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

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

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The EDQM Inspection Programme

EDQM TRAINING WEBINARS
7 JULY 2023

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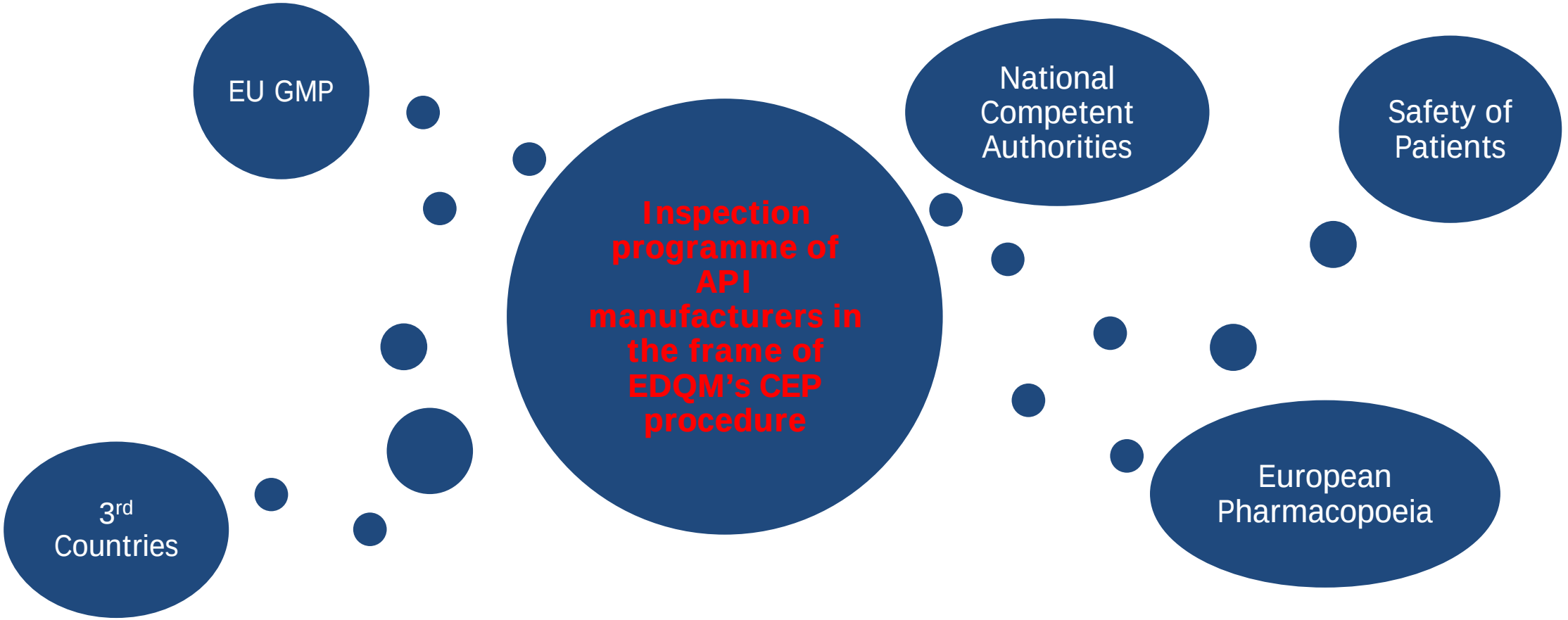
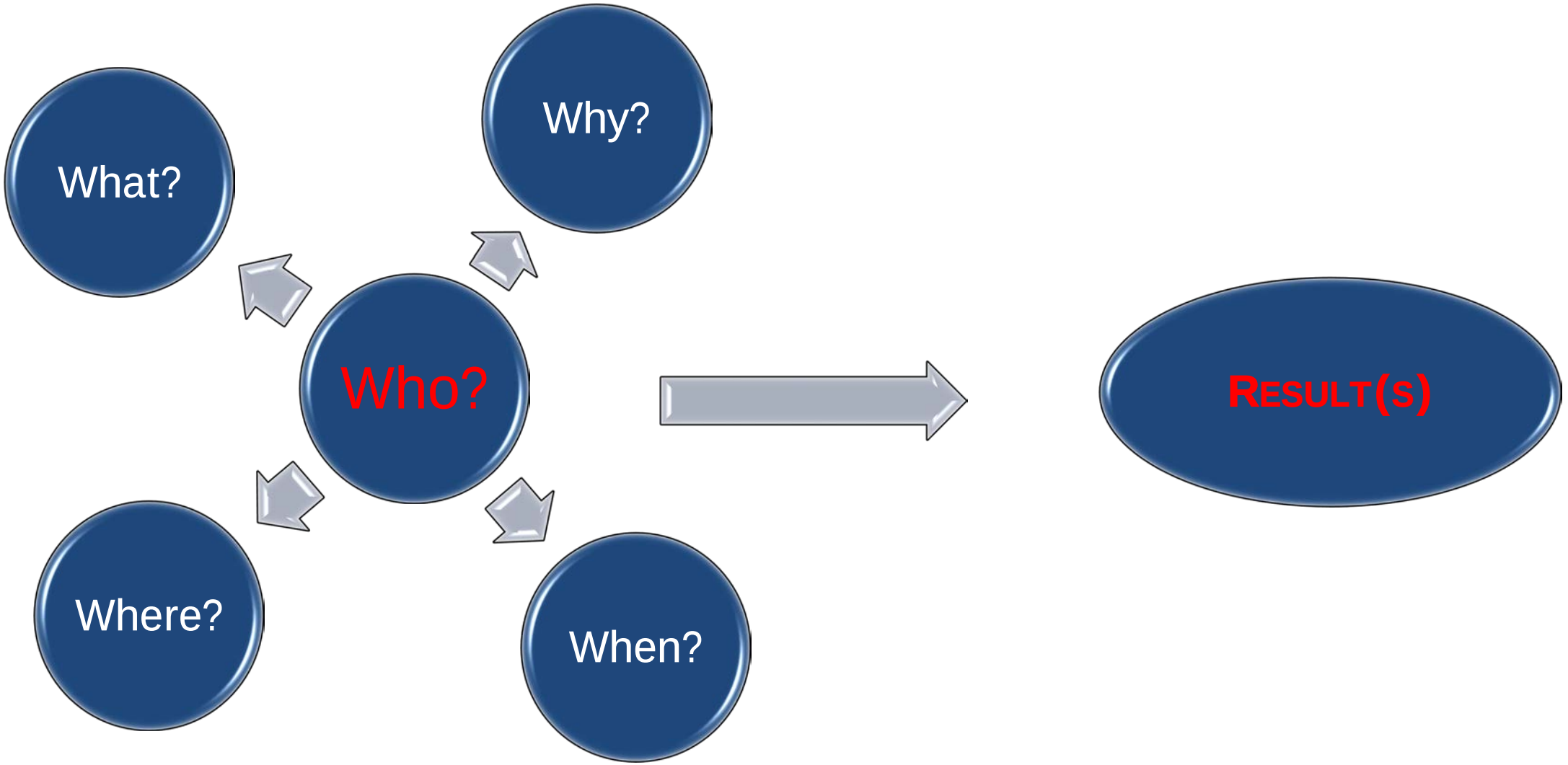
Certification of Substances Department, EDQM



Who is doing *What*, *Why*, *Where* and *When*?



