.

Inspectors may:

- Deviate from schedule and suggested directions
- Split during the plant tour
- Request access to any area of the site if they consider it relates to the scope of the inspection
- Ask questions directly to staff members involved in manufacturing operations
- Use digital cameras as auxiliary means (unless not permitted for safety reasons)
- Call for a daily wrap-up meeting if serious observations were made

AFTER the inspection

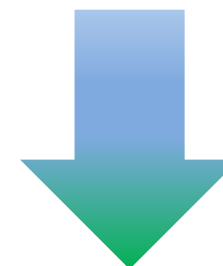
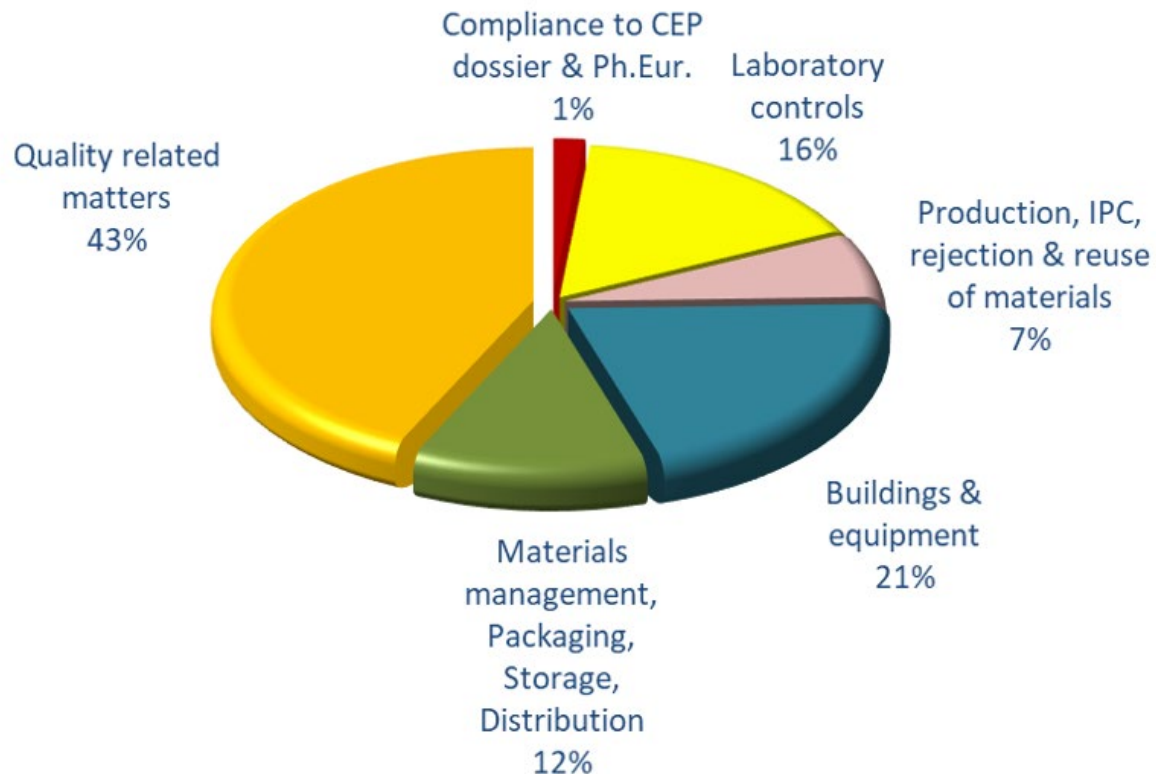
- Replies to be fully documented:
 - Commitments and descriptions of the corrective and preventative action plan with deadlines - should reflect what has or will actually be done
 - Copies of procedures (translated into English if needed)
 - Pictures
- Replies to be provided in electronic format
 - Pdf format
 - Annexes should be bookmarked
- Discrepancies with the CEP dossier are specifically addressed and managed by the revision process at EDQM

GMP Deficiencies

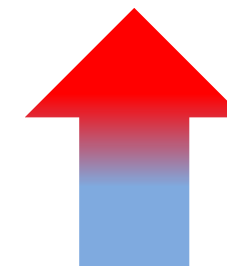


Current API inspections deficiencies & trends

Approx. distribution of deficiencies since 2015



Decrease:
Observations
in Facilities &
Equipment



Increase:
Quality
related
matters

Let's talk about the 43%: Why the increase?

Quality Risk Management

Lack of QA Oversight

Change Control

Investigations (OOS, Complaints, Deviations)

Inadequate overview of production and laboratory activities

Control of Documentation (paper and electronic)

Thoughts on Quality Risk Management

- ICH Q9 (R1): Introduction section

An **understanding of formality** in quality risk management may lead to **resources being used more efficiently**, where lower risk issues are dealt with via less formal means, freeing up **resources for managing higher risk issues** and more complex problems that may require increased levels of rigor and effort.

