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

The EDQM Inspection Programme

EDQM Training Webinars

13 December 2024

Oisín DALY
Certification of Substances Department, EDQM

Outline

- Background information
- EDQM inspection programme – who, what, where, when, & why
- A typical on-site inspection
- Inspection outcomes
- Other EDQM approaches to supervision of GMP compliance
  → Real time remote inspections (RTEMIS)
  → GMP assessment
- International collaboration
- Perspectives & final considerations

The CEP Procedure

- CEP = **C**ertificate of Suitability to the monographs of the **E**uropean **P**harmacopoeia

Three types of CEPs:

1. Chemical CEP
2. Herbal CEP

} To demonstrate that the quality of a substance is controlled by the Ph. Eur. monograph and additional tests if needed

3. TSE CEP → To demonstrate compliance with the Ph. Eur. general monograph on TSE

The CEP Procedure

- An international platform for the assessment of the quality of substances for pharmaceutical use (mainly APIs), with reference to monographs of the Ph. Eur.

- Benefits:
  - → Centralised assessment - saves time and resources
  - → Facilitates management of MAAs and variations
  - → Coordination and conduct of GMP inspections of API manufacturers
  - → Source of information to update Ph. Eur. monographs
  - → Open to any manufacturer of pharmaceutical substances regardless of geographical origin

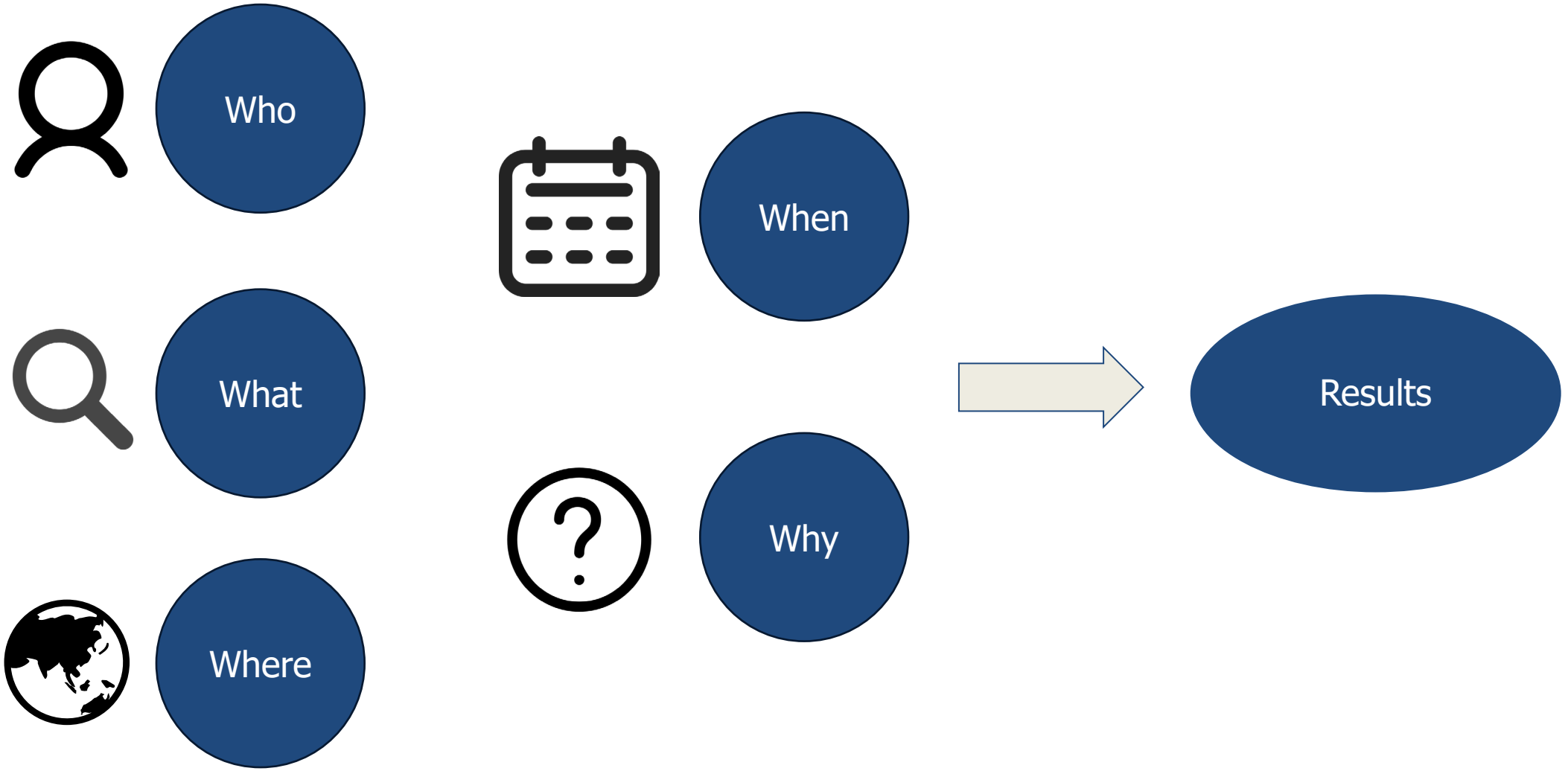
- Official implementation in 1994 with incorporation of inspection programme in 1999

EDQM Inspection programme

- Integral part of the Certification of Suitability (CEP) Procedure
- For manufacturing sites involved in CEP applications
- Inspections are performed in accordance with the European Compilation of Union Procedures
- EDQM website: https://www.edqm.eu/en/the-inspection-programme

EDQM Inspection programme

EDQM Inspection programme



Who

Team of **GMP** inspectors (usually 2)

EDQM Inspector

→ Currently 4 x GMP inspectors in EDQM
→ In charge for organisation, conduct and follow-up of inspections

European NCA inspector

→ Current qualified GMP inspectors from EEA NCAs & Swissmedic
→ Volunteer to join EDQM inspections
→ In charge for communicating EU GMP compliance information

MRA NCA Inspector?

→ Not very frequent
→ Mostly participating during joint inspections for sites of common interest

What

Compliance with EU GMP guidelines

→ EU GMP Part II / ICH Q7
→ EU GMP annexes as applicable (e.g. annex 1 for sterile APIs, annex 7 for herbal substances etc.)

