Inspection Trends of API and FPP Manufacturing Sites and Quality Control Laboratories

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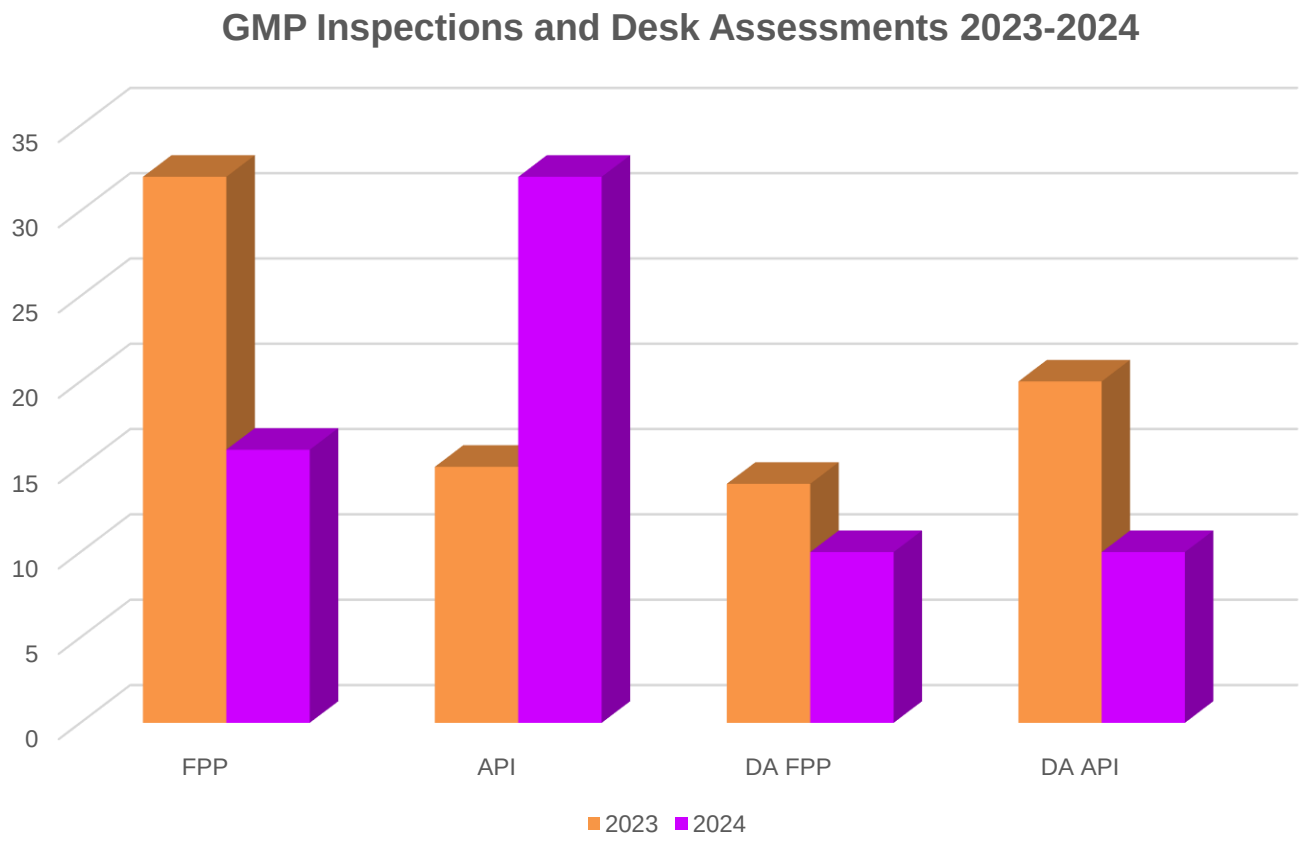
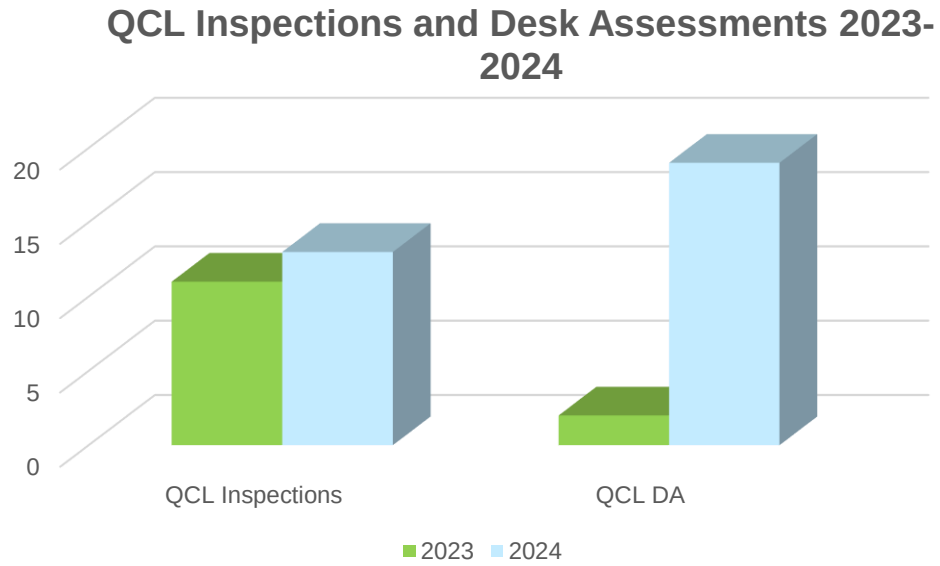
Overview