Who: team of GMP inspectors (usually 2)

EDQM Inspectors
- As of now four GMP inspectors in Certification Department
- In charge for organisation, conduct and follow-up of inspections

EEA Inspectors
- Volunteers from EEA NCAs
- Qualified GMP Inspectors that are included in EDQM's system of supervision of API manufacturers during the inspection(s)
- In charge for communicating EU GMP compliance information

Inspectors from MRA NCAs
- Not very frequent
- Mostly participating during joint inspections of sites with common interest

What

Scope: GMP Inspections of manufacturers of Active Pharmaceutical Ingredients (API) covered by CEP applications

AIM
To check:

- Compliance with CEP dossier
- Compliance with EU GMP Part II and Annexes as applicable
- Compliance with the monographs of European Pharmacopoeia

Why (1)

Protection of Public Health

Integral part of the Certification Procedure, but not mandatory (in line with EU legislation)

In application of EU Directives 2001/82/EC and 2001/83/EC on Compilation of Community Procedures as amended, EDQM was given a mandate by the European Commission to establish an annual programme for inspections

- Performed in accordance with the EU guidance published by European Commission: Compilation of Union Procedures
- Selection of sites eligible to be inspected by EDQM takes place according to a risk-based approach

Why (2)

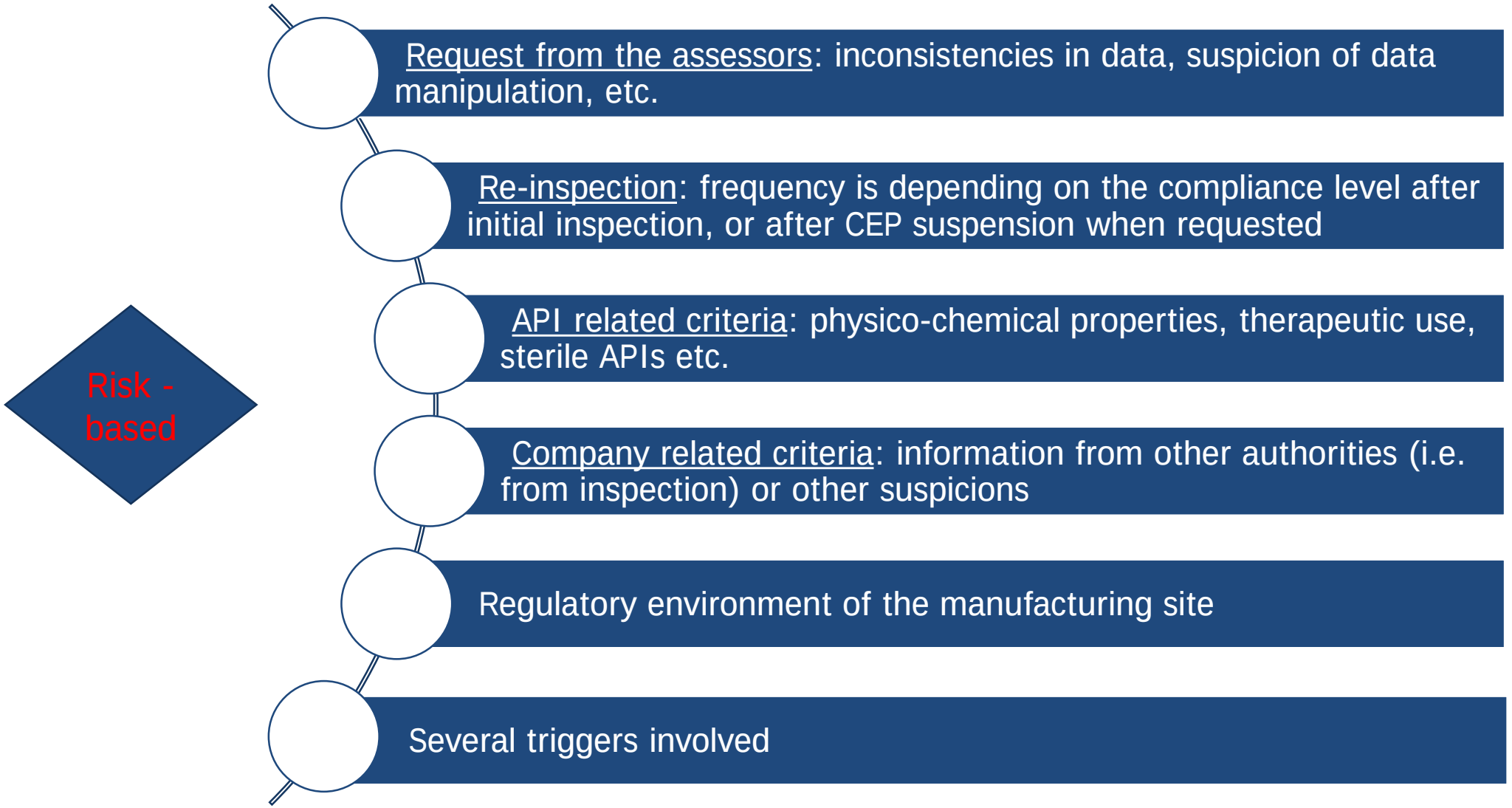
An increased oversight of 3rd country sites leads to:

- Better understanding and implementation of EU GMP requirements
- Manufacture of products of adequate quality
- Decrease in the number of regulatory actions needed to protect patients, such as:

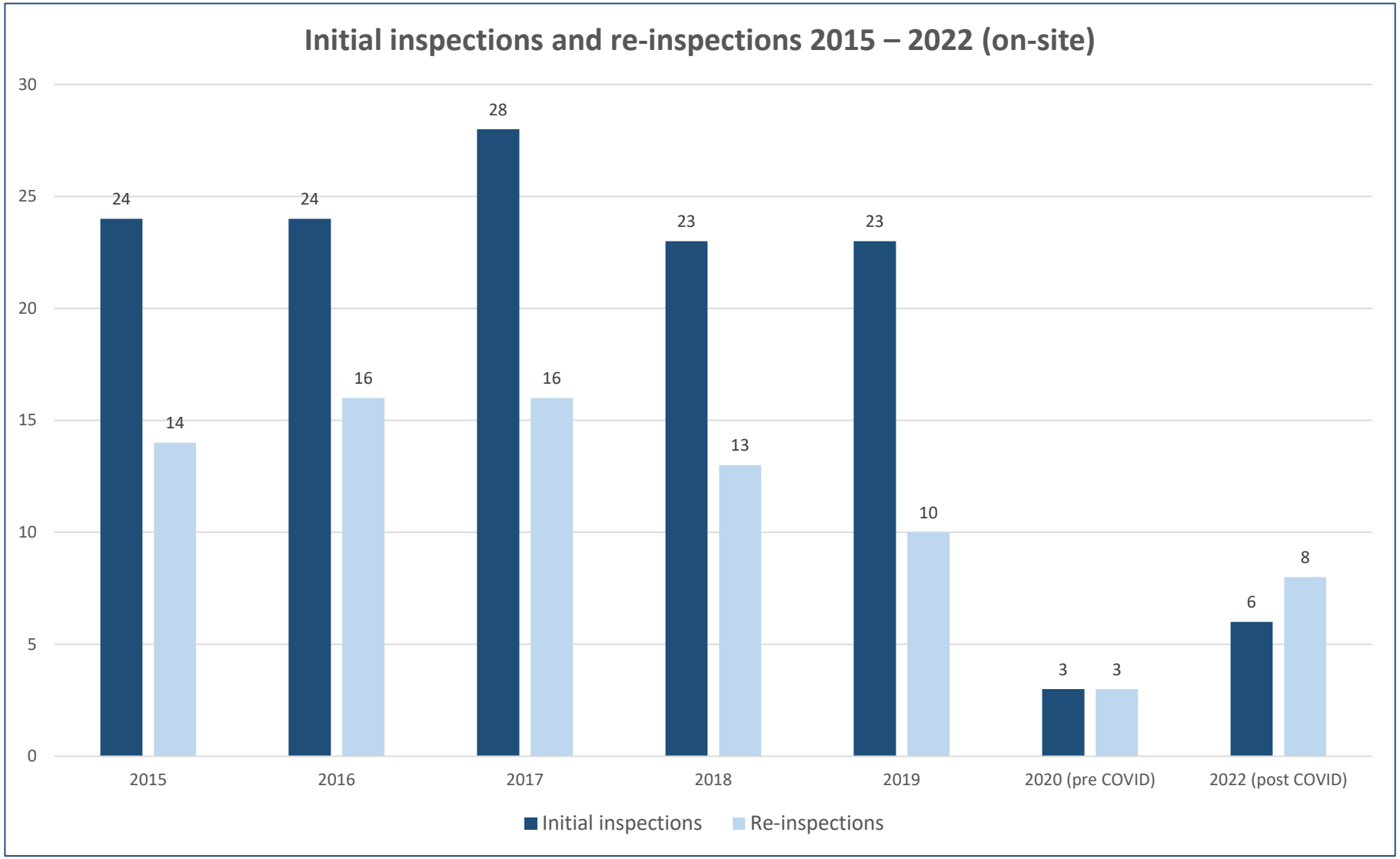
Nature of non-compliance : During the joint Swissmedic / EDQM inspection 1 critical, 7 major and 11 other deficiencies were identified. The critical deficiency is related to an insufficient QA oversight leading to a situation that constitutes a potential risk of producing products which could be harmful to the patient. The firm's approach on materials management, including the labelling, traceability, storage conditions, dispensing, cleaning, pest control of raw materials, intermediates, solvents and recovered solvents was considered as not in compliance with EU GMP. The company failed in multipurpose facility/ies to mitigate the risks of cross-contamination and was not aware of the necessary measures to be taken before introducing a new chemical entity in the sampling, dispensing and synthesis area. A lack of effective maintenance and/or cleaning resulting in rust and dirt in hardly cleanable premises in the distillation plant, manufacturing Unit 3A and 3B and in the drum and storage area were obvious. The recovery of solvents in the distillation plant was not properly managed and documented. Shortcomings were observed with regard to the process validation activities related to Dihydrotachysterol. No cleaning validation was performed in the multipurpose intermediate manufacturing Unit 3C despite highly active material (Progesteron) was handled. The identified critical and major deviations pose a risk for all manufactured intermediates and APIs in the multipurpose plant except for manufacturing Unit 9 (see section 3 Additional Comments).
Action taken/proposed by the NCA : **Suspension of the marketing authorisation(s)** This manufacturer should not be authorised in any new/ongoing marketing authorization or variation application. The submission of a variation application for introducing alternative manufacturers of the active ingredient is recommended. **Recall of batches already released** (Separate Rapid Alert to follow) The decision to be made by NCA, following an assessment between the NCA and MAH, whether to recall a batch of a particular product or not should be based on a risk assessment and on the criticality of the product. **Prohibition of supply** After issuance of the non-compliance report and as long as it remains active, prohibition of supply of APIs (except APIs manufactured in Unit 9 – see below) is recommended, unless there are no alternative suppliers and there is a risk of shortage. Several critical products will be concerned. Therefore, while qualifying alternative APIs suppliers for critical products, the MAH(s) are requested to perform risk assessments in order to establish measures – agreed by their NCA - to mitigate risks associated with the GMP deficiencies observed (e.g. full specification testing etc.). **Suspension or voiding of CEP (action to be taken by EDQM)** Suspension or withdrawal of CEPs is recommended.
Additional comments : Withdrawal of the GMP certificate # 16MPP065HPT01, issued by the French authority, is recommended. The GMP non-compliance applies to all APIs, but it is not possible to express an opinion on the applicability of the deficiencies observed with regard to the product(s) manufactured in Unit 9. This unit, dedicated to the manufacture of highly potent APIs, was segregated from other manufacturing units/areas with for instance dedicated storage and quality control facilities, and was not subject of the inspection. It is not possible to express an opinion on the applicability of the deficiencies observed with regard to products manufactured in Unit 10. This unit produces medicinal products, which are subject to different GMP requirements than those applied for APIs, thus the facility was out of the scope of the present inspection. Dishman Pharmaceuticals & Chemicals Limited and Carbogen Amcis (India) Limited were subject to a merger. The new name is Dishman Carbogen Amcis Limited and Survey No. 48 was added to the address.