Compliance with CEP dossier

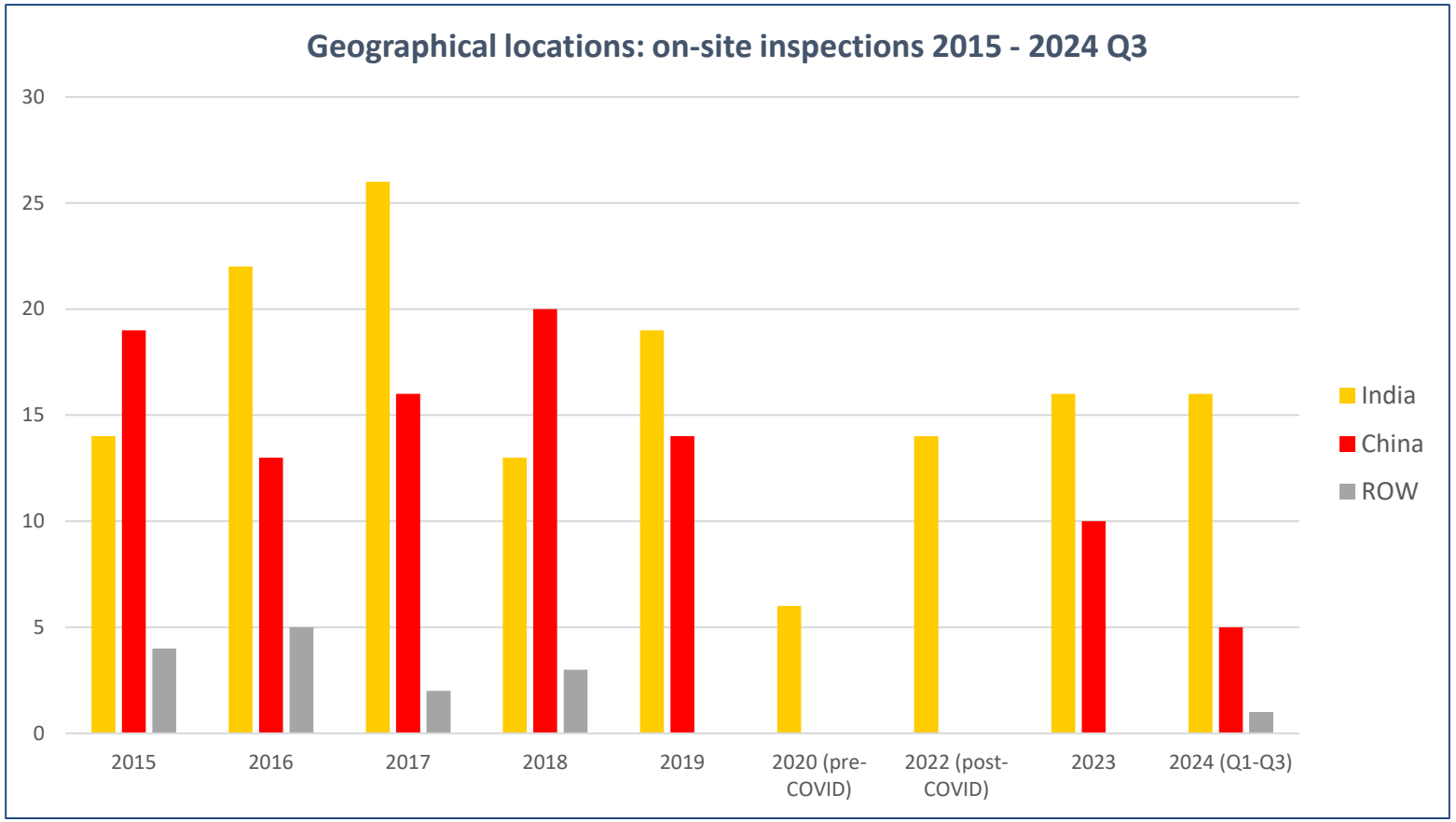
→ 3.2.S.2.2 Description of manufacturing process & process controls
→ 3.2.S.4.1 Specifications
→ 3.2.S.4.2 Analytical Procedures

Compliance with Ph. Eur. monographs

→ Pharmacopeial test methods
→ General Ph. Eur. monographs (e.g. purified water)

Where

- ~ 94% of on-site inspections since 2015 conducted in India & China
- No inspections in EEA & mutual recognition agreement countries



When

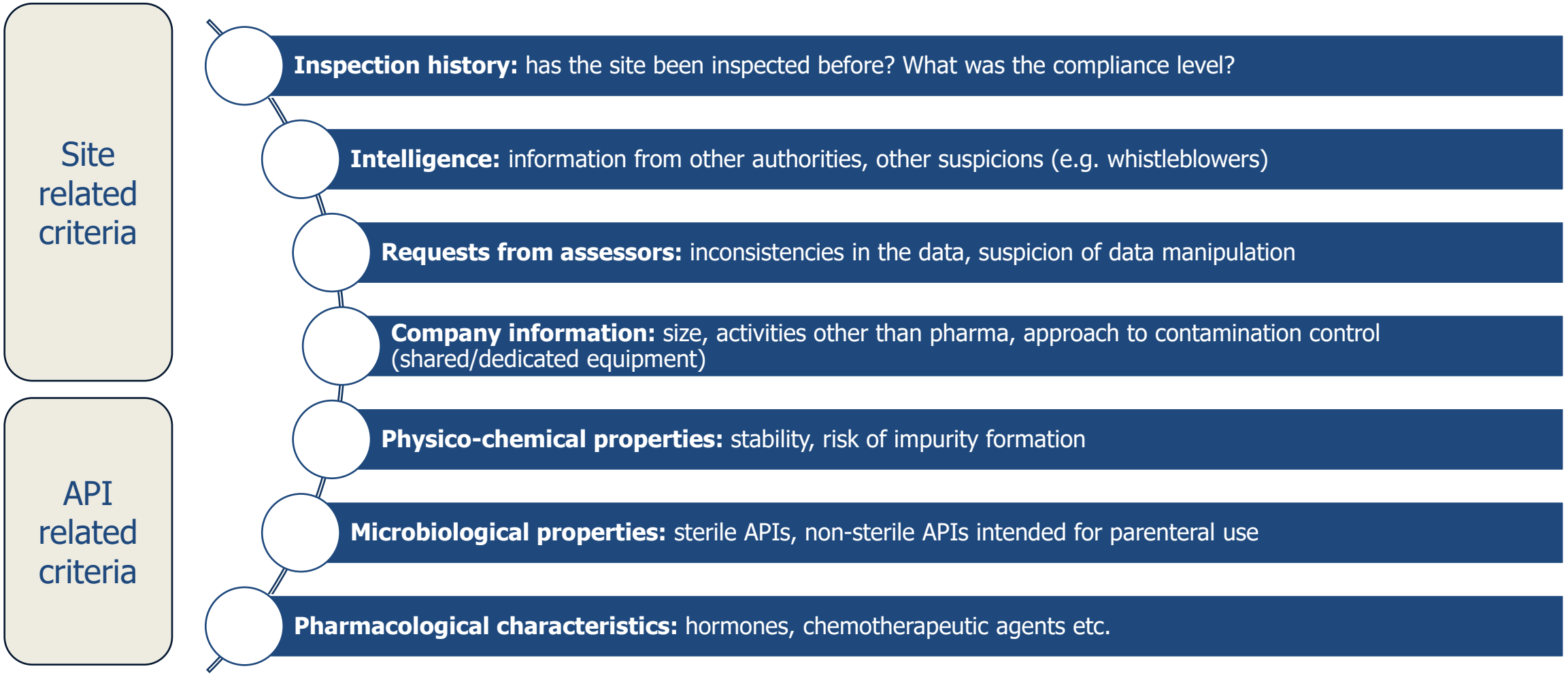
- Approximately 40 on-site inspections per year

