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

EDQM Training Webinar

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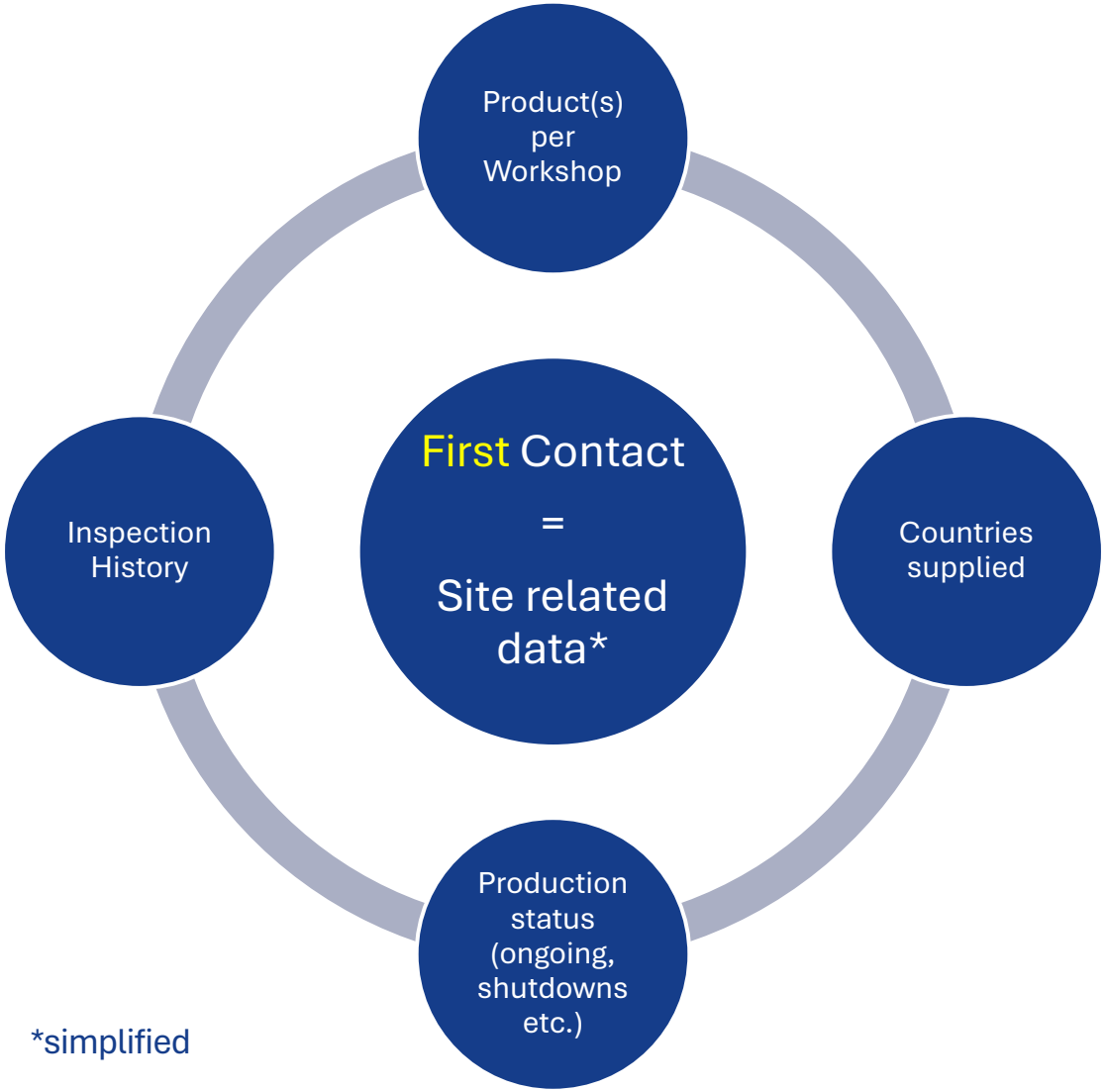
So it begins …



*simplified

*Refusal may lead to regulatory actions

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 previously 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 as well as recommendations are sent to the company about one week before inspection starts

! READ CAREFULLY THE INFORMATION IN THE SCHEDULE AND IN THE ACCOMPANYING EMAIL !