Source: EudraGMDP data base http://eudragmdp.ema.europa.eu/inspections/gmpc/index.do

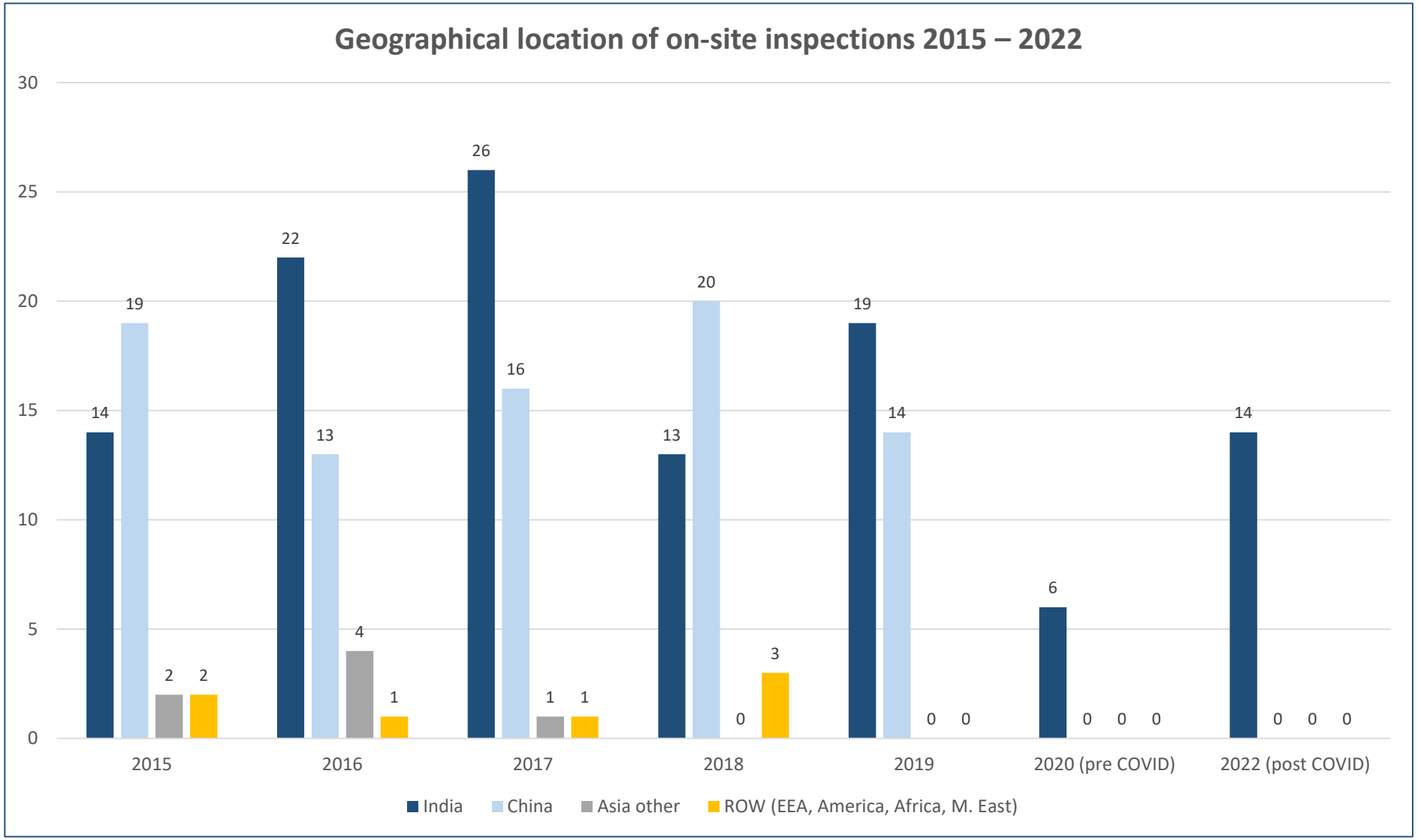
When (1)



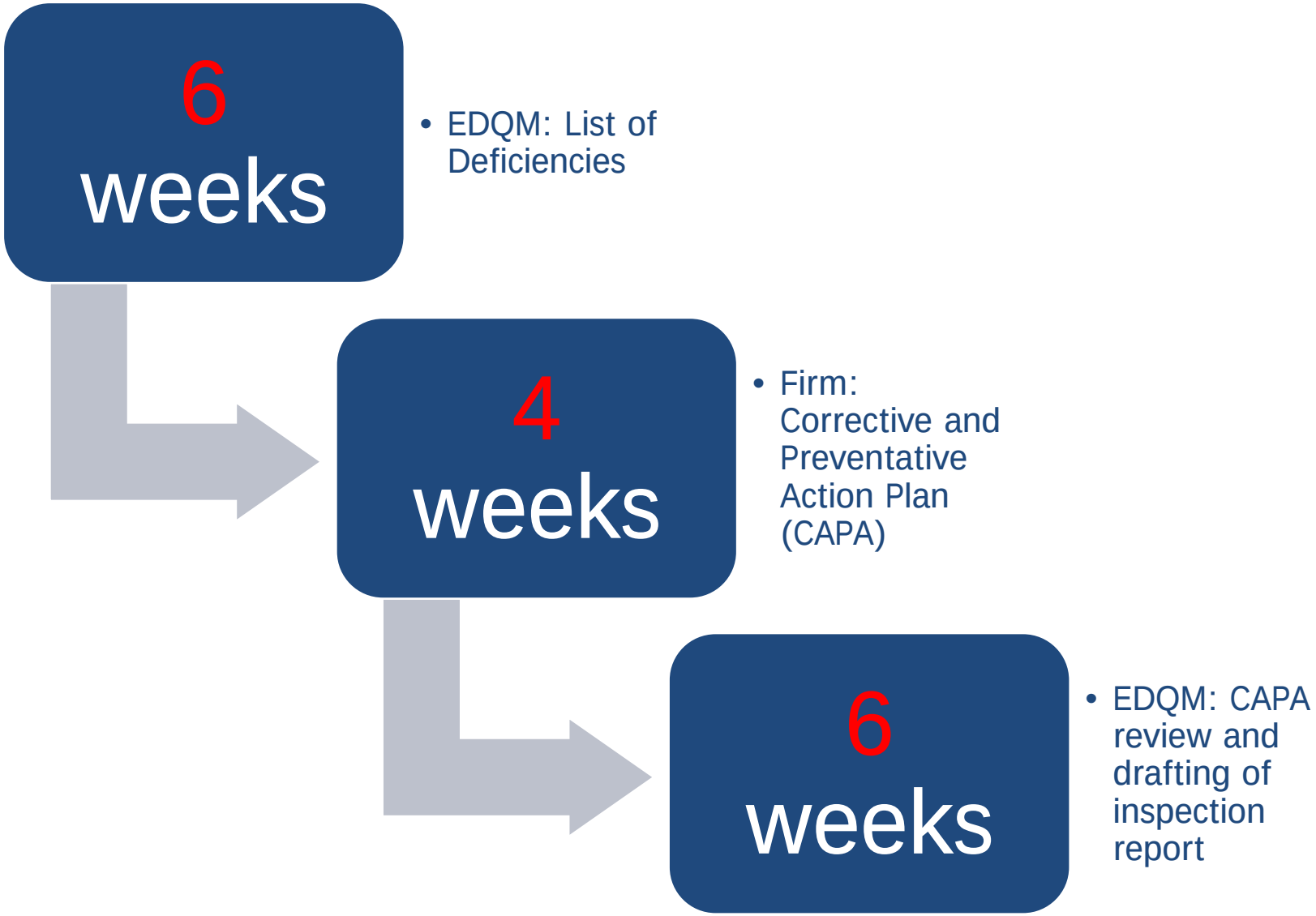
When (2)