- Annual inspection programme prepared
  → risk-based approach to site selection

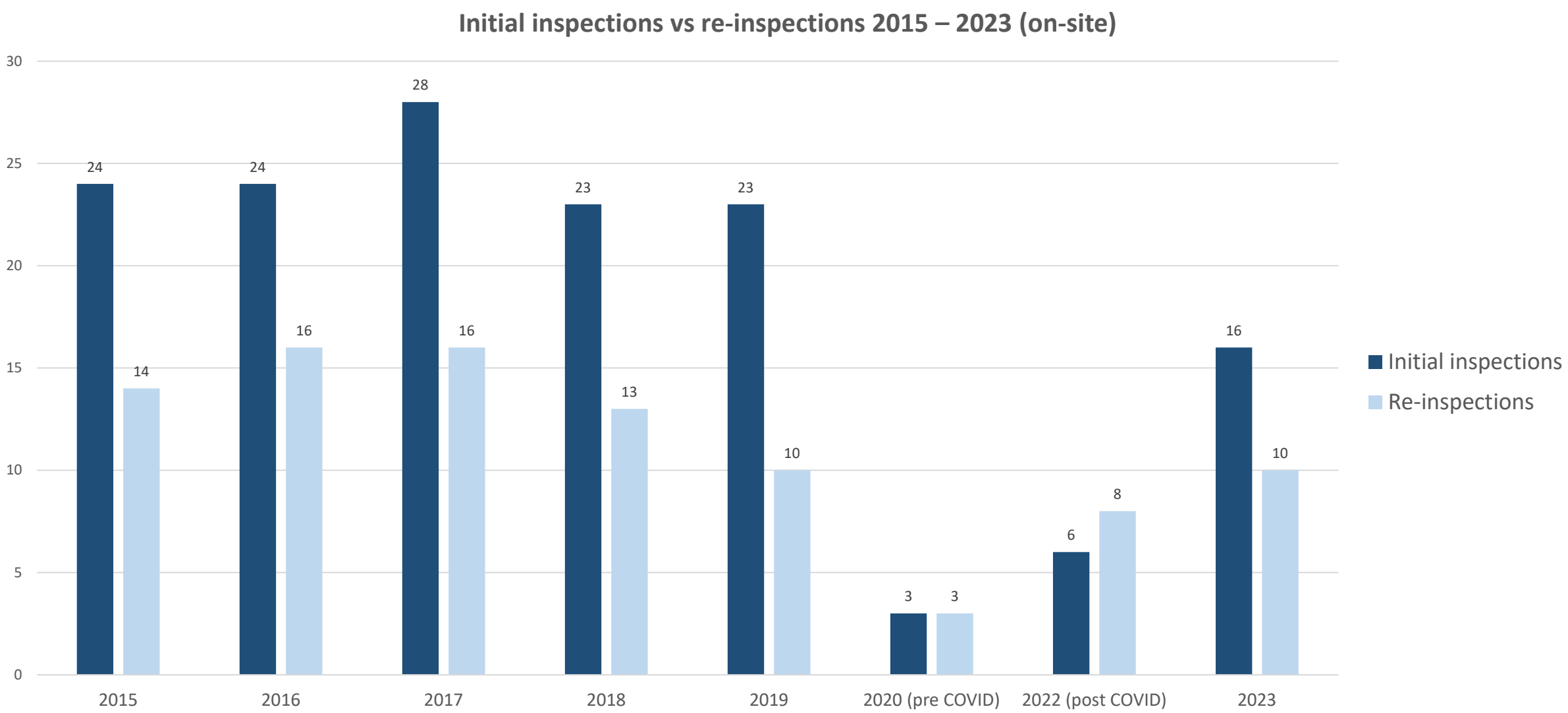
- Lifecycle management of sites
  → driven by Site Status Review (SSR) process
  → periodic review of site information & consideration for inclusion in inspection programme
  → site related risks & API related risks considered

When

- Risk based approach – examples of factors which may be considered:



When



Why

Protection of public health

→ Approx. 12% of EDQM inspections in 2023 & H1 2024 resulted in a non-compliant outcome

→ An increased oversight of 3rd country sites leads to:

- ✓ Better understanding and implementation of EU GMP requirements
- ✓ Manufacture of products of adequate quality
- ✓ Decrease in regulatory actions needed to protect patients