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 in a straightforward manner, clearly and honestly, to maintain trust and confidence

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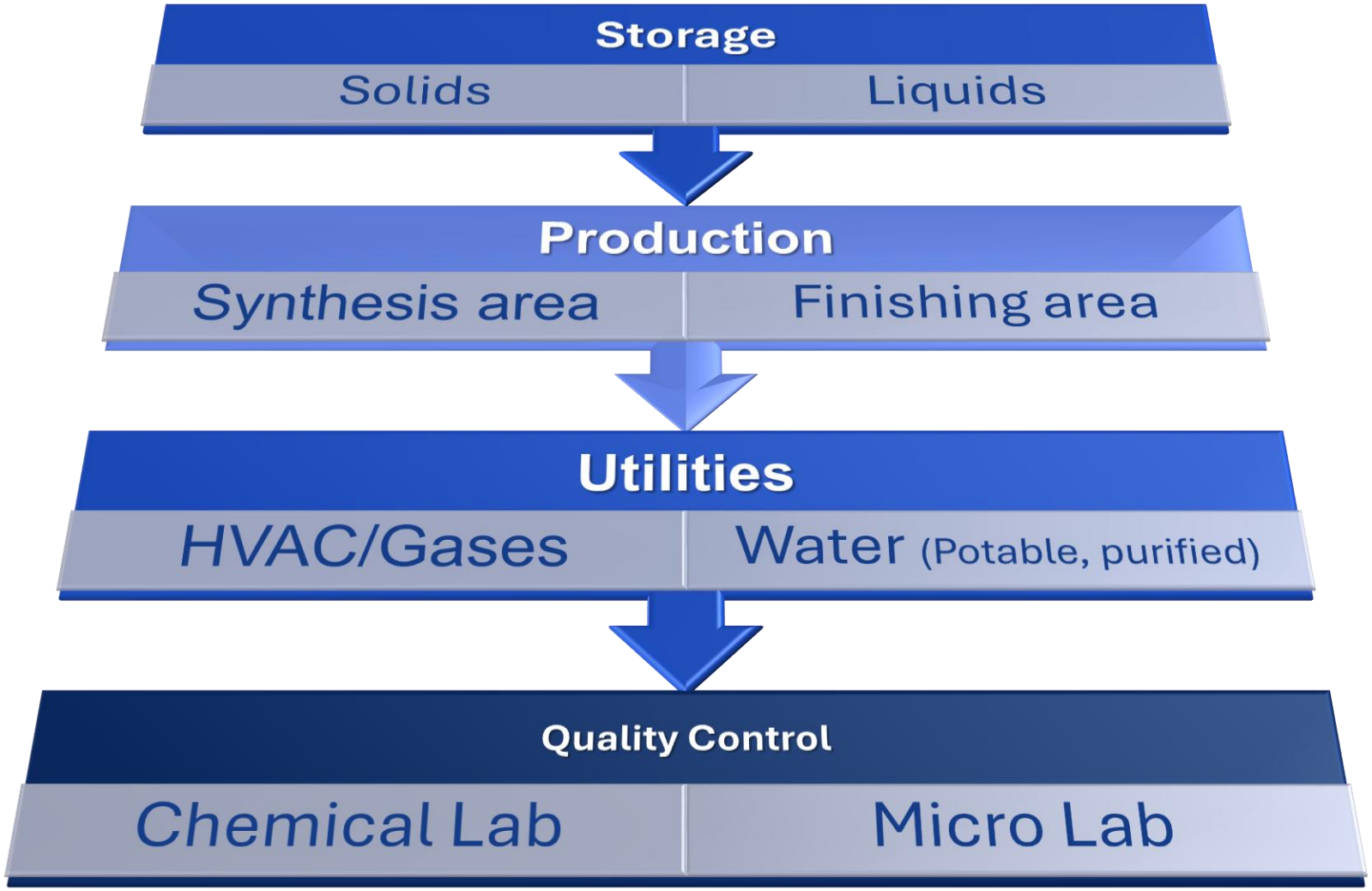
DURING: Plant Tour



