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

edqm

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

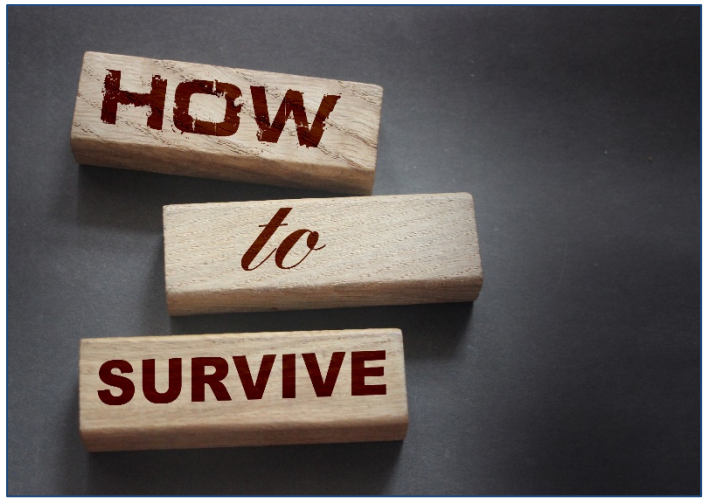
Module 8
The EDQM Inspection Programme

How to prepare for an Inspection
&
Most common GMP Deficiencies

Oisín DALY
GMP Inspector

Certification of Substances Department

Agenda



AVOIDING DEFICIENCIES

or

or

GETTING PREPARED?

?

BEFORE the inspection

*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

Pay Travel Expenses & Inspection Fees

Appoint skilled Interpreters (if needed)

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: Real-Time-Remote-Inspections (RTEMIS)

- Inspection of a site performed remotely by EDQM relying on technology (video meetings, document sharing, video streaming) to facilitate live interactions during the entire assessment period.
- Conduct of such an inspection strongly depends on the IT infrastructure and an appropriate data traffic from all areas
- Preparation includes:
  - Preparatory Teleconference to explain the approach
  - Connectivity test:
    - Verification of connection in areas to be inspected
    - Test of web conference tools
  - Document access prior to inspection:
    - Upload of core QA SOPs
    - Upload of API specific information

BEFORE: not over yet….

Some further points to be noted:

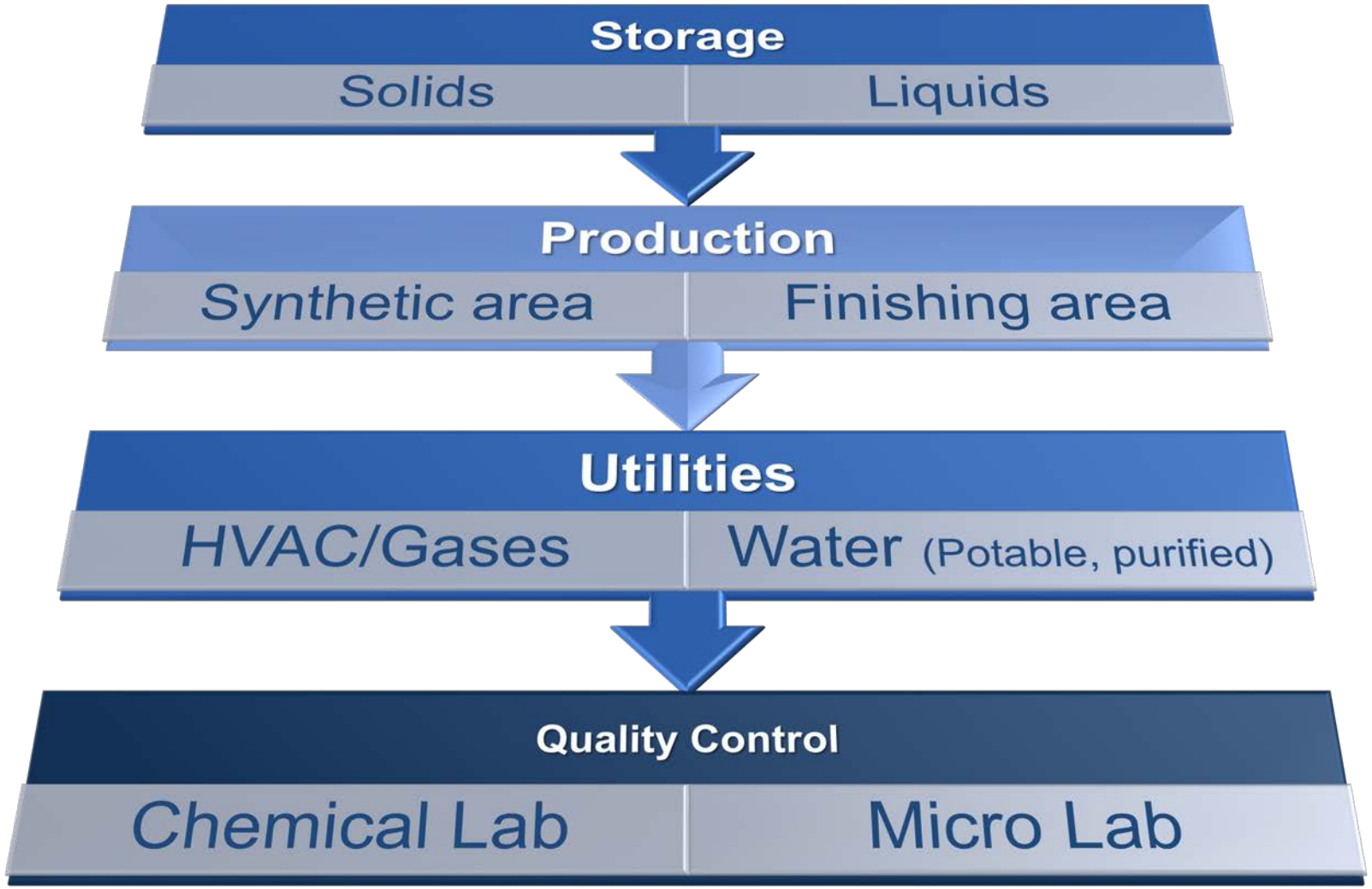
- EDQM informs the local Inspectorate about the dates and scope of the inspection
- EDQM welcomes the presence of local inspectors as observers
- An inspection schedule is sent to the company about one week before inspection starts