EU legislation

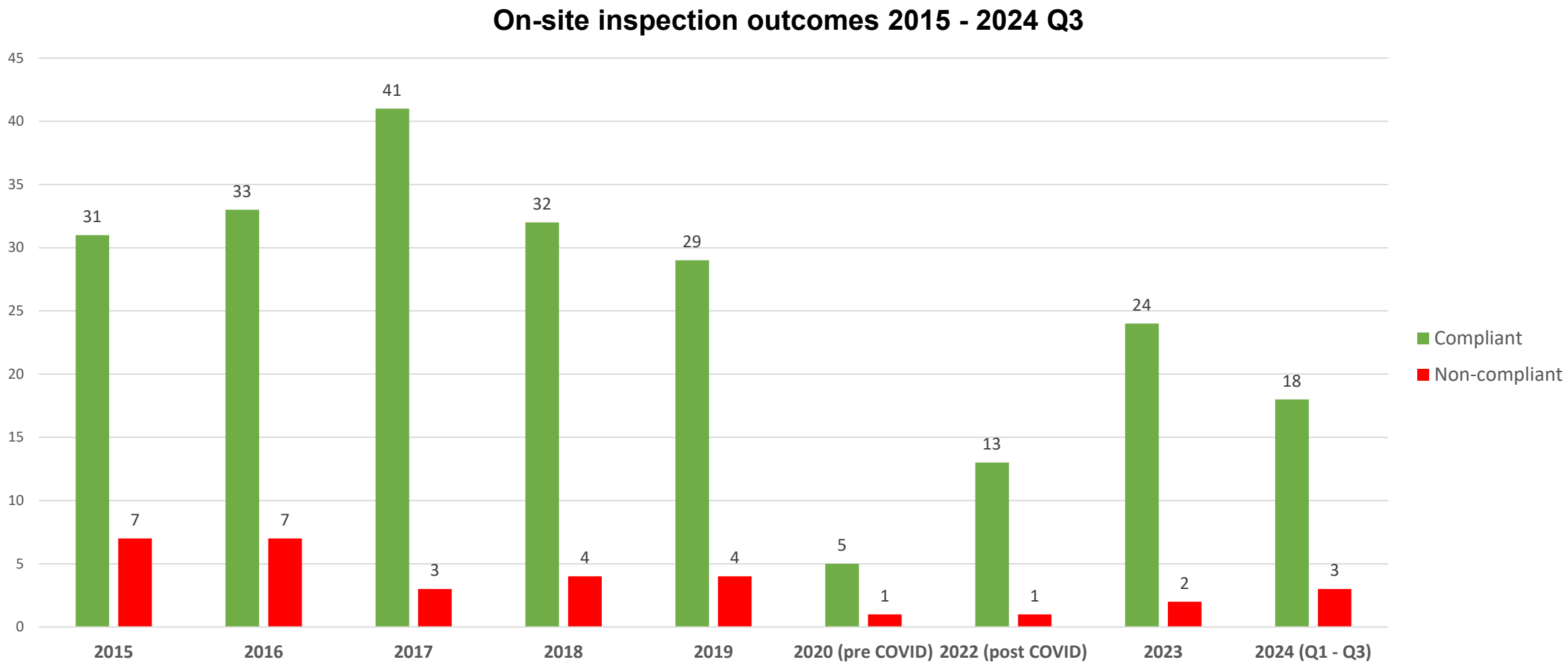
→ As per Regulation (EU) 2019/6 and Directive 2001/83/EC as amended, EDQM was given a mandate by the European Commission to establish an annual programme for inspections

Integral part of CEP procedure

→ Inspections are not mandatory (in line with EU legislation)

→ But manufacturing sites must provide a declaration for their willingness to be inspected as part of the CEP application

Results



A typical inspection

- Two inspectors
- 3-day duration (usually):
  → One API within scope
  → Non-sterile, standard process
- Duration extended if:
  → the substance is sterile (normally 5 days)
  → the process is complex
  → the scope is extended (specific issues to examine e.g. nitrosamines, or if more APIs are to be checked)
- Local authorities informed and invited to participate as observers

Pre-inspection correspondence

Site status review (SSR)

→ relevant to all manufacturing sites listed in CEPs
→ information gathering for input into risk assessment
→ used for preparation of EDQM inspection programme and inspection reliance activities
→ periodic re-evaluation

Pre-inspection data (PID)

→ site under consideration for inspection
→ final information gathering exercise
→ inspection may/may not be performed

Official inspection notification

→ decision made to perform inspection of site
→ dates of inspection, names of inspectors, and API within scope officially communicated
→ normally 6 – 10 weeks' notice

Inspection agenda - example

Day 1

→ Opening meeting

→ Documents/quality system review:
- ✓ Deviation management
- ✓ Change control
- ✓ Complaints & recalls
- ✓ Laboratory investigations
- ✓ Etc..

→ Site tour:
- ✓ Company overview of manufacturing process
- ✓ Inspection of manufacturing areas

Day 2

→ Site tour:
- ✓ Warehouse areas
- ✓ Outdoor & solvent storage areas
- ✓ QC laboratories

→ Documents/quality system review
- ✓ Process validation
- ✓ Cleaning validation
- ✓ Equipment qualification
- ✓ Supplier management
- ✓ Batch release
- ✓ Reprocessing/rework
- ✓ Maintenance & calibration
- ✓ Personnel
- ✓ Etc..

Day 3

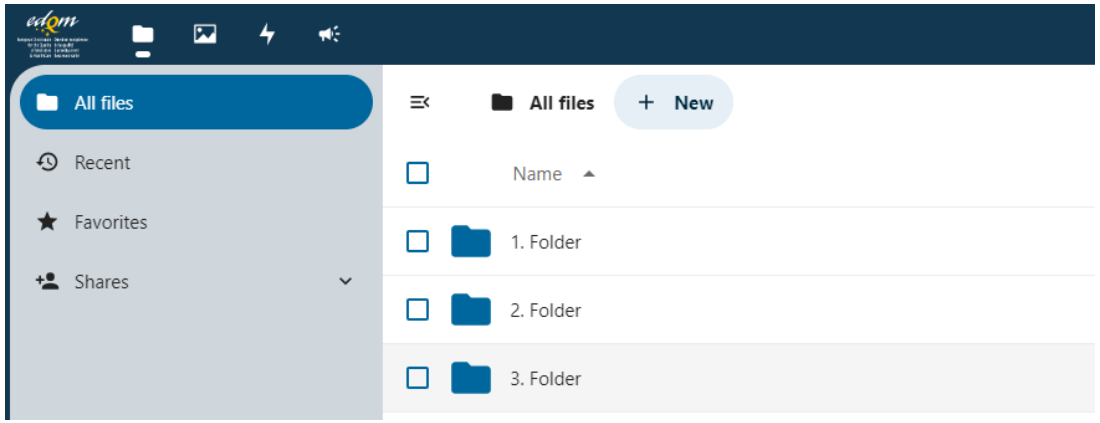
→ Quality system topics
- ✓ Batch record review
- ✓ Documentation management
- ✓ Quality risk management
- ✓ Outsourced activities
- ✓ Self-inspection
- ✓ Check of compliance with CEP dossier & Ph. Eur.
- ✓ Etc..

