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Certification of suitability to the Monographs of the European Pharmacopoeia

EDQM Inspection Programme

EDQM inspections and trends of deficiencies Overview 2006 to 2018

Address: 7 Allée Kastner, CS 30026 F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

1) INTRODUCTION

All sites involved in the manufacturing of Active Pharmaceutical Ingredients (API) for which a CEP has been requested or granted may be subject to an inspection by the EDQM. A negative outcome of an inspection may result in actions against related CEPs (suspension or withdrawal of CEPs or closure of CEP applications). Re-inspections are performed either to verify the return to compliance after a negative inspection outcome, or in the context of monitoring the sustainability of the GMP status.

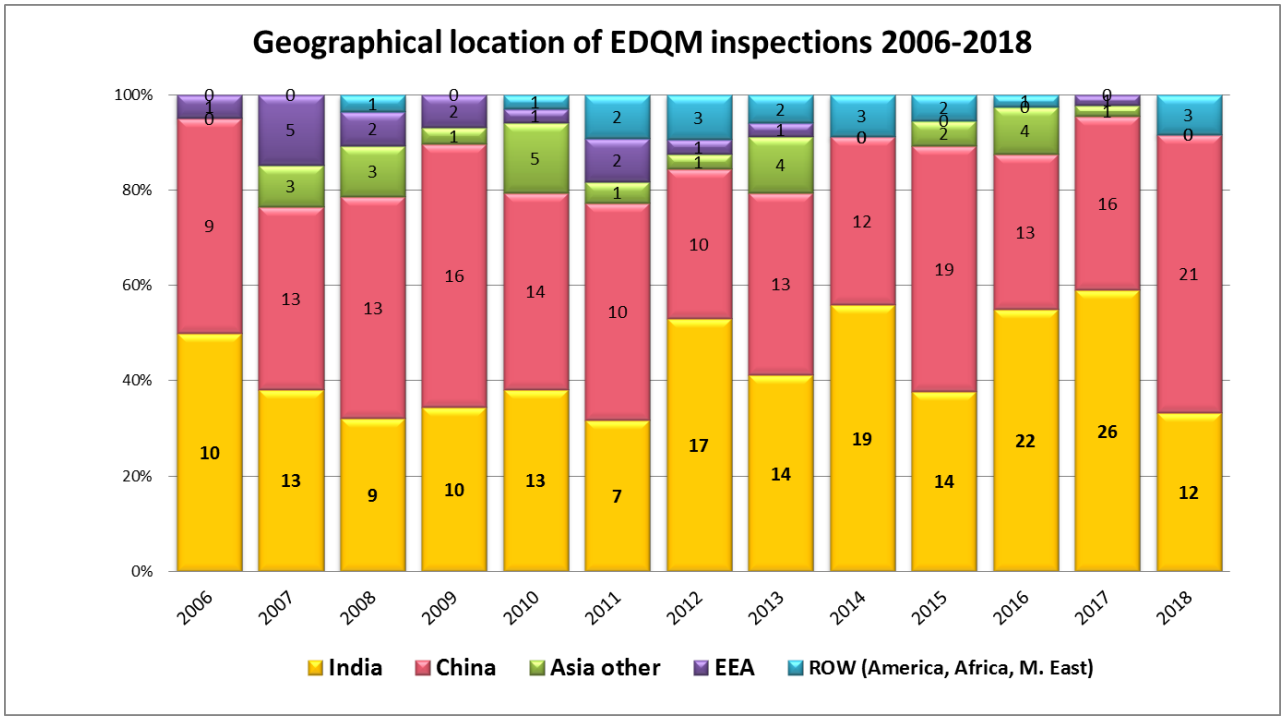
This document is a review of data from API inspections conducted by the EDQM between 2006 and 2018. It covers:

- the location of the inspections;
- whether they were initial or re-inspections;
- their outcome;
- the distribution of the observed deficiencies to EU Good Manufacturing Practice (GMP) Part II area and criticality;
- the frequency of the findings;
- issues of data integrity.