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:

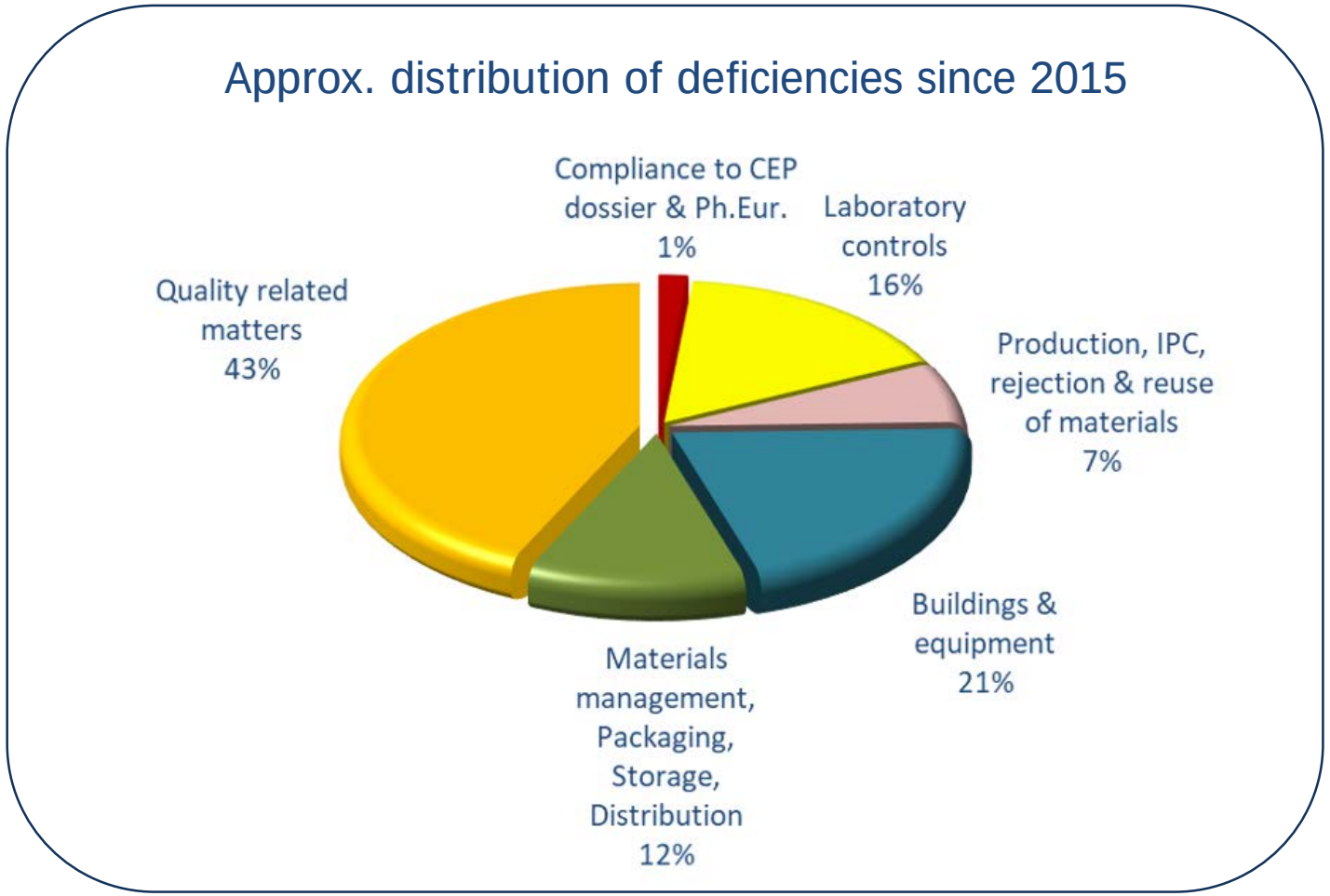
- Deviate from schedule and suggested directions
- Split during the plant tour
- Request access to any area of the site if they consider it related to the scope of the inspection
- Ask questions directly to staff members involved in manufacturing operations
- Use digital cameras as auxiliary means (unless 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