→ Site tour:
- ✓ Utilities (e.g. purified water, HVAC)
- ✓ Solvent recovery premises

→ Closing meeting

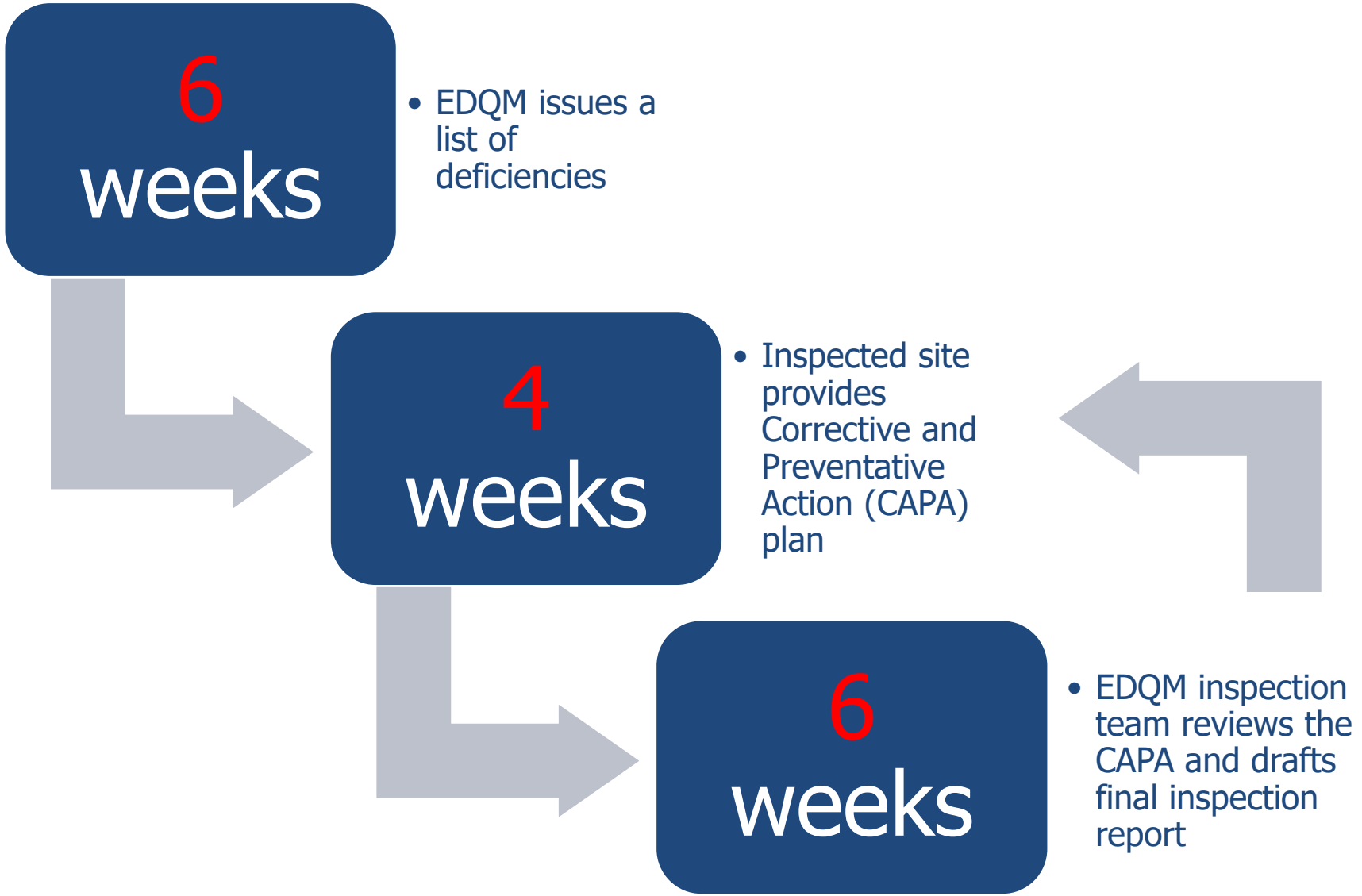
Document sharing

- EDQM Active Collaboration Tool (ACT)
  - → Inspected company is granted access to a defined folder structure for upload of documents before and during the inspection
  - → Data stored on a secure EDQM server (located on-site in Strasbourg)

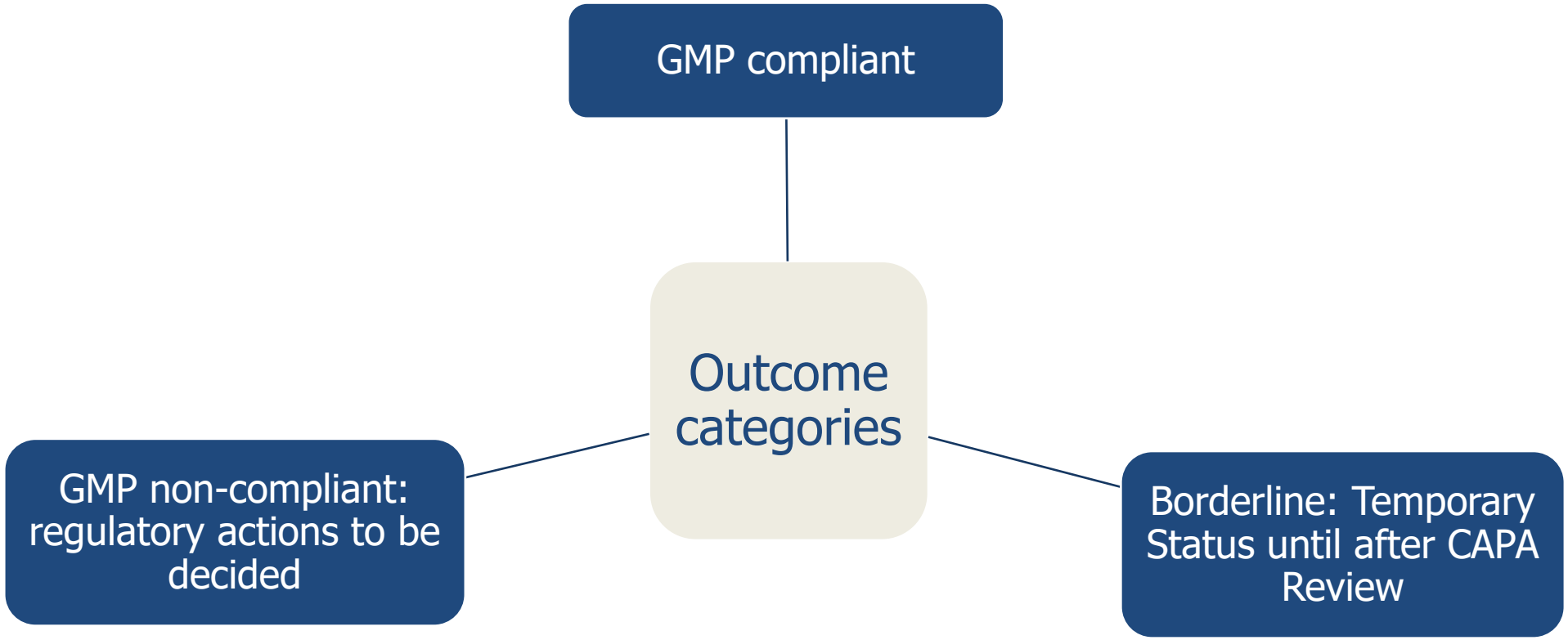


- Common European Submission Platform (CESP) also used for submission of certain documents (e.g. CAPA post inspection)