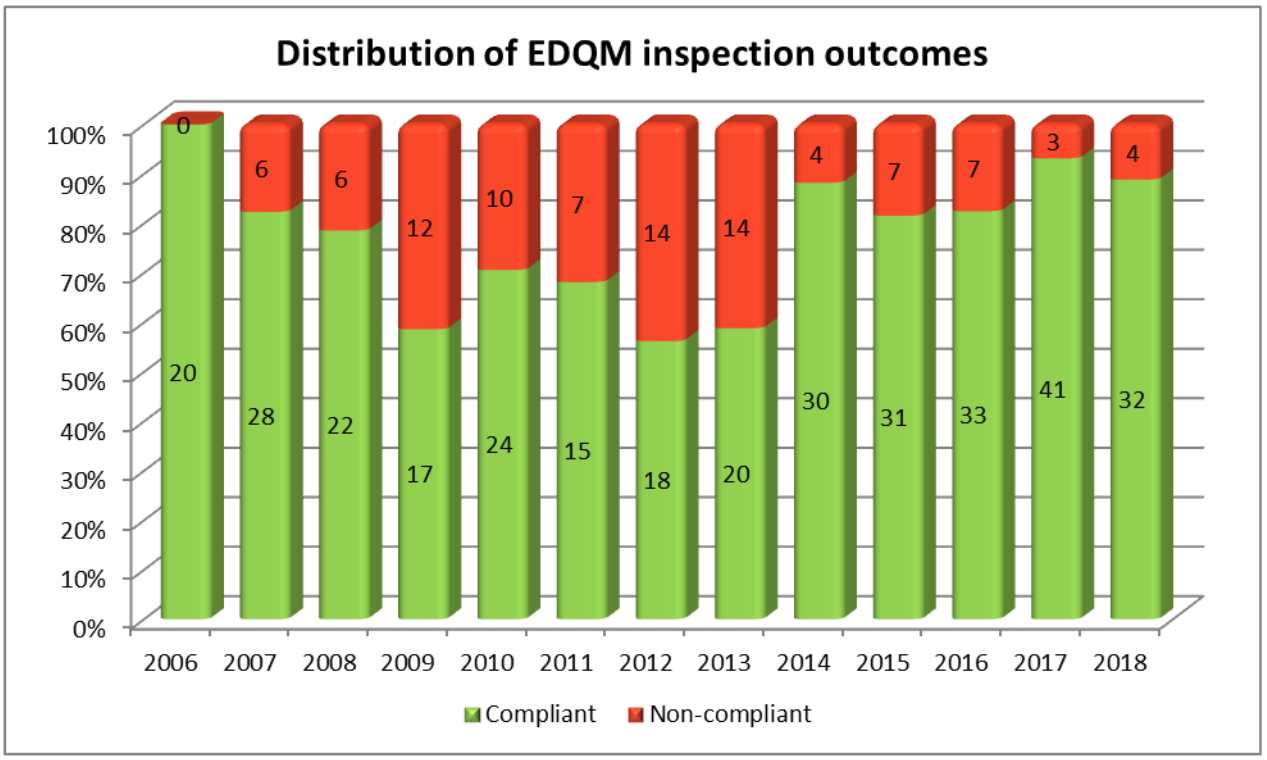
The deficiencies observed during EDQM inspections are referenced to EU GMP Part II and the relevant Annexes, or to the corresponding CEP dossiers and the European Pharmacopoeia (Ph. Eur.) in general.