Where

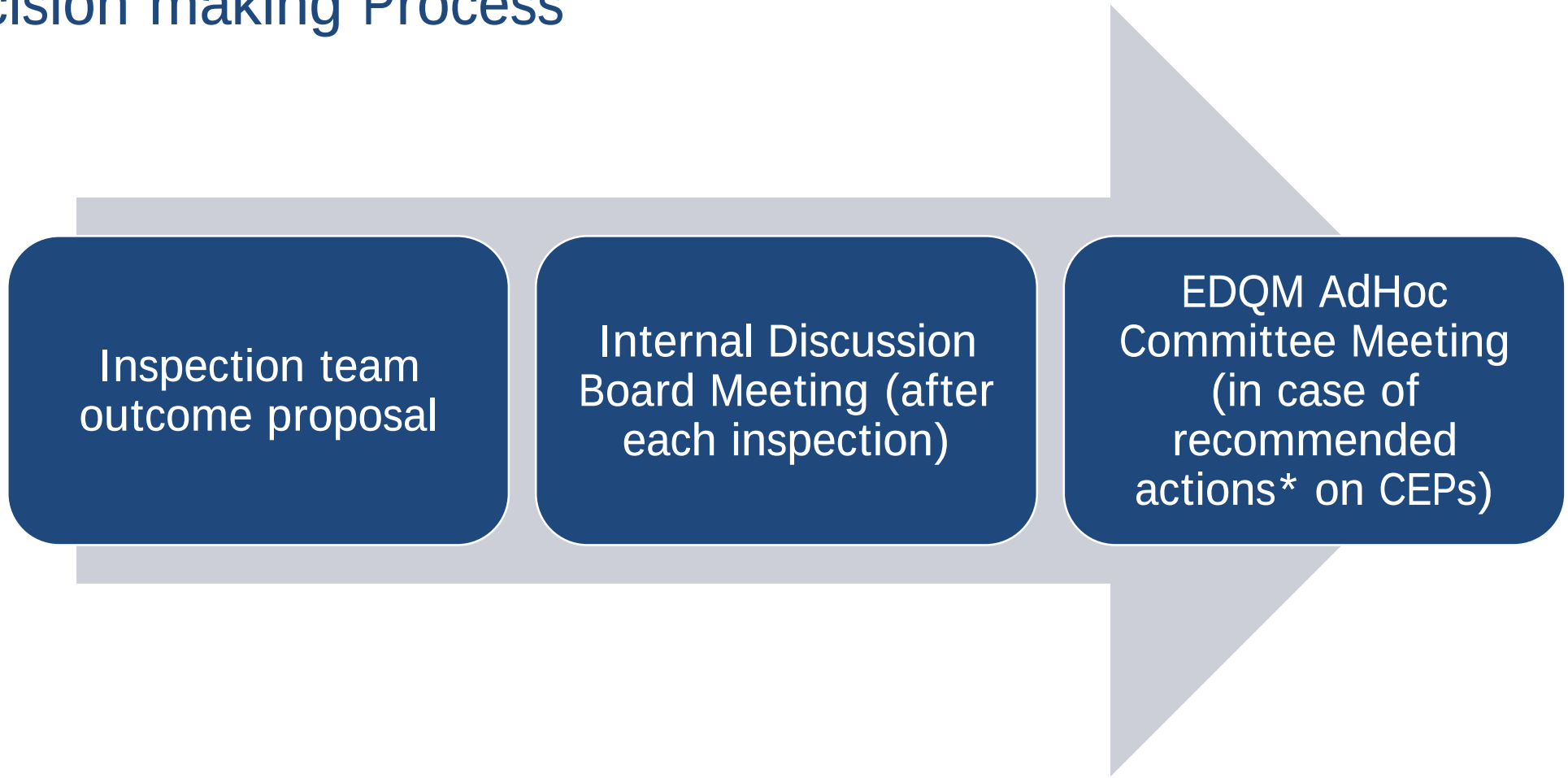


After the inspection...