- Inspections and Desk Assessments
- Geographical Distribution of Inspections
- Critical and Major Observations
- Examples of Observations

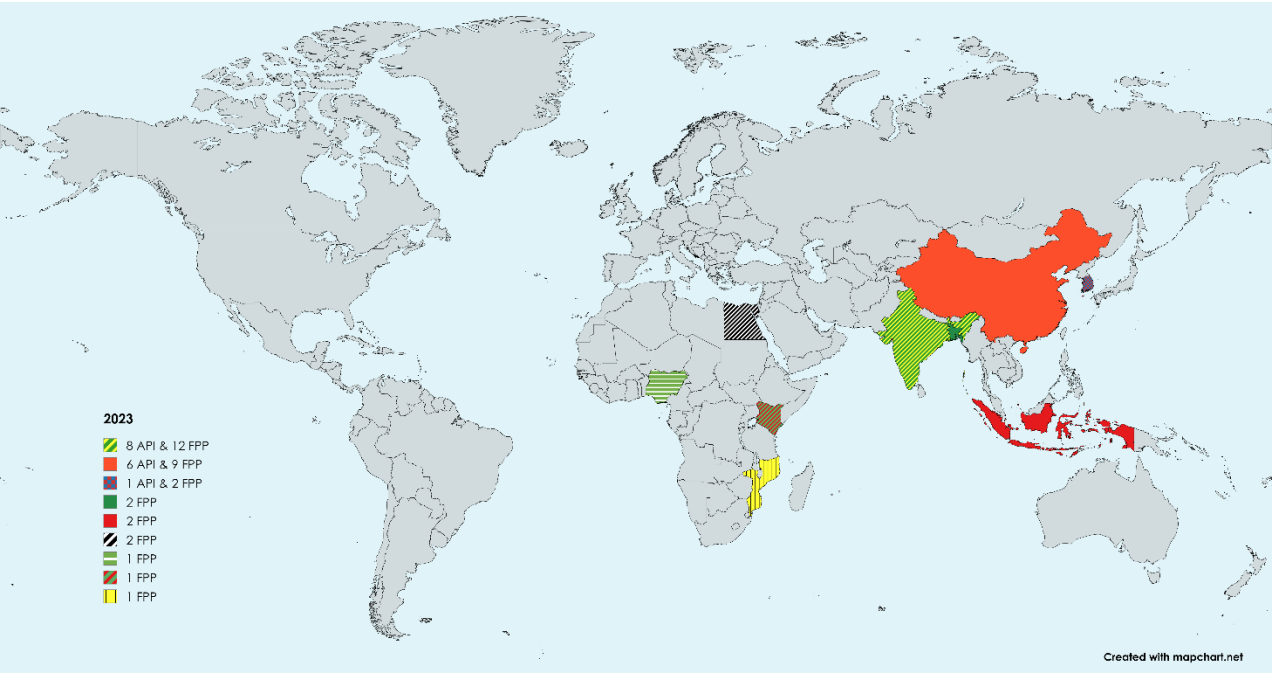
Inspections and Desk Assessments



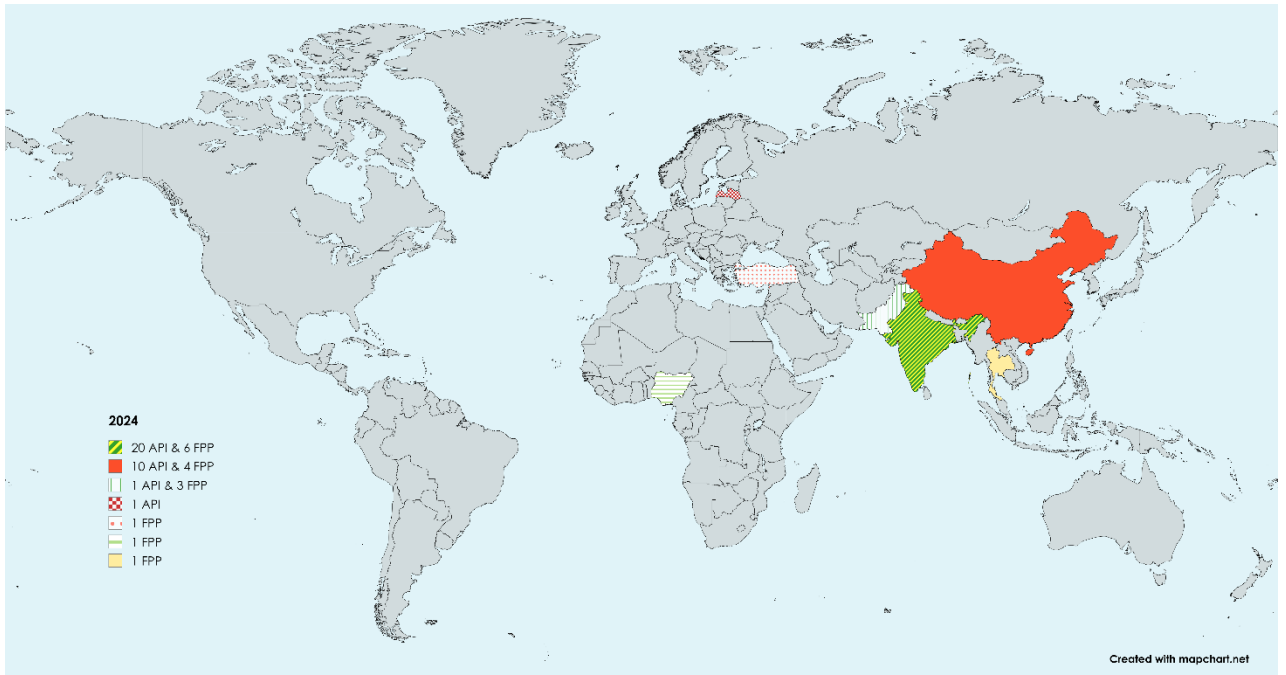