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 be done
  - Copies of procedures (translated into English if needed, at least for the impacted sections)
  - Pictures
- Replies to be provided in electronic format
  - Pdf format
  - Annexes should be bookmarked
- Discrepancies with the CEP dossier are specifically addressed and managed via the EDQM revision process

GMP Deficiencies

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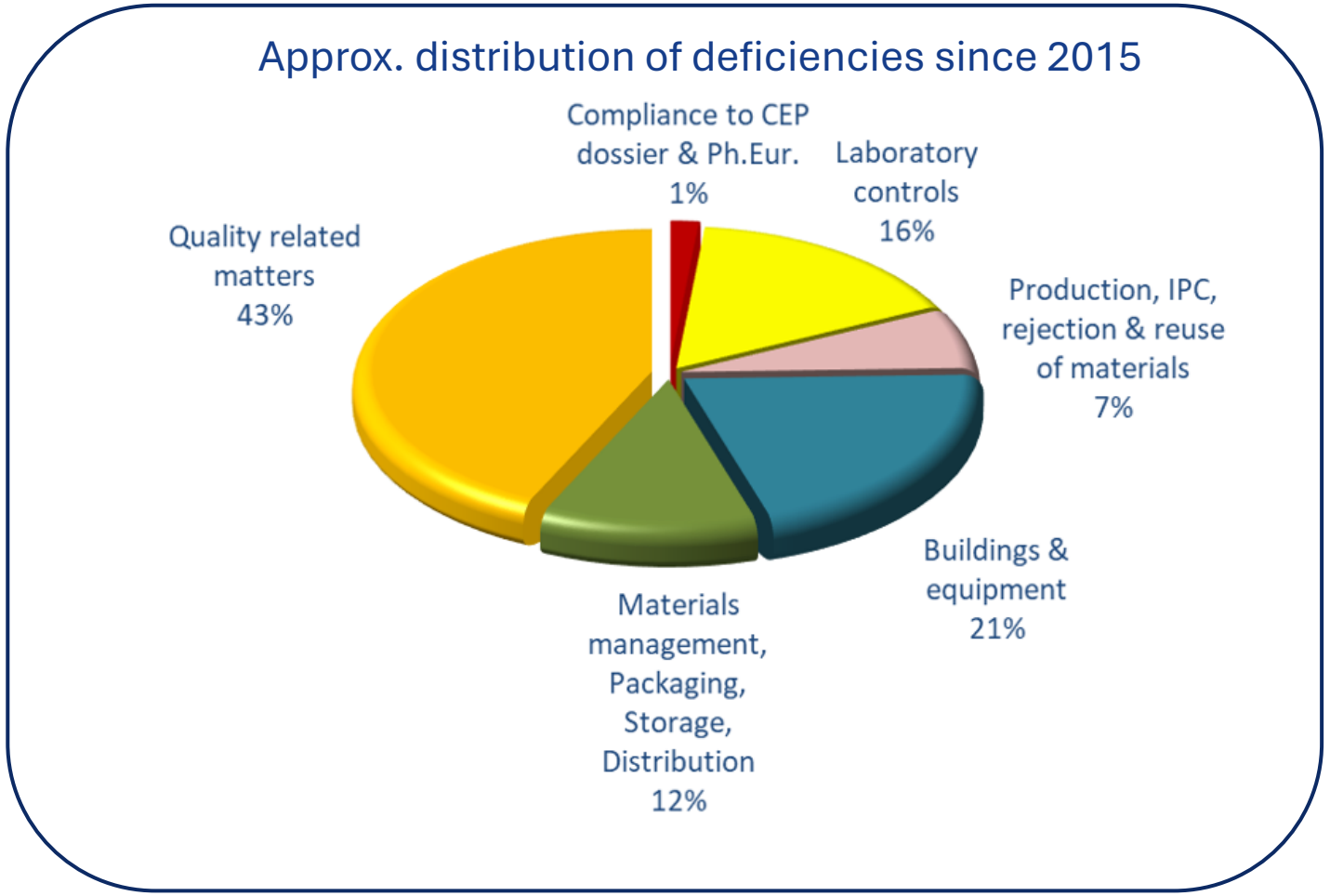
Current API inspections deficiencies & trends