Results

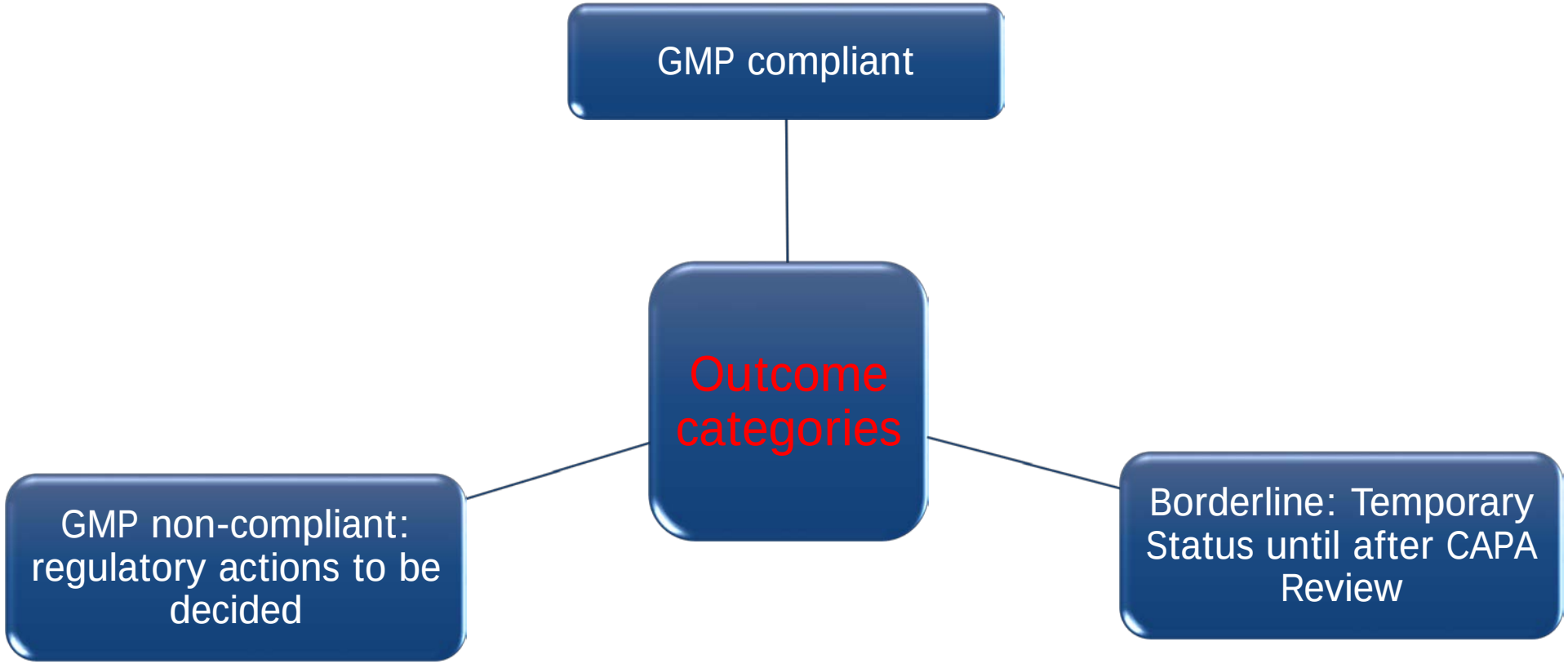
- Decision making Process



*) e.g. CEP suspension(s), withdrawal(s), removal of site(s) concerned, closure of application(s)

Results

- Inspection Outcome(s)



Results

In case of compliant outcome of the inspection combined with a satisfactory evaluation of the submitted CAPA, and if any expected application for CEP revision has been submitted, an inspection attestation is delivered by EDQM, stating the compliance with the CEP and with GMP.

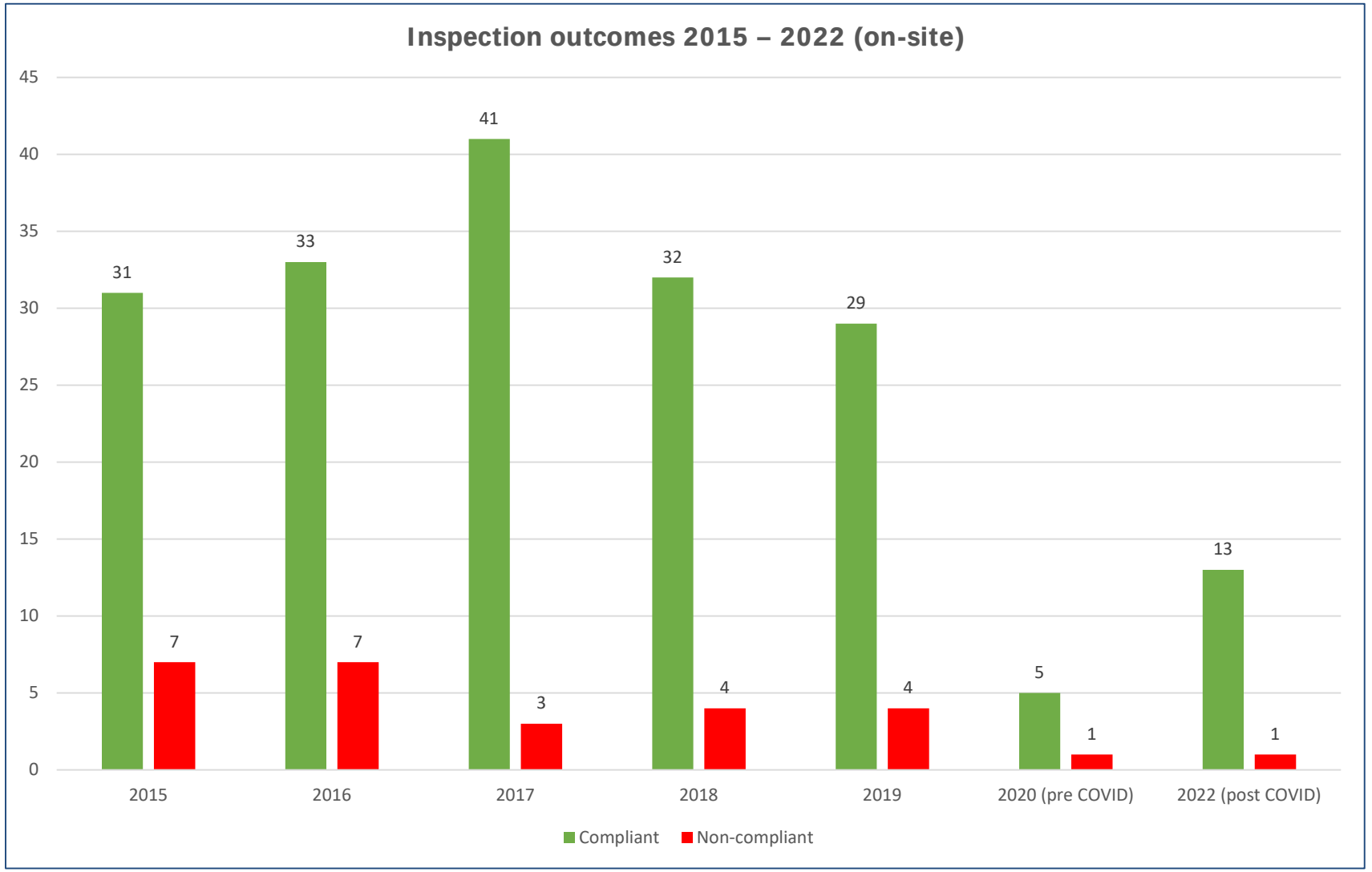
A GMP Certificate should be issued by the EEA participating inspectorate and published via the EUDRA GMDP database