After the inspection



Inspection outcomes



Inspection outcomes

Compliant

After satisfactory evaluation of CAPA and if any expected application for CEP revision has been submitted:

→ Final inspection report issued

→ EDQM Attestation of Inspection provided which states compliance with GMP & the CEP dossier within scope

→ GMP Certificate issued by the participating European inspectorate and published on the EUDRA GMDP database

Non-compliant

Risk to public health:

→ The CEP holder and manufacturer are notified and given a possibility of hearing within 14 days

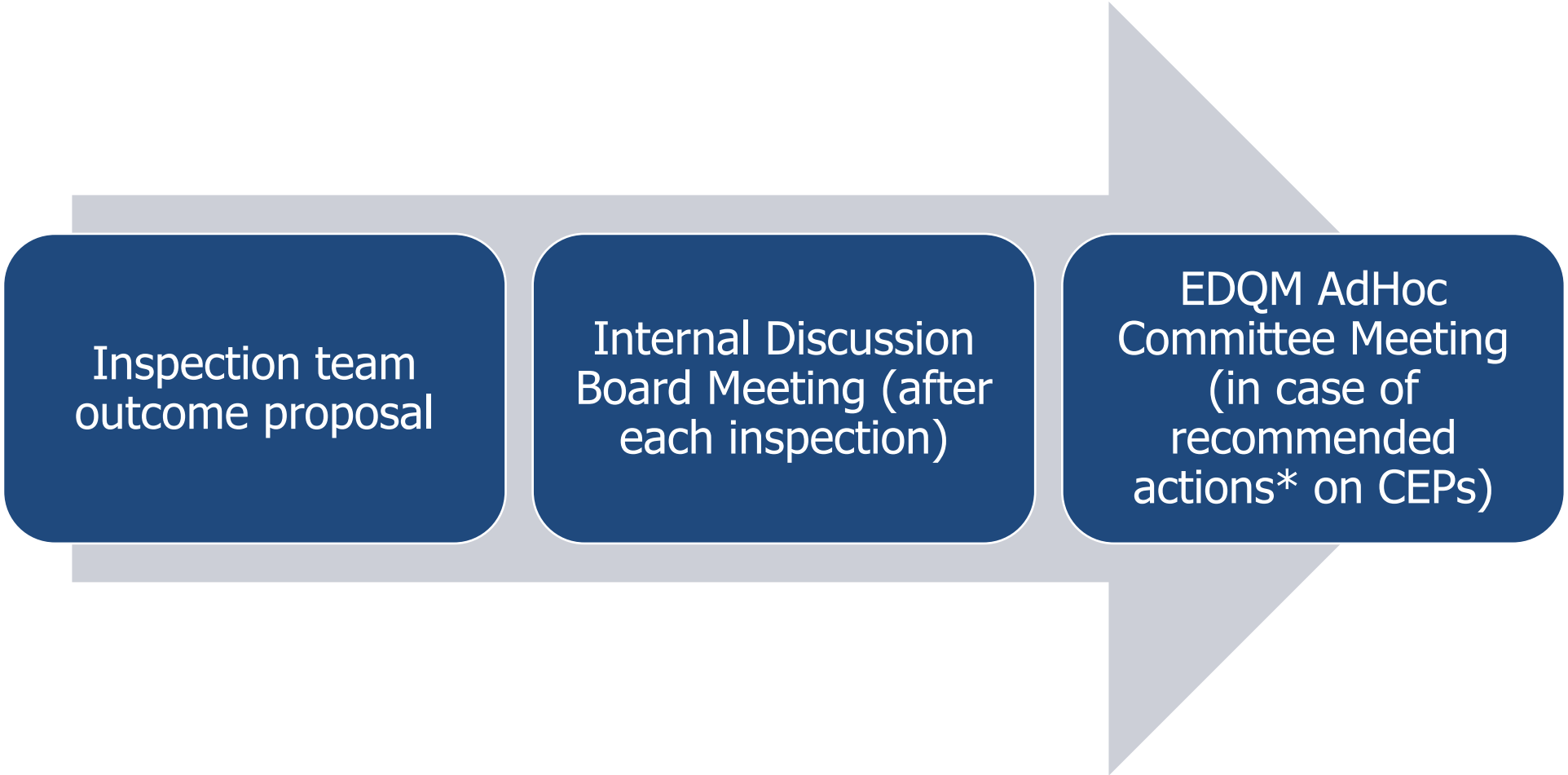
→ all relevant CEP(s) of the site may be suspended or withdrawn

→ if more than one manufacturer is listed on the CEP, the non-compliant manufacturer may be removed

→ On-going CEP application(s) may be closed

→ A Non-Compliance Report is issued by the participating European inspectorate and published on the EUDRA GMDP database