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 Risk Assessment

Two examples of major deficiencies observed in 2025:

- **Risk-assessment gaps across the quality system** - A systemic weakness in the organization's risk-assessment framework affecting several critical elements of the quality system was observed. The fragmented and under-documented risk-assessment practice compromises the organization's capacity to proactively identify and mitigate quality-related risks

- **Inadequate procedural guidance** – The existing Quality Risk Management procedure provides only a high-level description of a formal, multi-step risk-assessment methodology. It lacks practical guidance, decision trees, or simplified approaches for low-complexity activities. Therefore, as confirmed by the company during the inspection, users find the procedure cumbersome and unsuitable for many routine tasks, leading to non-adherence and the omission of risk assessments altogether.

Typical flaws in Change Control

- 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 and evaluation by QA coordinator and forwarding to relevant department for impact assessment” and QA Head evaluation and approval 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 did not provide sufficient guidance on when risk assessments should be performed and which criticalities should be considered in different cases.
  - 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. **Important question to always include in such a risk assessment: "Is it ok to manufacture this product in a shared facility?"**
  - Although identified as necessary, no risk assessment was executed at the time of the inspection and no documentation was available to justify this.

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 tra
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;

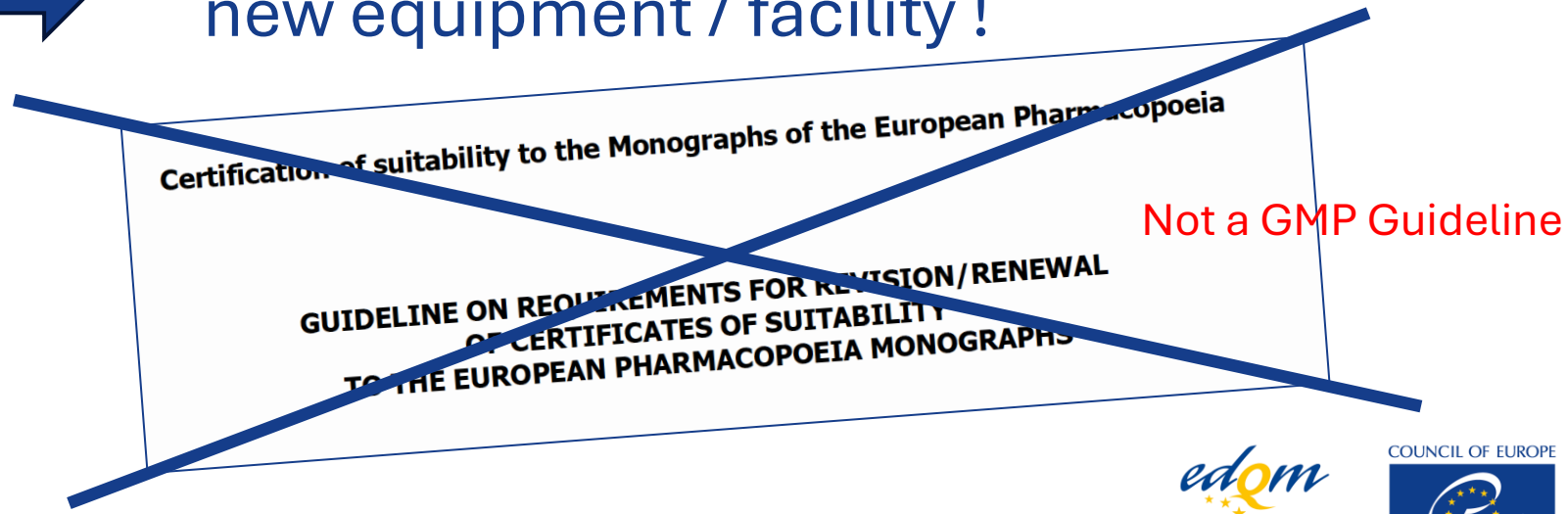
ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;

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 !