An understanding of formality can also **support risk-based decision-making**, where the level of formality that is applied may reflect the **degree of importance of the decision**, as well as the level of uncertainty and complexity which may be present.

Thoughts on Quality Risk Management (cont.)

- ICH Q9 #4.6: Risk Review

... Once a **quality risk management process** has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are **planned** (e.g., results of product review, inspections, audits, **change control**) or **unplanned** (e.g., root cause from **failure investigations**, recall). ...

Typical flaws in Change Control

Major deficiency observed in September 2022 and related to The “proposal of zero drum handling” approved in February 2022 and in an *advanced stage* (purchase orders signed, delivery date fixed to October 2022):

- Proposed change was not supported by any change control management.
- The firm did not follow the change control procedure in various aspects, such as
 - “whenever the need for any change arises, the user department shall initiate a change request”
 - “the initiator shall provide a brief description, existing system, proposed change, provide reasons.”
 - “Reviews by initiating head of department (section 6.5) and evaluation by QA coordinator and forwarding to relevant department for impact assessment” (6.6) and QA Head evaluation and approval (6.10.1 – 6.10.3) were not documented

Typical flaws in Change Control, cont.

- Change Control related to the introduction of new chemical entities/APIs with *typical* observations:
 - The impact of such a change was not correctly addressed, as major areas which are impacted by such a substantial change, were not identified as such, e.g. Process Validation, Cleaning Validation, risk assessment, qualification, SOPs, etc.
 - SOP identified circumstances when risk assessments shall be performed. However, the execution of RAs was restricted to new processes at facility, QMS and to assess existing controls. *What's missing?*
 - The change control documentation did not address the impact related to the proposed manufacture of XX in terms of assessing critical process step operations and its impact on the facility and area qualification.
 - Although identified as necessary, no risk assessment was executed at the time of the inspection and no documentation was available to justify its delay.

EU GMP Part I, Chapter 5 - Production

5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:

Technical Measures

- i. Dedicated manufacturing facility (premises and equipment);
- ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;
- iii. Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning;
- iv. Use of “closed systems” for processing and material/product transfer equipment;

Sometimes, non-applicable official guidance documents can provide a great deal of food for thoughts ...

- xiii. For common general wash areas, separation of equipment washing, drying and storage areas.

Organisational Measures

- i. Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;
- ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;

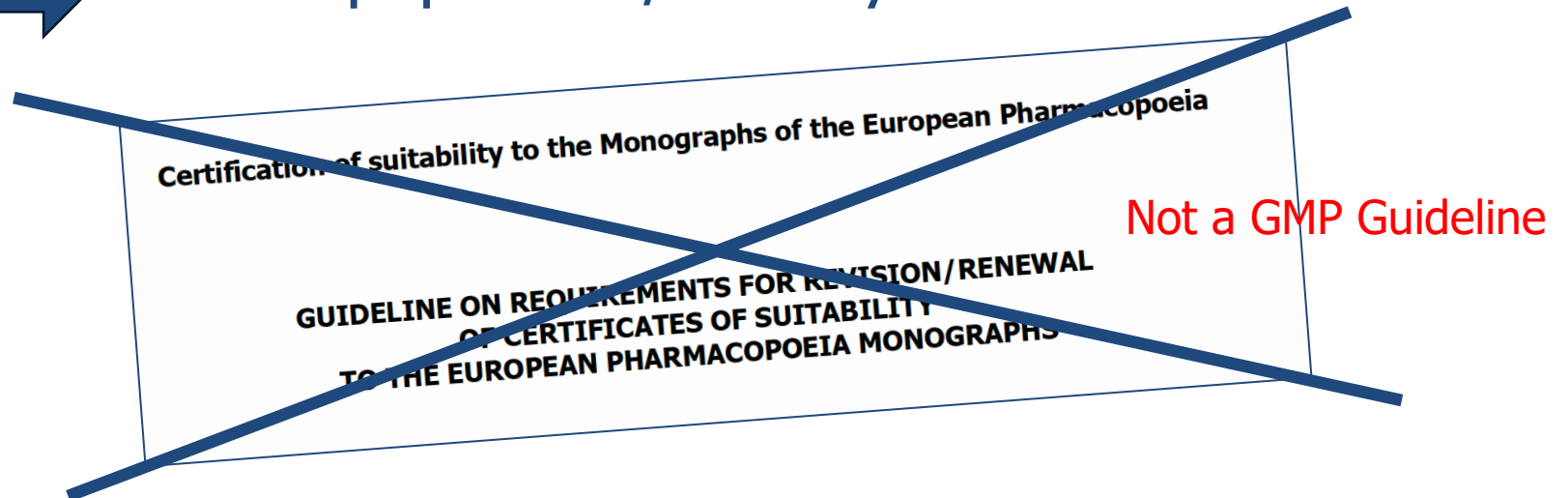
Experience - Change Categorisation

- **No**, the up to **10-fold** increase of batch size compared to the original approved batch size is **not** by default a **minor change in the field of GMP**



Imagine ... a typical 400kg input goes up to 4000kg

➔ new equipment / facility !