Number of inspections and desk assessments until October 2024

Geographical Distribution of GMP inspections

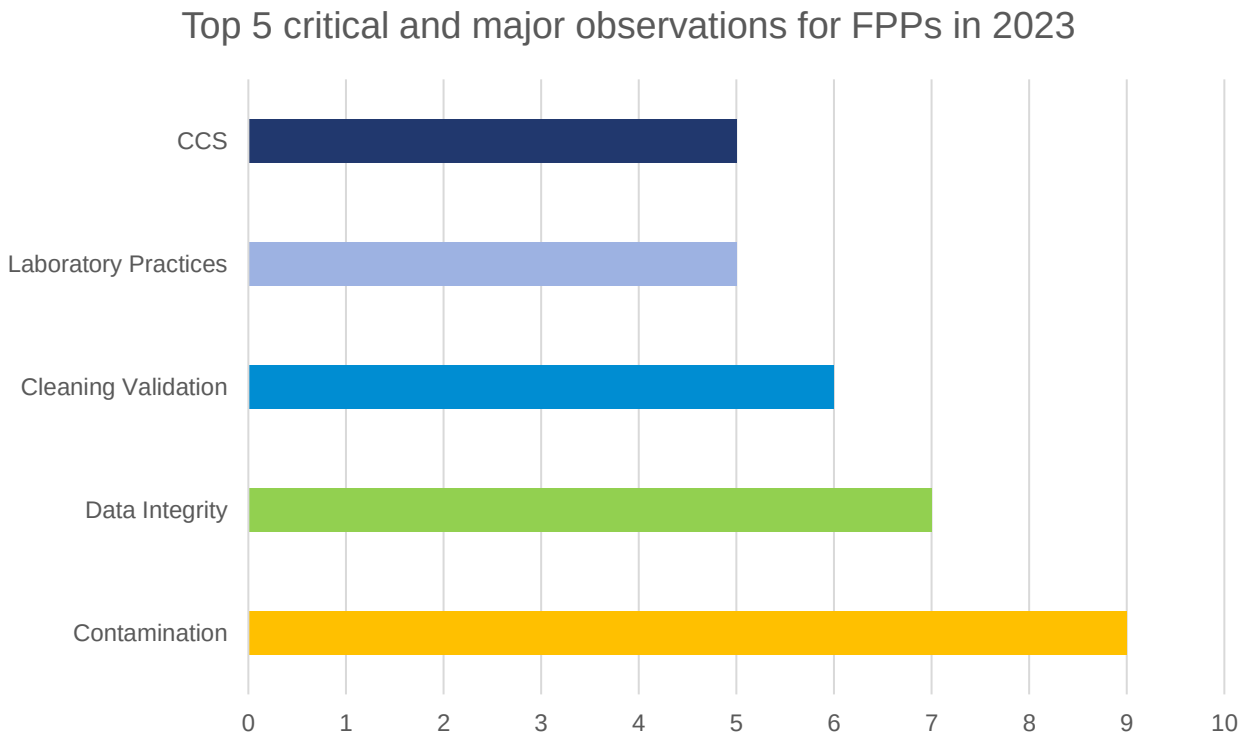


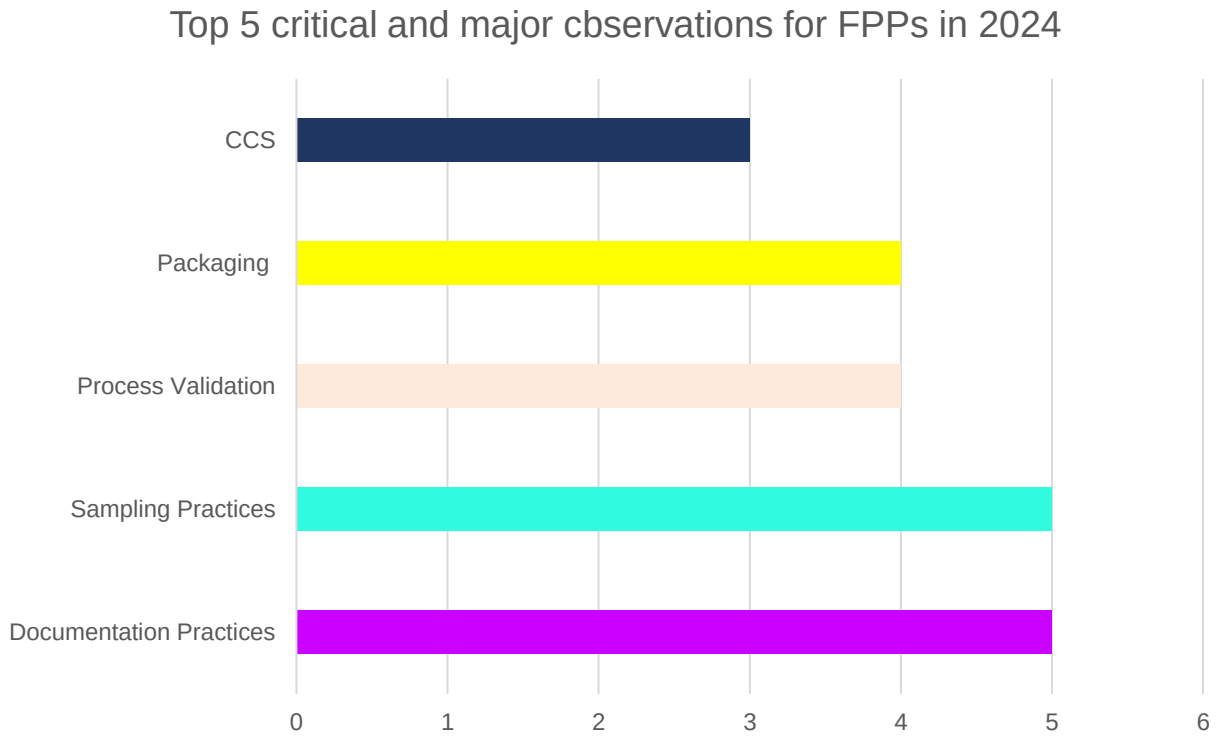
2023



2024

Critical and Major Observations for FPPs 2023-2024





Contamination Control Strategy – An Example of a Major Observation

The following areas were not adequately addressed in the CCS:

a. The procedure and controls for the gloves in RABS were not assessed as part of the CCS.