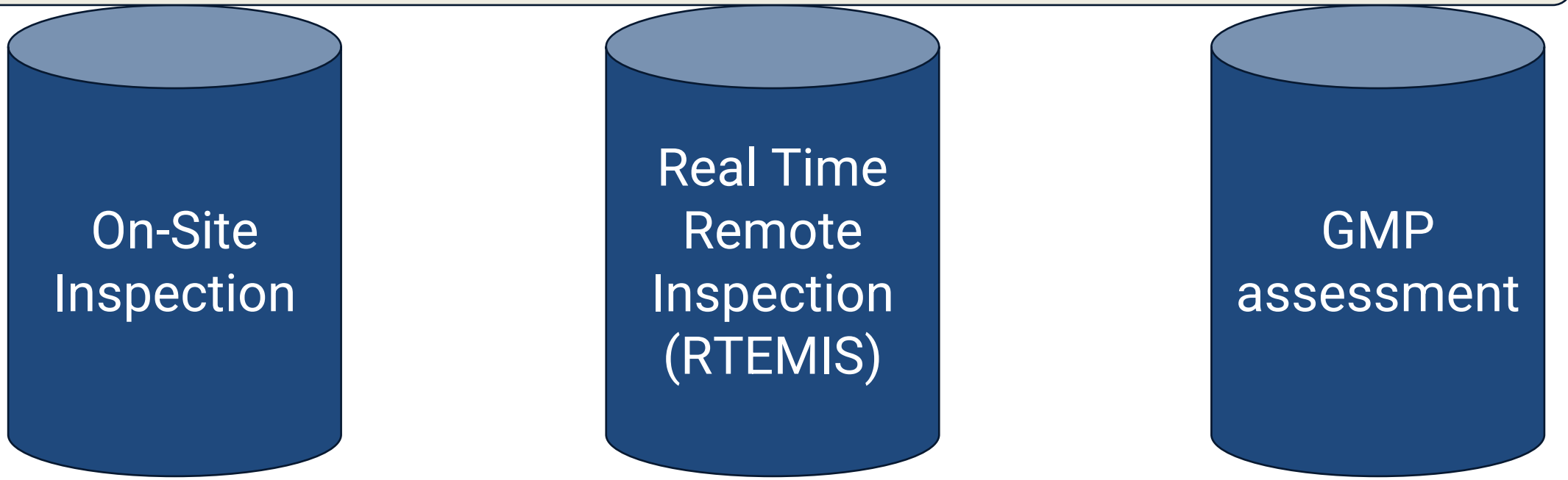
EDQM Decision Making Process



*) e.g. CEP suspension(s), withdrawal(s), removal of site(s) concerned, closure of application(s)
→ Further information available in the policy document on *suspension or withdrawal of a certificate of suitability, closure of an application* on the EDQM website

EDQM supervision of manufacturing sites

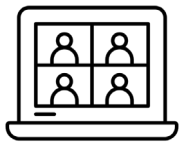
Three pillars for the supervision of the GMP compliance of pharmaceutical manufacturers



RTEMIS

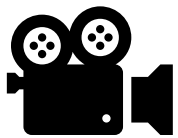
- Process of on-site inspection replicated virtually insofar as possible using:

Document scanners & sharing platform (ACT)



Web conference meeting applications

Wi-Fi & mobile data



Cameras

→ Opening meeting

→ Real time visit of manufacturing areas & site facilities

→ Real time document review & discussion with subject matter experts

→ Closing meeting

→ Connected with firm for the entire inspection

→ Time zone difference
- days can be shorter (6-7 hours/day)
- duration normally extended (5-6 days)

RTEMIS

Advantages

Possibility to evaluate the GMP compliance of a company when an on-site inspection cannot be performed or is deemed of lower priority/risk

Allows real time visual interaction with the company concerned

Saves financial resources (both for EDQM and the company)

No travel: reduces carbon footprint, beneficial for environment

Limitations/challenges

Not all inspection techniques can be utilised remotely:

→ Element of surprise and body language interpretation
→ Periphery activities
→ Staff conversations
→ Sense of smell (risks in manufacturing areas)