Not a GMP Guideline

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 falling 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
  - Deviations open for a long time
  - Few deviations (underreporting)
  - Incorrect categorisation

Similar indicators for OOS and complaint investigations

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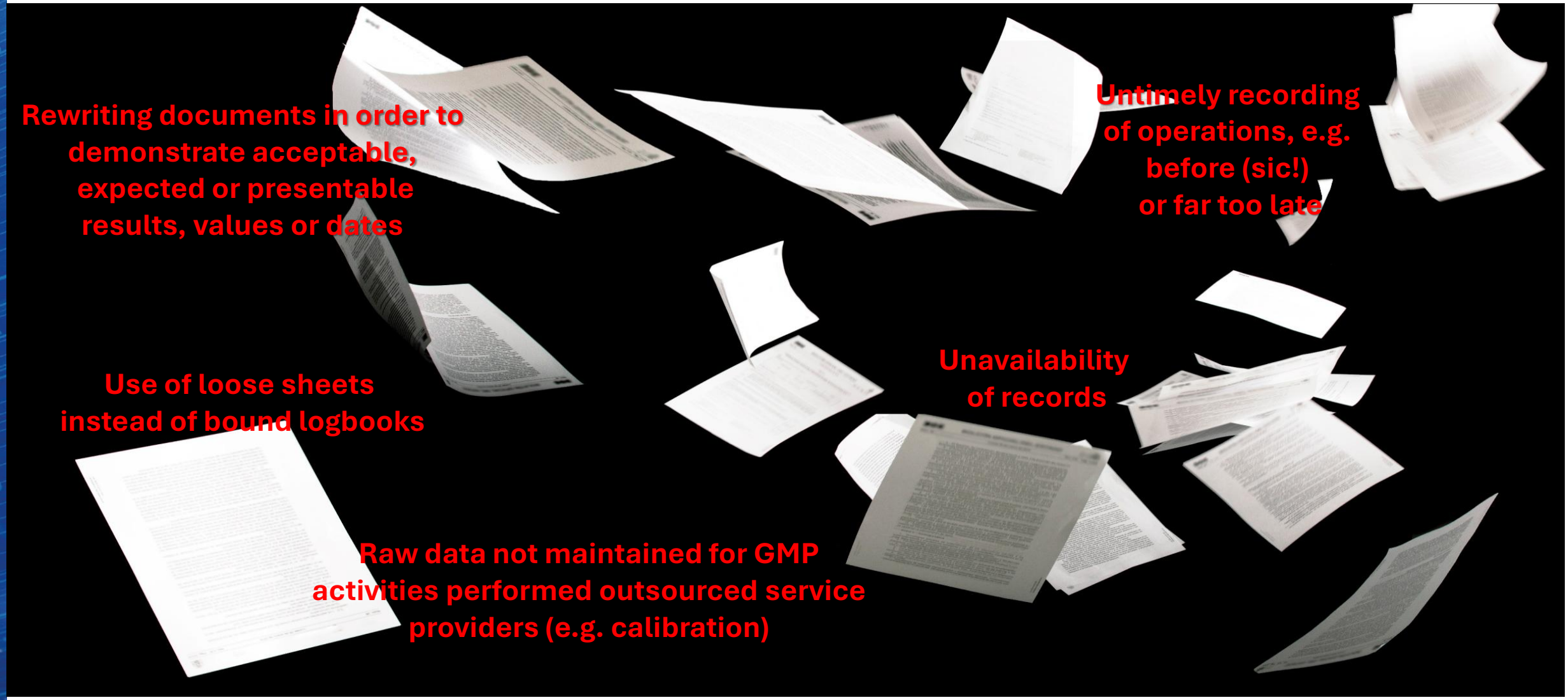
Points to consider