Example of insufficient Investigations and Actions

Complaint Management: Drug product Manufacturer found gasket in API

“Although the company identified a butterfly valve of the microniser as origin of the gasket found in the product, the **preventative actions cannot be considered as appropriate**. Instead of removing the inadequate valve because of a design that enabled the fall off of its gasket (likelihood) and the poor detectability of its missing gasket during cleaning, the company decided to add a sieving step after micronisation. It is acknowledged that this step increased the detectability of foreign matters, but **did not remove the root cause**. In addition as the consequence of the additional manufacturing step, the product is **unnecessarily exposed** to the environment”

Indicators of ineffective Deviation and CAPA management

- Examples that raise attention of inspectors and **should** raise attention of QA
 - Investigations not holistic and/or comprehensive
 - Root causes not supported by scientific rationale; not robust
 - High rate of recurrent deviations
 - Recurring CAPAs for the same issue
 - Significant number of critical deviations
 - “planned deviations”
 - Deviations open for a long time
 - Few deviations (underreporting)
 - Incorrect categorisation

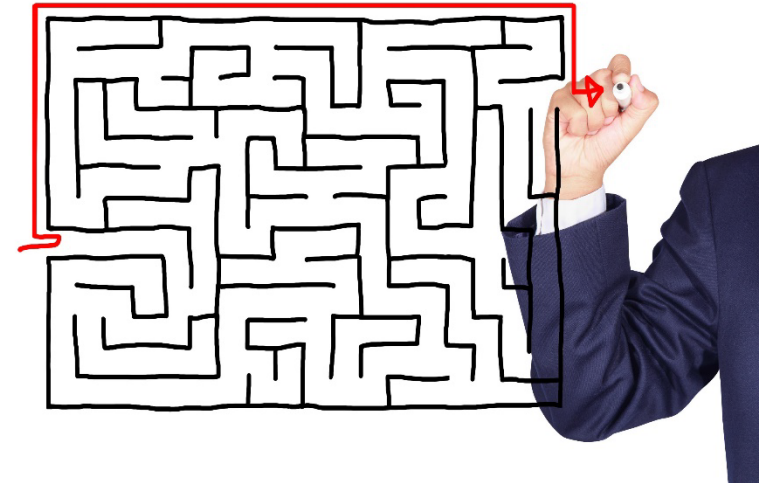
Similar indicators for OOS and complaint investigations

Points to consider

- Terminology: what is a deviation, complaint, incident, OOS, etc.
 - Consistent with GMPs (e.g. ~~planned~~ deviation....)
- Scope: Products, areas covered, investigation trigger
- Assignment of responsibilities
- Chain of notifications (initiator, receiver, etc.)
- Immediate actions
- Investigation & Risk Analysis
 - Level of detail
 - Holistic approach?
 - Recurrence
 - Analyst(s) to be included

Points to consider, cont.

- Root cause determination: exhaustive, conclusive, sound & justified
- Impact assessment: released / to be released products, products on the market
- Flow of investigations, review boards, approval
- Thorough documentation
- Corrective Actions
- Preventative measures
- Evaluation by Quality Assurance



GMP violations: Documentation

Rewriting documents in order to demonstrate acceptable, expected or presentable results, values or dates

Untimely recording of operations, e.g. before (sic!) or far too late

Use of loose sheets instead of bound logbooks

Unavailability of records

Raw data not maintained for GMP activities performed outsourced service providers (e.g. calibration)

GMP violations: Personnel

- Insufficient personnel training:
 - No training of contract personnel performing GMP activities.
 - No training given to upper management with regard to GMP related matters.
 - No assessment of training or with limited value.
 - No training programmes defined for different role profiles.
- Gowning in controlled areas:
 - Operator gowning not in line with procedure.
 - Gowning requirements not defined.