In case of non-compliant outcome, which constitutes a potential risk to public health:

- all relevant CEP(s) of the site may be suspended or withdrawn
- Manufacturer may be removed if more than one involved in CEP
- on-going CEP application(s) may be closed

Holder and manufacturer notified and given a possibility of hearing within 14 days
A statement of GMP non-compliance should be issued by the EEA participating Inspectorate and published via the EUDRA GMDP database

Results



EDQM approaches to GMP assessment until 2020

On-Site Inspections

- Traditional inspection approach
- EDQM inspects about 40 sites per year

Paper based GMP Assessment

- Complementary to on-site inspections
- Up and running since 2010

Introduction of Real Time Remote Inspections (2020-2022)

Fully interactive

- Connected with firm the entire time of the inspection
- Video, screen and computer sharing
- 5-6 days
- 6-7 hours/day

Live video streaming

- Meeting room
- Storage facilities
- Production facilities
- QC facilities
- Utilities

QA Documentation

- Substantial number of SOPs and information uploaded prior of inspection
- Discussion with SMEs during inspection

Follow-up

- CAPA Assessment
- Inspection Report
- Official closure of inspection (NCA & EDQM)
- Same timelines as for on-site inspections

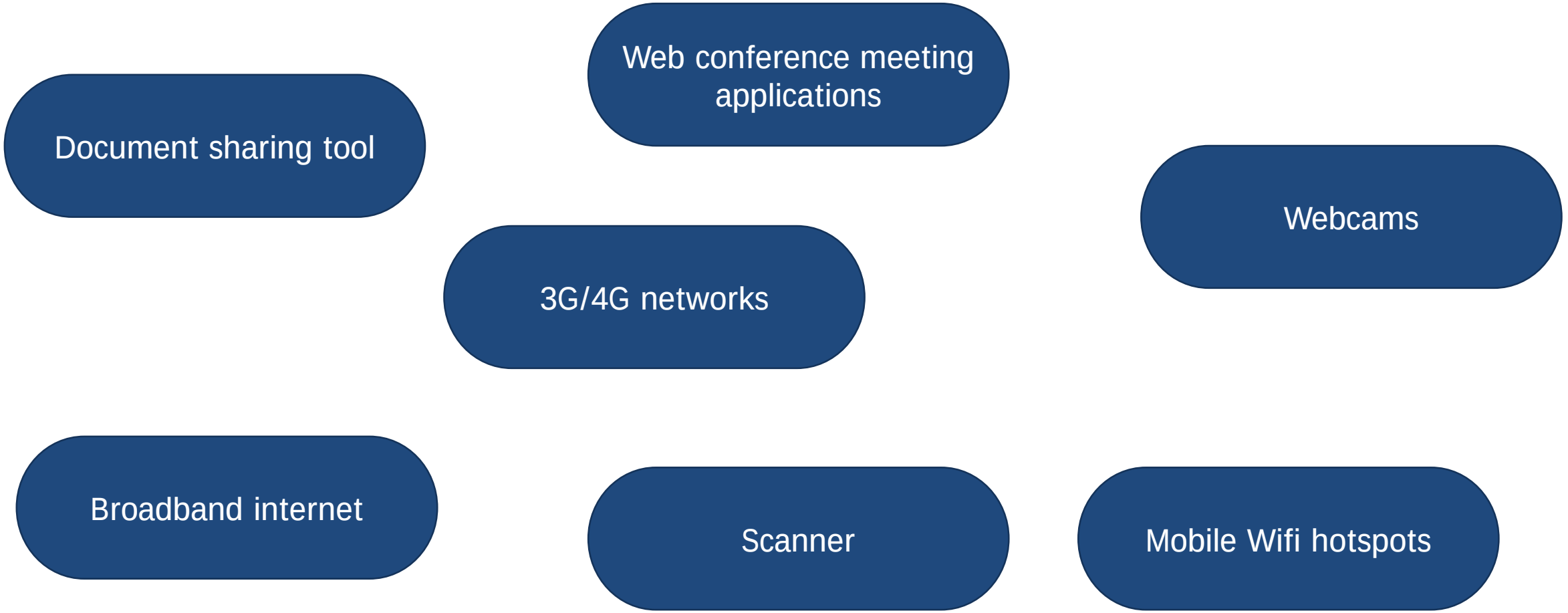
Main site selection criteria used so far

Site already inspected by EDQM: Knowledge of site

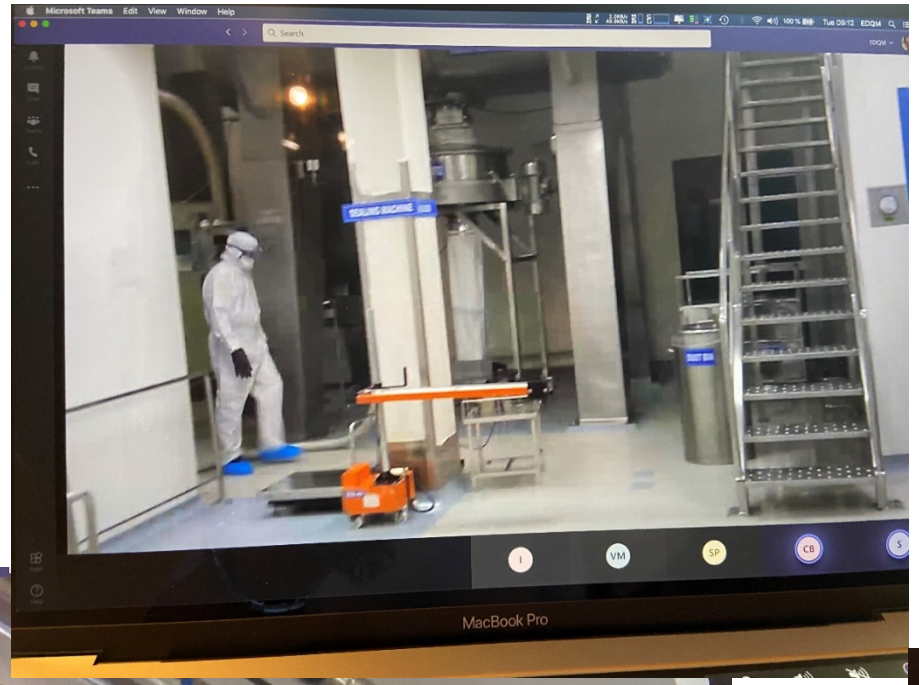
No negative compliance information in databases