- Terminology: what is a deviation, complaint, incident, OOS, etc.
- 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: on released / to be released products, products on the market, other products in shared facilities, etc.
- Flow of investigations, review boards, approval
- Thorough documentation
- Corrective Actions
- Preventative measures
- Evaluation by Quality Assurance

GMP violations: Documentation



GMP violations: Personnel

- Insufficient personnel training:
  - No training of contract personnel performing GMP activities.
  - No training given to upper management on 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.
- Unspecific and/or non validated analytical methods used during cleaning validation studies
- Residue observed on “cleaned” equipment during inspection.

GMP violations: Process validation

- Processes such as use of recovered solvents/materials, blending or micronisation not always addressed.
- No data available to support maximum permitted drying times: “dry until LOD complies” is NOT acceptable
- 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

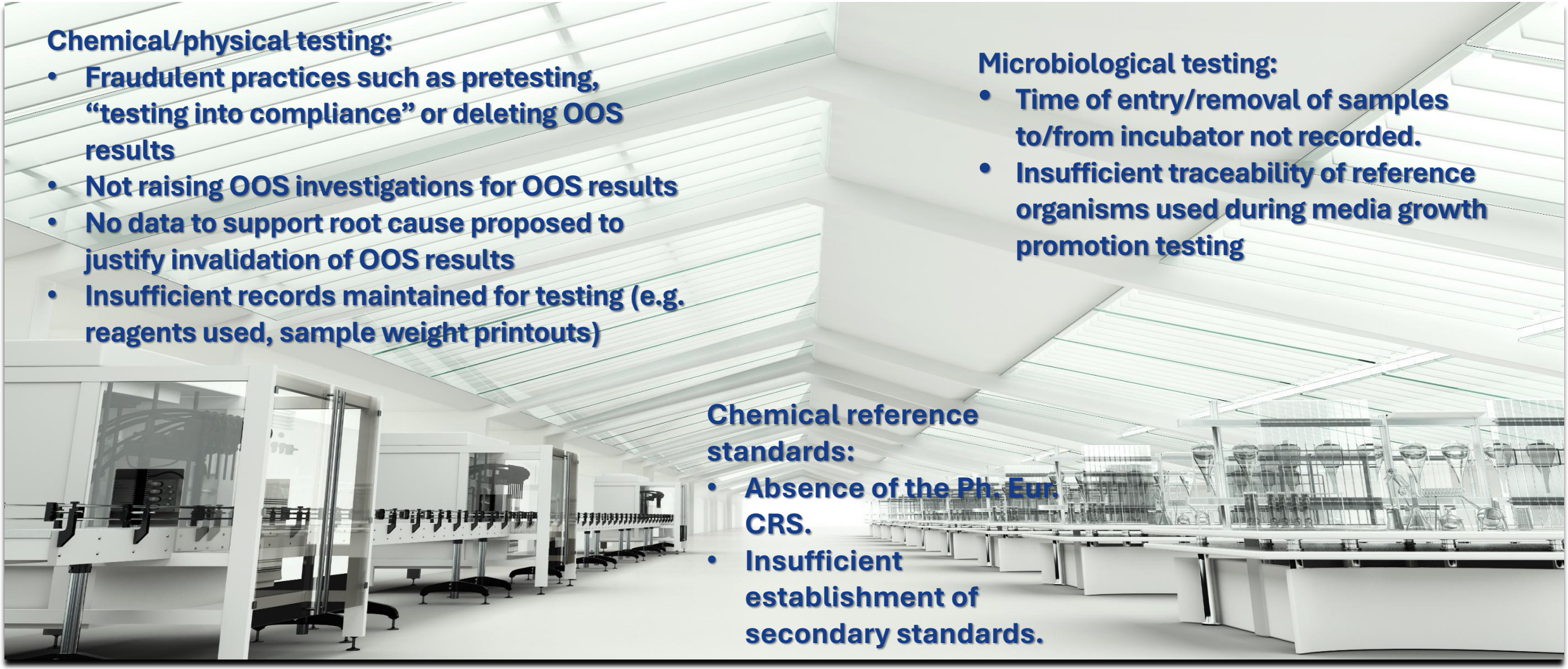
Production:

- 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 (e.g. solvent recovery)

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.