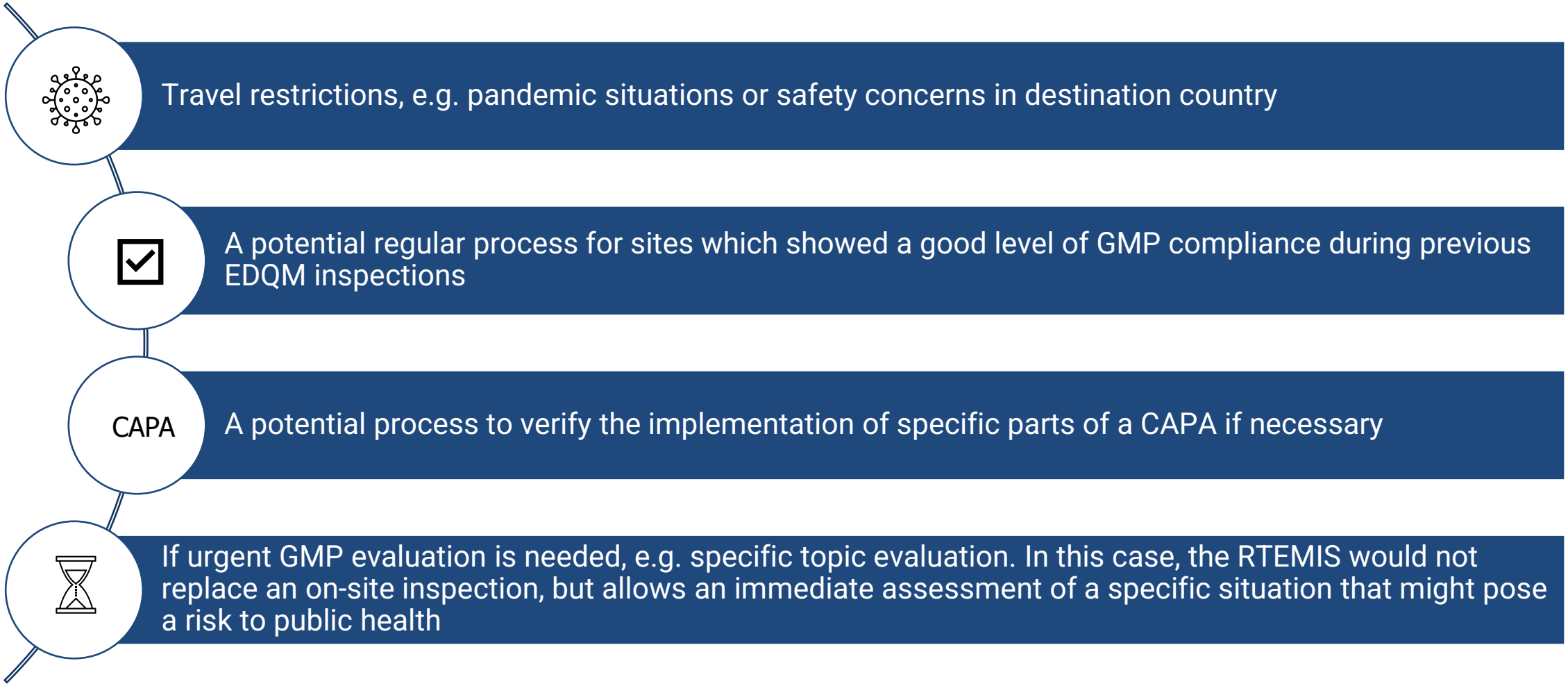
Generally takes longer

Sometimes technical difficulties

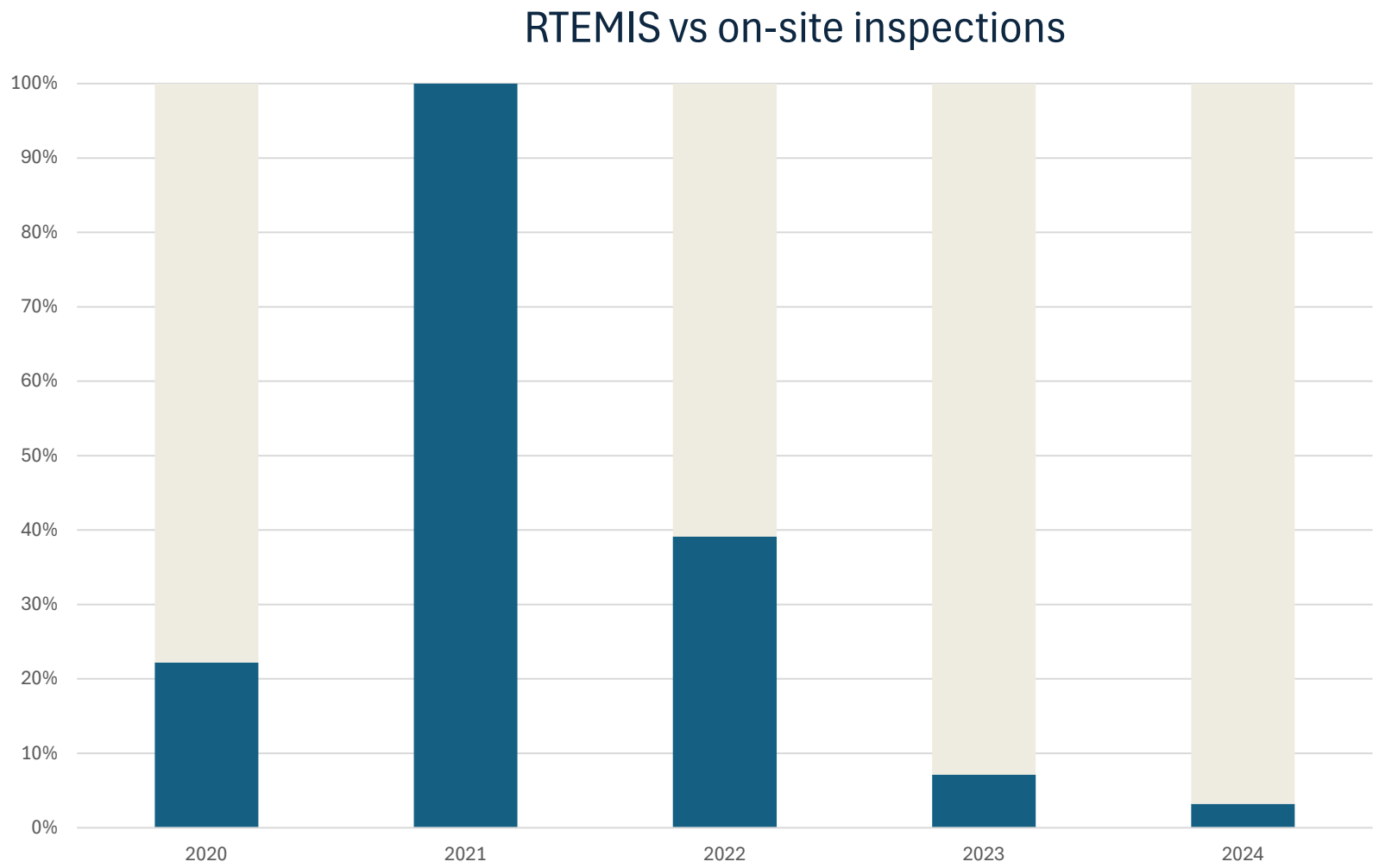
Time differences & translation requirements

RTEMIS

- When RTEMIS could be used:



RTEMIS statistics



→ Aug 2022: on-site inspections resumed in India

→ Aug 2023: on-site inspections resumed in China

on-site

RTEMIS

GMP Assessment

- Up and running since 2010
- Programme for **recognition** & **reliance** on inspections performed by EEA/Swiss authorities and other trusted partners
- Desktop/paper-based assessment
- Optimisation of inspection resources & reduction in duplication of inspections for manufacturing sites

Recognition/Reliance of Inspections

Source: EEA/Swiss inspections

- No API inspections on EEA/Swiss territory
- Use of GMP Certificates for API sites involved in CEP scheme
- Direct recognition possible in most of the cases
- Use of Statement of GMP Non-Compliance for API sites involved in CEP scheme

Source: Inspection Reports

- Documentation based assessment
- Evaluation of inspection reports from Trusted Authorities* (e.g. PIC/S)
- Comparison of scope, duration, extent
- Result: accept outcome and include in re-inspection framework

* high degree of similarity between EU and the authority's inspection procedures and GMP standards (currently equivalent inspections can be considered in connection with an MRA, AACA and PIC/S).

International collaboration

more info here

Objectives:

- ✓ Optimise use of inspection resources worldwide
- ✓ Foster greater international collaboration and information sharing
- ✓ Increase inspectional oversight and reduce duplication to allow more sites to be monitored
- ✓ Build on equivalent GMP standards and mutual confidence

Monthly meetings:

- ✓ To share and coordinate planned inspections
- ✓ To share information on inspection outcomes

International collaboration

- GMDP Inspector Working Group (EMA)
- PIC/S Committee of officials
- Working groups for elaboration & revision of GMP guidelines and documents
  → PIC/S, EMA & ICH
- Confidentiality agreements
  → sharing of inspection reports

Final considerations

- Impact of inspection programmes:

  → Increased inspectional oversight of API manufacturers during the last decade has led to higher level of GMP compliance and less regulatory actions

  → Increased understanding and implementation of EU GMP regulations

  → Lower level of discrepancies to the CEP dossiers inspected, which demonstrates the increased efforts of companies to comply with their commitments and the conditions under which their CEPs were granted

- Finished products manufacturers should still improve their ability to select GMP compliant API suppliers and audit/monitor them accordingly

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**