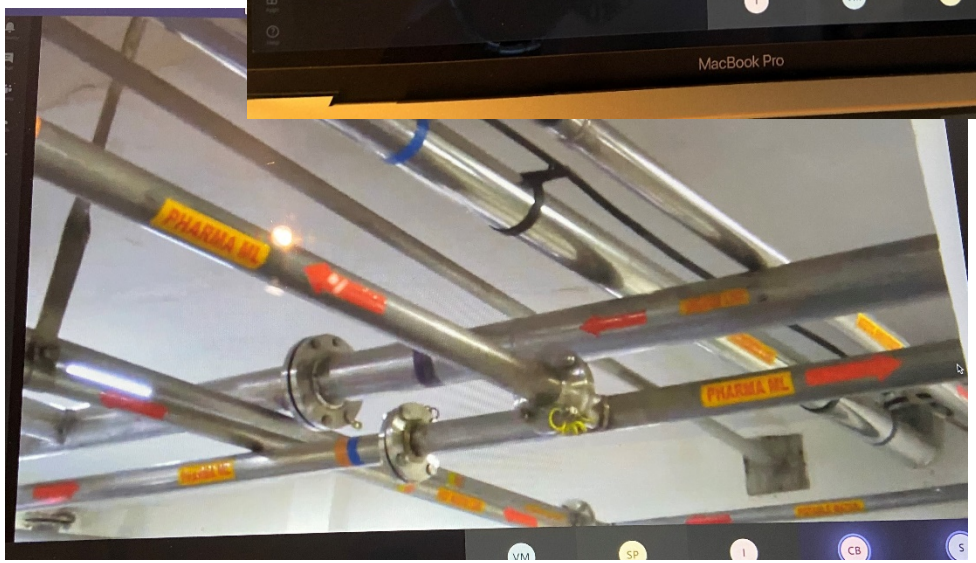
Site ideally located in industrial areas: communication infrastructure

Essential Tools (apart from inspectors...)

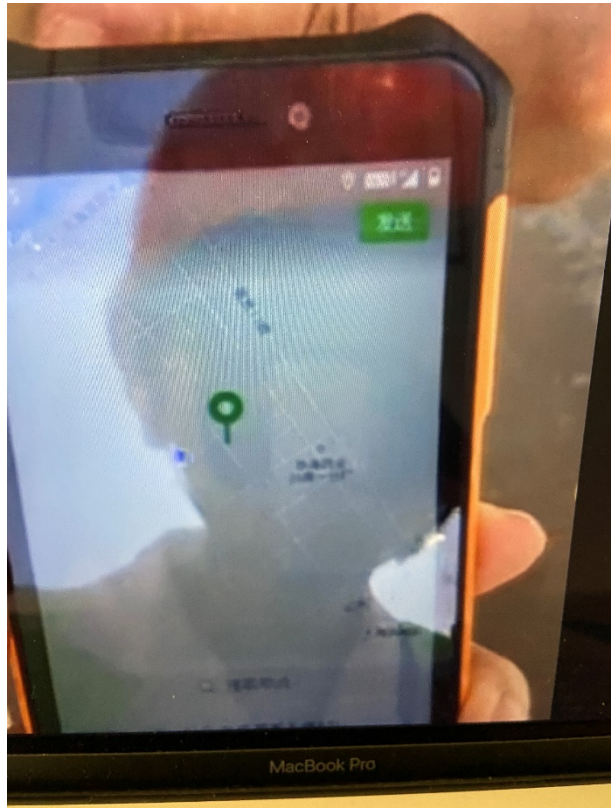


First experience gained – visual feedback





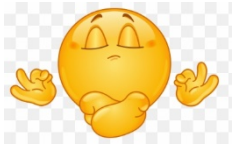
Site location verification (if needed)



Using GPS functionalities of mobile devices

Limitations / Challenges

- Technical difficulties depending on area connectivity, staff's technical experience etc.
- Inspection techniques that cannot be utilised remotely:
  - Element of surprise and body language interpretation
  - Periphery activities
  - Staff conversations
  - Sense of smell (risks in manufacturing areas)
- New challenges in China in addition to time difference: local language
- And... an additional soft skill of inspectors is needed:



Advantages

- Provides a possibility to evaluate the GMP compliance of a company when an on-site inspection cannot be performed or is deemed of lower priority
- Allows real time visual interaction with the company concerned
- Saves financial resources (both for the EDQM and companies)
- No travel: no carbon dioxide footprint, therefore beneficial for environment

And what from now on?

A new, third pillar for the supervision of the GMP compliance of pharmaceutical manufacturers

When a remote inspection could be used

- Travel restrictions, e.g. pandemic situations, safety concerns in destination country etc.
- A potential regular process for sites which showed a good level of GMP compliance during previous EDQM inspections
- A potential process to verify the implementation of specific parts of a CAPA if deemed necessary
- If urgent GMP evaluation is needed, e.g. specific topic evaluation. In this case, the RTEMIS would not replace an on-site inspection, but allows an immediate assessment of a specific situation/aspect that might pose a risk to public health

Some final considerations

- Increased inspectional oversight of API manufacturers by trusted international authorities (cf. definition in Compilation of Union Procedures) during the last decade 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

Perspectives

- Further development of the risk-based approach when selecting sites to be inspected
- Continual reinforcement of collaboration and sharing of information with EU and International Inspectorates
- Optimisation of use of inspection resources by:
  - ✓International API Inspection Programme (EMA) - increasing number of contributors expected
  - ✓GMDP Inspector working group (EMA)
  - ✓Committee of officials of PIC Scheme (PIC/S)
  - ✓Confidentiality agreements
- Using EDQM's GMP assessment procedures to evaluate sites that cannot be inspected in case of travel restrictions

Acknowledgements

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

Thank you for your attention

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