2) REVIEW OF INSPECTIONS BY LOCATION, HISTORY AND OUTCOME

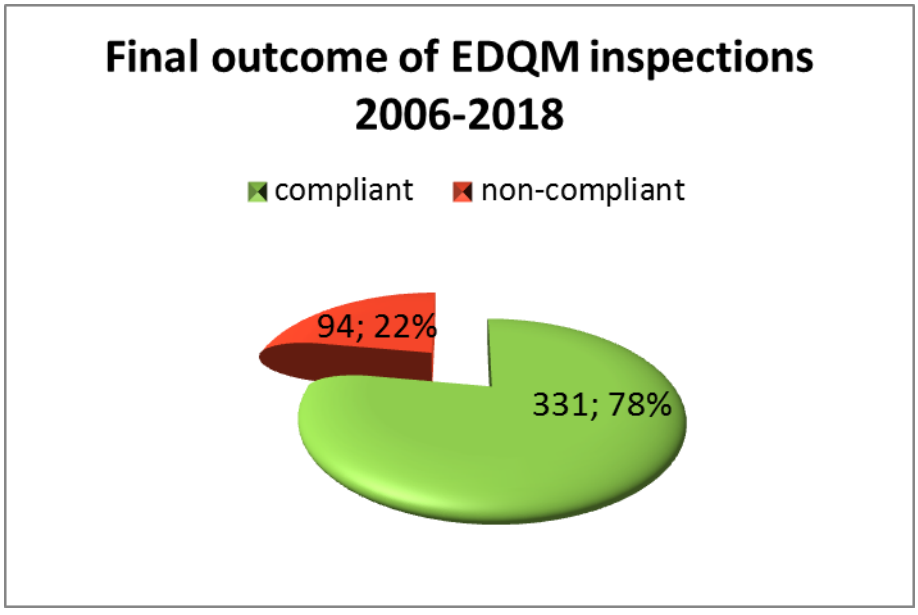
2.1 The distribution of EDQM inspections by geographical location of inspected sites is given in the following chart:



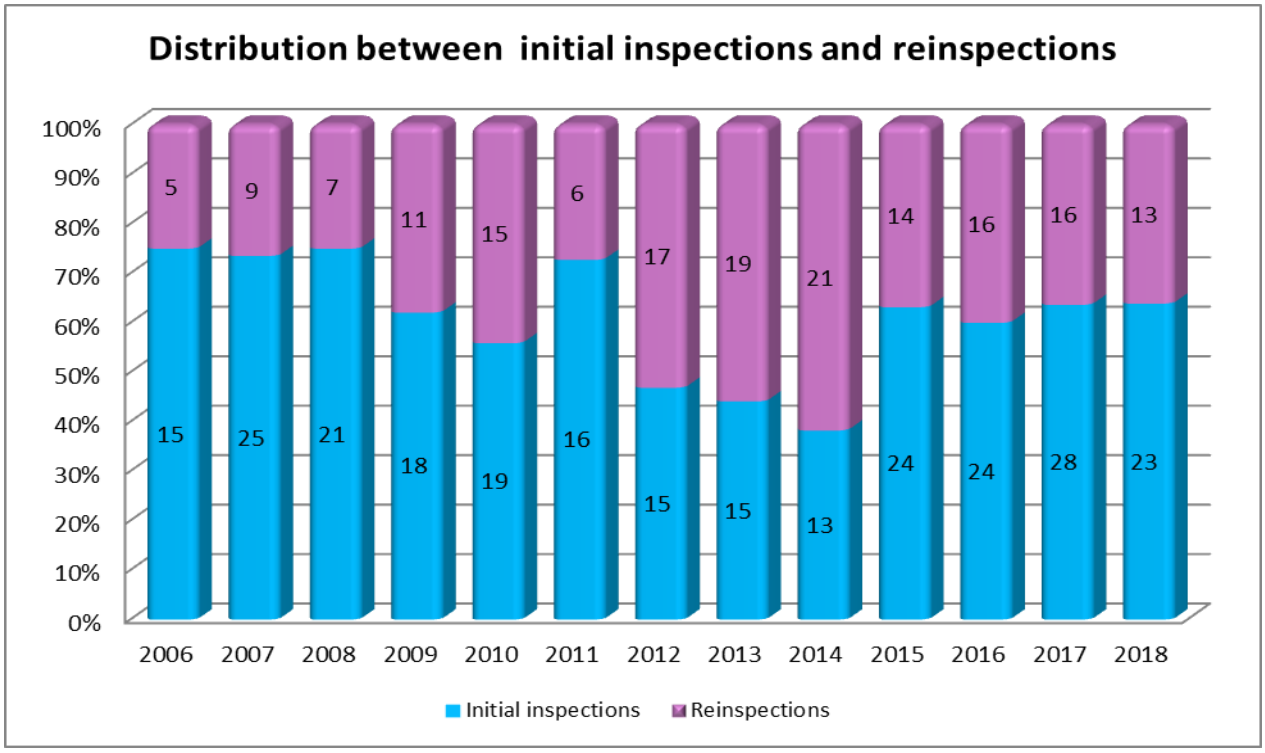
2.2 The distribution of outcomes of EDQM inspections is given in the following chart:



The chart below displays the total number and ratio of outcomes of EDQM inspections during the review period:



2.3 The distribution of EDQM inspections (initial or re-inspections) is given in the following table:



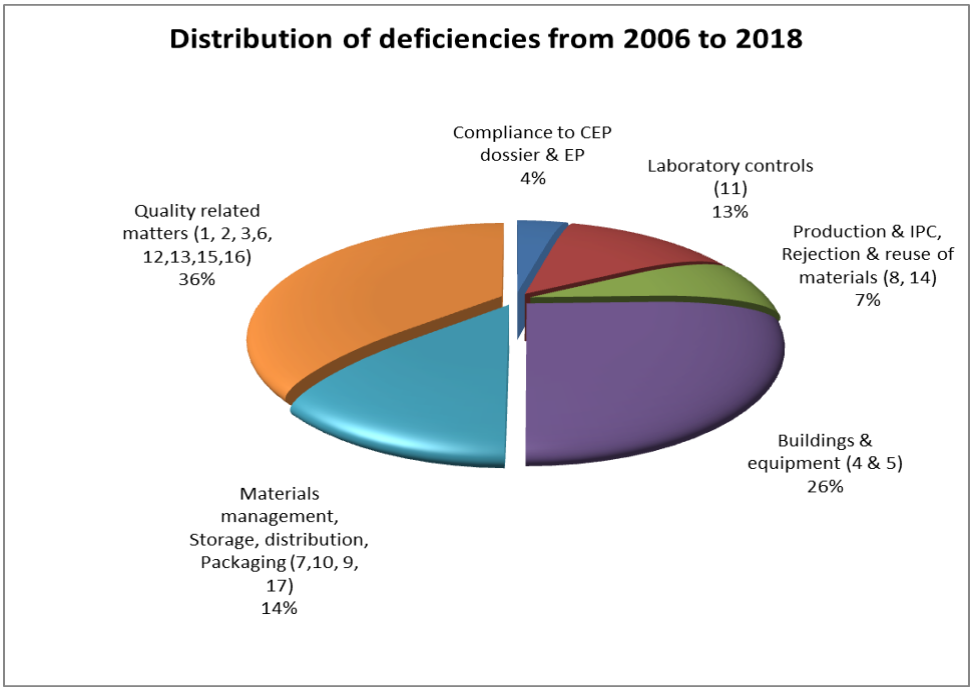
3) DISTRIBUTION OF DEFICIENCIES BY GMP AREA (including compliance with CEP) & CRITICALITY

The deficiencies reported during EDQM inspections are classified as critical, major or other, depending on the risk they may pose to public health and the degree of deviation from EU GMP, the relevant CEP dossier and European Pharmacopoeia (Ph. Eur.).