GMP violations: Materials Management

- Insufficient approval and/or management of vendors of key starting materials or **intermediates** (e.g. unreliable on-site audits);
- No data available to support re-test/expiry dates for intermediates or starting materials.
- Inadequate identification of material status (no status labels or barcodes linked to a computerised system).
- Solvent deliveries received and approved from manufacturers which were not qualified or on the approved vendor list.
- Inadequate documentation of solvent tanker cleaning and insufficient requirements outlined in the associated quality agreement with the supplier.
- Risk of loss of traceability due to insufficient identification of containers.
- Improper storage conditions (temperature, humidity, non-controlled storage facilities...).

GMP violations: Buildings & Equipment

- Risks of contamination and/or cross-contamination arising from:
 - improper design of facilities.
 - inadequate cleaning of equipment.
 - insufficient maintenance of equipment.
- P&IDs not reflective of equipment layouts.
- Inadequate labelling of equipment and transfer lines.
- Lack of appropriate user requirement specifications concerning equipment qualification.

GMP violations: Cleaning validation

- Maximum allowable carryover (MACO) limits, swab sample limits, and rinse sample limits not based on a sound scientific approach.
- No data available to support dirty hold times or maximum campaign lengths.
- No deviations raised to investigate failures in routine cleaning verification samples post validation.
- No swab sample recovery studies performed for surfaces sampled.
- Limits of Detection and Quantification above the swab sample limit.
- Residue observed on “cleaned” equipment during inspection.

GMP violations: Process validation

- Processes such as use of recovered solvents, blending or micronisation not always addressed.
- No data available to support maximum permitted drying times.
- No data available to support permitted process parameter ranges.
- Critical process parameters not appropriately defined.
- Conclusions not drawn with regard to the reason(s) of the the validation, e.g. scale up or new equipment.

GMP Violations: Other areas

Production:

- Blending of batches without prior appropriate testing.
- Lack of control of solvent recovery operations:
 - Receiver tanks not identified.
 - No cleaning instructions or cleaning records for non-dedicated receiver tanks.
 - Traceability of solvent transfers not maintained or recorded in batch records.
- Not defined what specific equipment should be used during manufacture.

Outsourced/sub-contracted activities:

- Insufficient qualification of subcontractors (against GMP).
- Quality agreements without or poorly identified responsibilities.
- Insufficient oversight of GMP activities performed by subcontractors.

GMP violations: Quality Control

Chemical/physical testing:

- Fraudulent practices such as pretesting, “testing into compliance” or deleting OOS results
- Not raising OOS investigations for OOS results
- No data to support root cause proposed to justify invalidation of OOS results
- Insufficient records maintained for testing (e.g. reagents used, sample weight printouts)

Microbiological testing:

- Time of entry/removal of samples to/from incubator not recorded.
- Insufficient traceability of reference organisms used during media growth promotion testing

Chemical reference standards:

- Absence of the Ph. Eur. CRS.
- Insufficient establishment of secondary standards.

GMP violations: Computerised Systems

Lack of appropriate user requirement specifications

Outdated OS or applications

No or insufficient management of access levels (risk of loss of traceability)

Insufficient knowledge of computer system validation requirements

No or insufficient review of audit trail

Insufficient controls to prevent data manipulation

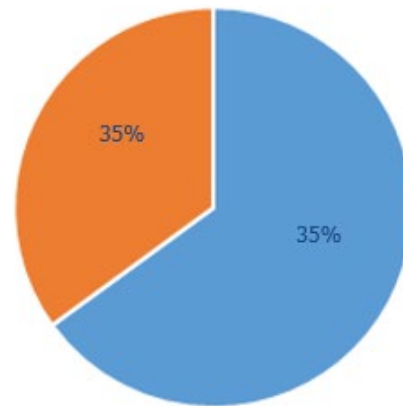
IT staff lacking or without knowledge of GMP requirements

GMP Violations: Data Integrity

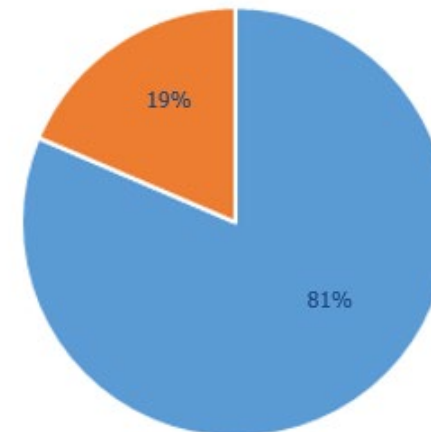
- Usual breaches of data integrity:
- Documentation practices;
- Laboratory controls;
- Validation and controls on computerised systems (absence or gaps).

Approx. proportion of DI deficiencies in recent years

Critical deficiencies



Major deficiencies



■ Non DI related

■ DI related

Acknowledgements

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Thank you for your attention



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