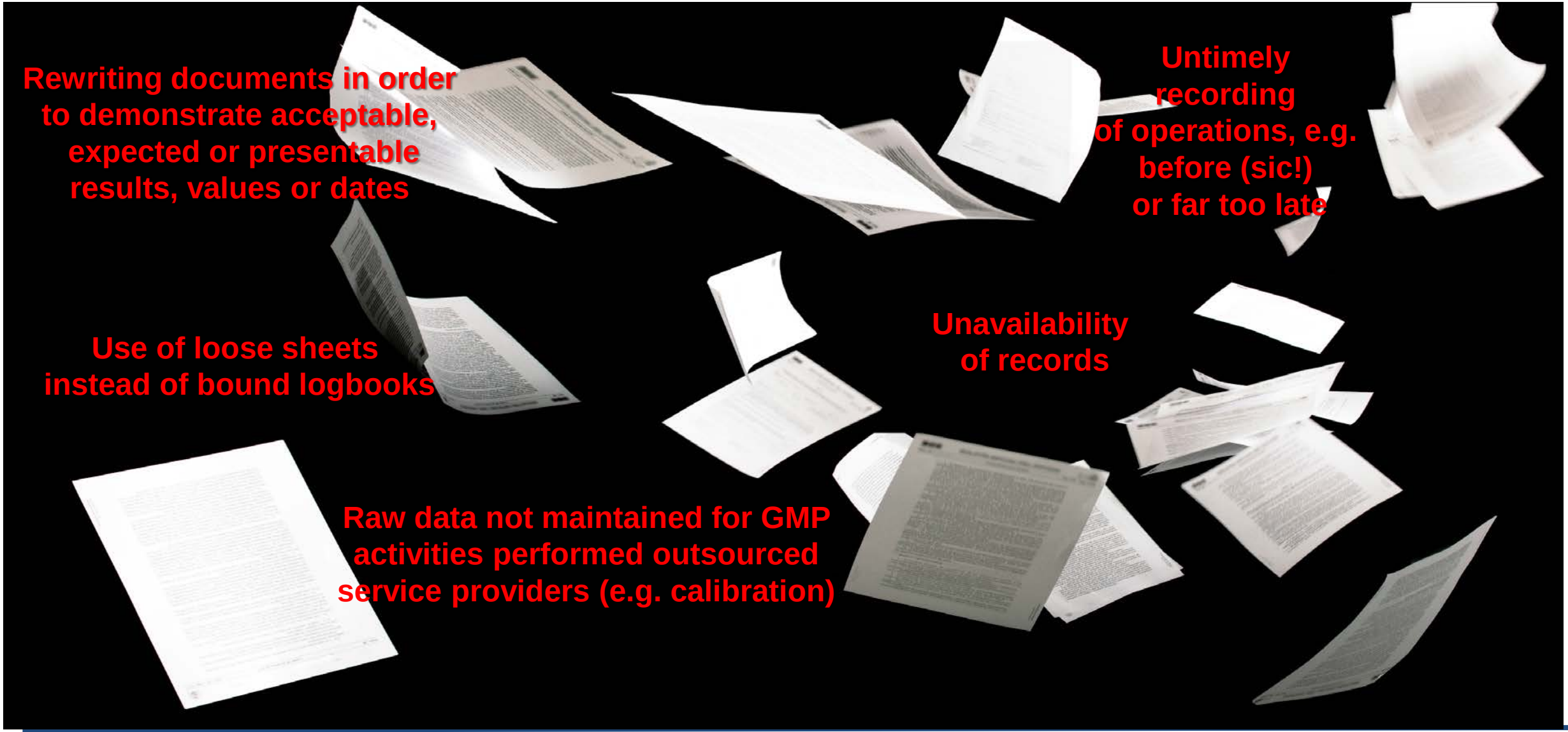
On-site inspections deficiencies



GMP violations: QMS & QA oversight

- Management of quality events (complaints, deviations, out-of-specification results, change controls):
  - Underreporting.
  - Insufficient investigation.
- Quality Risk Management principles not applied or inadequately implemented in areas such as production activities, deviations, change control, etc.
- Documentation control (both paper and electronic):