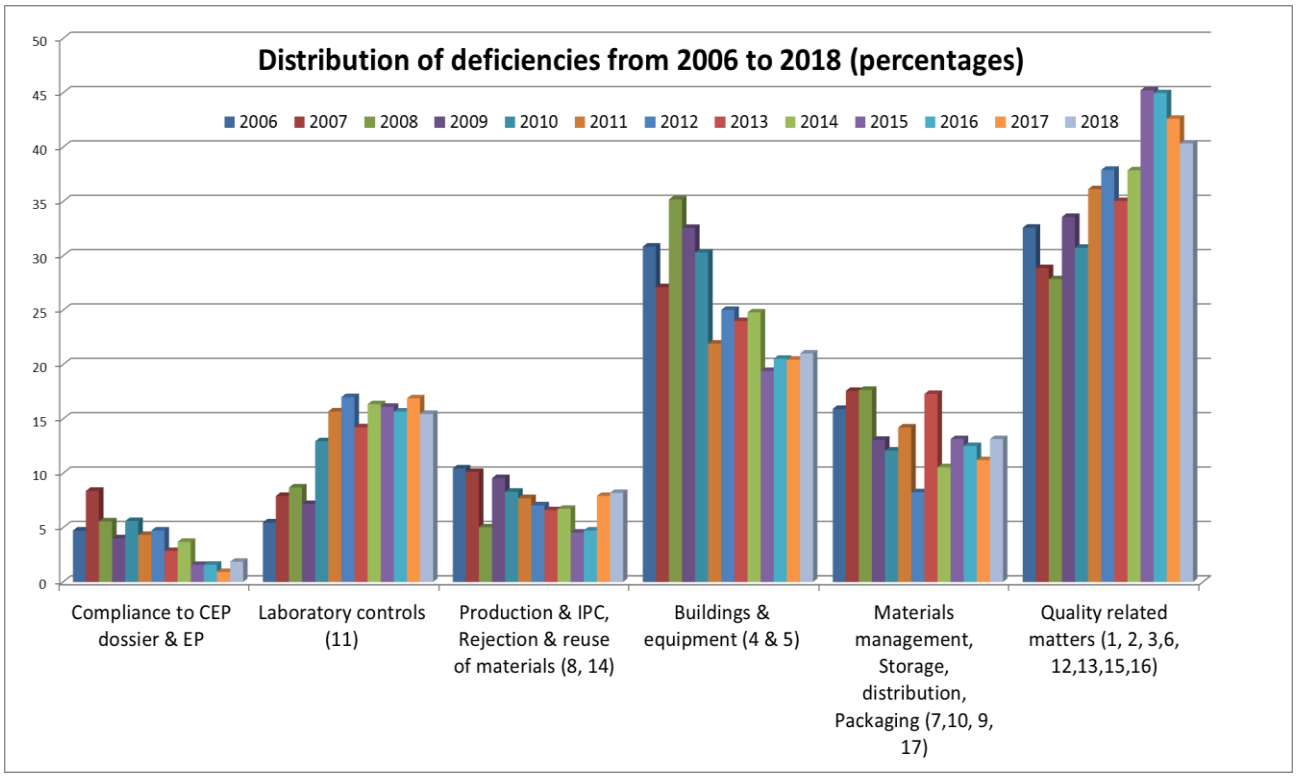
For this review, they have been distributed according to the respective chapters of EU GMP Part II as well as compliance with the CEP dossier and the Ph. Eur. Some items group several chapters of the EU GMP Part II. One item gathers all CEP dossier and Ph. Eur. compliance issues. The grouping aims at avoiding the variability linked with the fact that some deficiencies may be related to different chapters.

Only the numbers of the EU GMP Part II chapters are mentioned for each group in the charts; for the detailed grouping, see Annex I.

3.1 The overall distribution of deficiencies from EDQM inspections between 2006 and 2018 by GMP area and CEP compliance is displayed in the chart below:



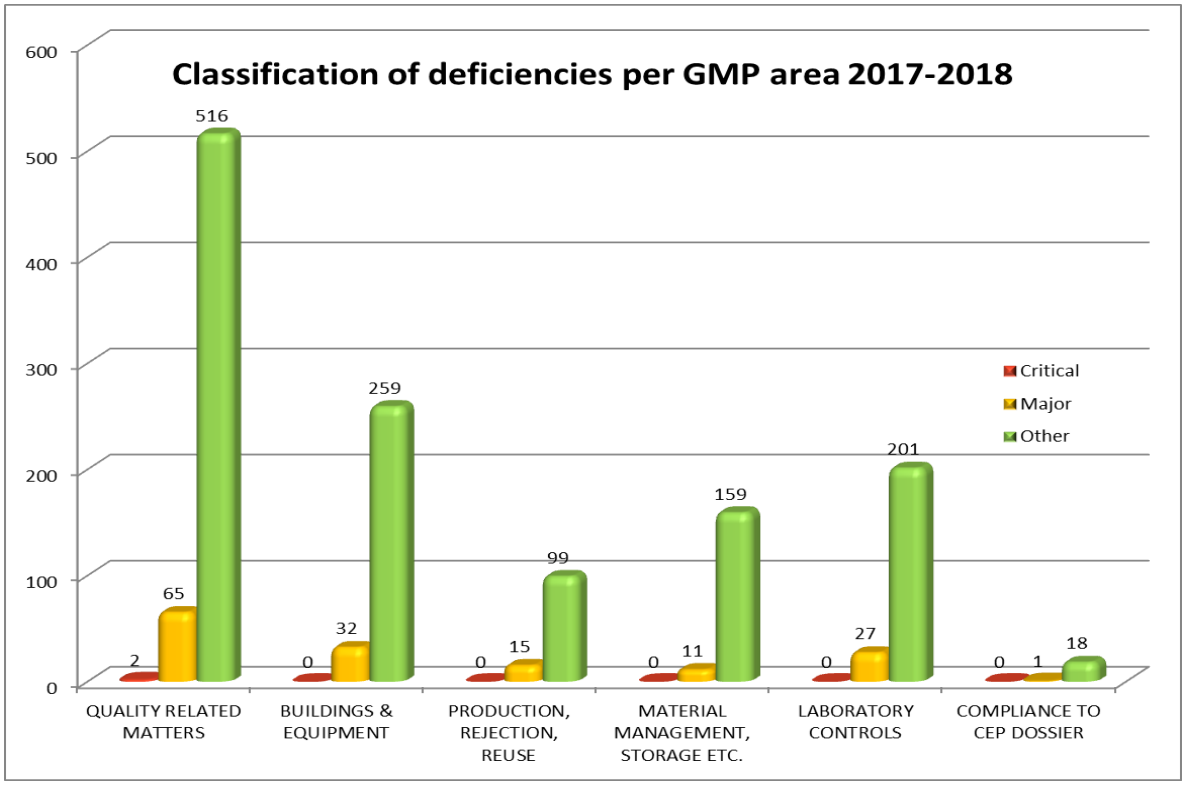
3.2 The chart below displays the trends in the deficiencies throughout the years by GMP area and CEP compliance (percentages of the total number of deficiencies for each year):