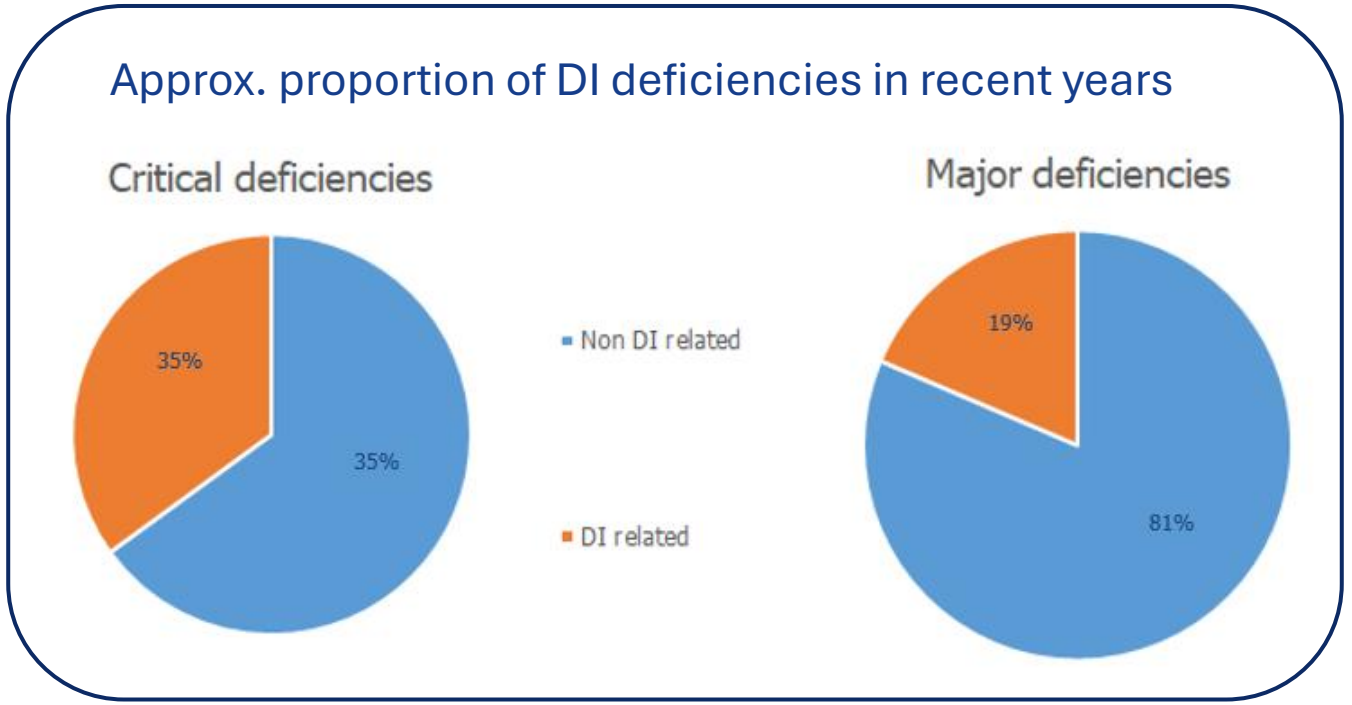
GMP violations: Computerised Systems (EU GMP Annex 11)

- Lack of appropriate user requirement specifications
- Outdated operating systems 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
- Absence of periodic review
- IT staff lacking (or without) knowledge of GMP requirements

Revision - https://health.ec.europa.eu/consultations/stakeholders-consultation-eudralex-volume-4-good-manufacturing-practice-guidelines-chapter-4-annex_en

GMP Violations: Data Integrity

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



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