  - No control over issuance of records and forms used to record GMP activities.
  - Duplicate master copies of documents (“same revision”) found with different issuance dates.
- Insufficient oversight of quality unit over GMP activities (e.g. production and laboratory activities, equipment maintenance and cleanliness, outsourced activities).

GMP violations: Documentation



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.

GMP Violations: Other areas

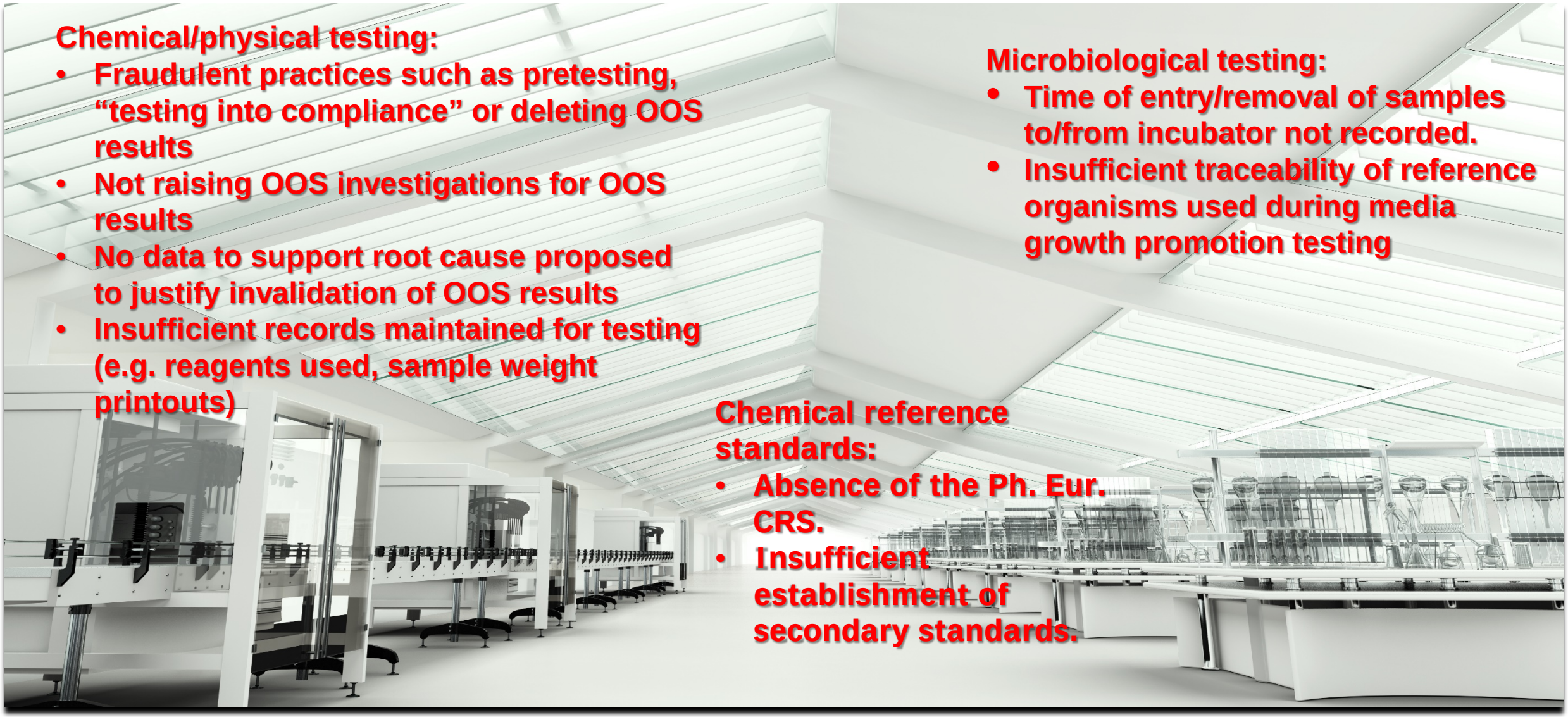
Production:

- 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 (e.g. sieve screens) 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

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

Insufficient knowledge of computer system validation requirements

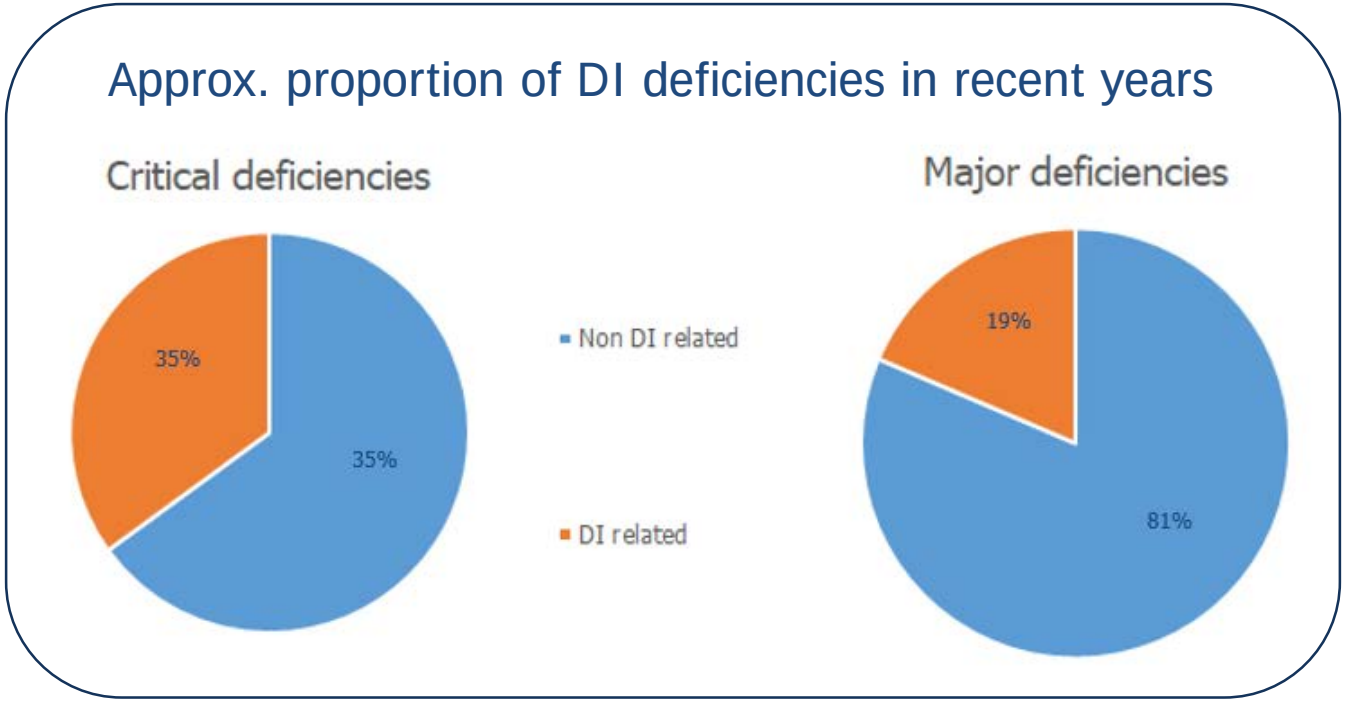
No or insufficient review of audit trail

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).



Acknowledgements

- Thomas Hecker, Inspector, EDQM
- Cristina Baccarelli, Inspector, EDQM
- Sotirios Paraschos, Inspector, EDQM

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**