The following trends can be seen from the chart:

- Quality related matters: overall increase until 2015 (up to 45% from 32% in 2006), slight drop since then (down to 40% in 2018);
- Materials management: initially variable, overall stable since 2014 (10-13%);
- Buildings and equipment: decrease from 2008 (35%), overall stable since 2015 (19 to 21%);
- Production: consistent decrease until 2016, increase in 2017-2018 (from 5% to 8%);
- Laboratory controls: general increase until 2012 (17%), overall stable since;
- Compliance to CEP dossier and Ph. Eur.: regular decrease (from 8% in 2007 down to 1% in 2018).

3.3 For recent inspections (2017-2018) the number of deficiencies by level of criticality (critical, major and other) in each GMP area have been analysed and are presented in the chart below.



It can be seen from the chart that the largest occurrence of major and critical deficiencies is observed in Quality related matters, followed by Buildings & Equipment, and by Laboratory controls in third place (details in section 4).

It should be pointed out that the combination of major findings may lead to an overall critical risk for public health (and therefore a non-compliant inspection outcome without individual critical deficiencies), which is not reflected in the chart.

4) MOST FREQUENT TYPES OF DEFICIENCIES BY GMP AREA

The most frequent types of deficiencies identified in each GMP area during EDQM inspections between 2006 & 2018 are listed below.

4.1 Quality related matters

Insufficiency and/or ineffectiveness of quality system rendering operations not reliable as evidenced by:

- Insufficient oversight of quality unit over GMP activities, e.g.:
  - failure to effectively control documentation (both paper and electronic);
  - inadequate overview of production and laboratory activities;
  - underreporting and/or insufficient investigation of quality events (complaints, deviations, out-of-specification (OOS) results, change controls);
- Fraudulent documentation practices, e.g.:
  - rewriting documents in order to demonstrate acceptable, expected or presentable results, values or dates;
  - untimely recording of operations;
  - unavailability of records;
  - use of loose sheets instead of bound logbooks;
- Quality Risk management principles not applied or inadequately implemented in areas such as production activities, deviations, change control, etc.
- Annual quality review not used as a quality tool by companies, e.g.:
  - not all batches reflected (especially "non-CEP" grade, even though manufactured by same process);
  - trends not detected or investigated;
- Insufficient personnel training, e.g.:
  - no training given to upper management with regard to GMP related matters;
  - no assessment of training's efficiency or with limited value;
- Insufficient validation, e.g.:
  - processes such as use of recovered solvents, blending or micronisation not always addressed;
  - lack of sound knowledge of different approaches regarding cleaning validation.

4.2 Materials management

- Insufficient approval and/or management of vendors of key starting materials or intermediates (e.g. unreliable on-site audits);
- Risk of loss of traceability due to insufficient identification of containers;
- Improper storage conditions (temperature, humidity, non-controlled storage facilities…).

4.3 Buildings and equipment

- Risks of contamination and/or cross-contamination arising from:
  - improper design of facilities;
  - inadequate cleaning of equipment;
  - insufficient maintenance of equipment.
- Lack of appropriate user requirement specifications concerning equipment qualification;

- Lack of sound scientific approach regarding the management of computerised systems used for material management, production, laboratory controls etc., e.g.:
    - lack of appropriate user requirement specifications;
    - insufficient knowledge of validation requirements;
    - no or insufficient management of access levels causing risk of loss of traceability;
    - insufficient controls to prevent data manipulation;
    - lack or insufficient review of audit trail;
    - IT staff lacking or without knowledge of GMP requirements.

4.4 Production

- Blending of batches without prior appropriate testing;
- Lack of control of solvent recovery.

4.5 Laboratory controls

- Fraudulent practices regarding testing activities, e.g.:
    - pretesting or "testing into compliance";
    - deleting OOS results;
    - unreliability of analytical results;
- Unreliable microbiological results;
- Issues with Chemical Reference Standards (CRS):
    - absence of the Ph. Eur. CRS;
    - insufficient establishment of secondary standards;
- Lack of proper monitoring of potable water.

4.6 Sub-contracted activities

- No or insufficient review and/or acceptance for such activities (e.g. equipment/instrument calibration, computerised systems validation, further powder processing).

Specific cases of deficiencies related to data integrity

Most breaches of data integrity occurred in documentation practice and in laboratory controls. Additional issues have been observed, such as absence or gaps of validation and controls on computerised systems.

Importantly, 44% of critical and 25% of major deficiencies observed between 2015 and 2018 were related to data integrity issues.

5) CONCLUSION

From the geographical distribution of EDQM inspections (see 2.1), it is clear that manufacturing sites in India and China are the ones mostly visited, which is in line with the share of these two countries in the repartition of CEP manufacturers outside Europe (82% in March 2017). On the other hand, inspections in the European Economic Area (EEA) have practically dropped to zero, due to the monitoring of the compliance status of European sites being a responsibility of the respective National Competent Authorities.

Regarding the trends of inspection outcomes, the high level of non-compliances observed in the first few years after implementation of the EDQM inspection programme (especially between 2009 and 2013) is considered to demonstrate the ability of the EDQM to detect sites at risk from a GMP point of view. Since 2014, the relatively stable and comparatively low rate of non-compliance observed is seen as a result of the manufacturers' efforts to adapt and comply with regulatory & GMP requirements, promoted by the EDQM's continuous presence in the field of inspections (see 2.2).

An overall decline in findings related to buildings, equipment and materials management over the years (see 3.2) is considered as an achievement resulting from raising the companies' awareness in these fields. This improvement in the status of the majority of the facilities consequently allowed the inspectors to focus more on quality systems and subsequently identify more quality related issues, as shown by them consistently occupying the first place in the distribution of deficiencies in recent years.

A significant portion of the issues resulting in GMP non-compliance (critical and major deficiencies) are related to data integrity.

Another result of the review is the low level of discrepancies to the CEP dossier (see 3.2), which demonstrates the increased efforts of companies to comply with their commitments and the conditions under which their CEPs were granted throughout their lifecycle.

Annex I

Detailed grouping of chapters of EU GMP part II:

- **Quality related matters**
  Quality management (chapter 2)
  Personnel (chapter 3)
  Documentation (chapter 6)
  Validation (chapter 12)
  Change control (chapter 13)
  Complaints and recalls (chapter 15)
  Contract manufacturers (chapter 16)

- **Materials management**
  Materials management (chapter 7)
  Storage and distribution (chapter 10)
  Packaging (chapter 9)
  Distribution (chapter 17)

- **Buildings and facilities / Process equipment**
  Buildings and facilities (chapter 4)
  Process equipment (chapter 5)

- **Production**
  Production and in-process control (chapter 8)
  Rejection and reuse of materials (chapter 14)

- **Laboratory controls**
  Laboratory controls (chapter 11)

- **Specific group: Compliance to CEP dossier and Ph. Eur.**
  Compliance of process to CEP dossier
  Compliance of analytical specifications and methods to CEP dossier
  Compliance to Ph. Eur. general methods and general monographs