b. A video review of the vial filling line indicated that the operator during the setup of the line, entered the Grade A. This practice and the control measures were not discussed in the CCS.

c. The mobile LAFs used for transferring partially stoppered vials from the filling machine to the lyophilzers in Grade B were open on one side. It was not clear how Grade A environment was maintained, and this was not adequately elaborated in the CCS.

d. PVC strip curtains were used for separating the loading/unloading areas of the lyophilizers (Grade A) from the background area (Grade B). PVC strip curtains did not provide complete separation between Grade B and Grade A areas. This practice and the relevant risks were not adequately discussed in the CCS.

e. Similarly, the capping machines (Grade A) for the above-mentioned vial filling lines were not isolated from the background environment (Grade B). No risk assessment had been performed.

f. No limits were set for the number of sterilization cycles for the goggles used in the filling areas. No specifications were available. No monitoring was performed. No sterility test and validation had been performed.

g. The differential pressure (DP) in ampoule filling line X, between the depyrogenation zone and the preheating zone, the preheating zone and the ampoule washing area as well as the depyrogenation zone and the cooling zone were not part of the qualification and were not routinely monitored during manufacturing. This approach was not consistent with other ampoule and vial lines (e.g. vial filling line Y) where these DP tests were performed. The different approaches for qualification and monitoring were not discussed in the CCS.

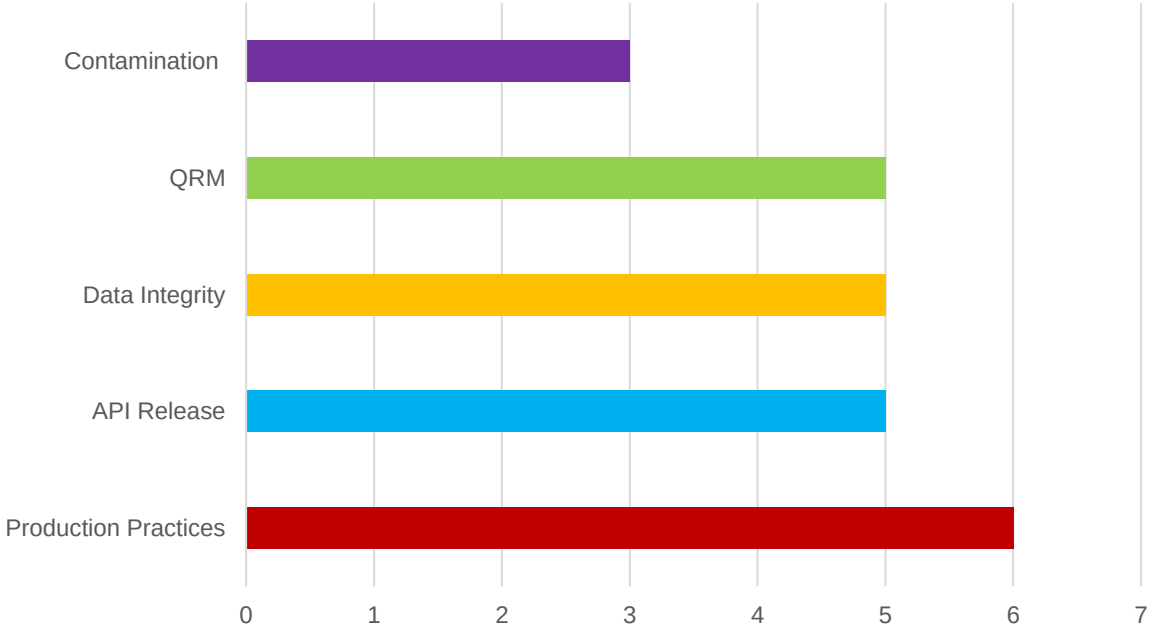
Contamination Control Strategy

Elements to be considered within a CCS should include:

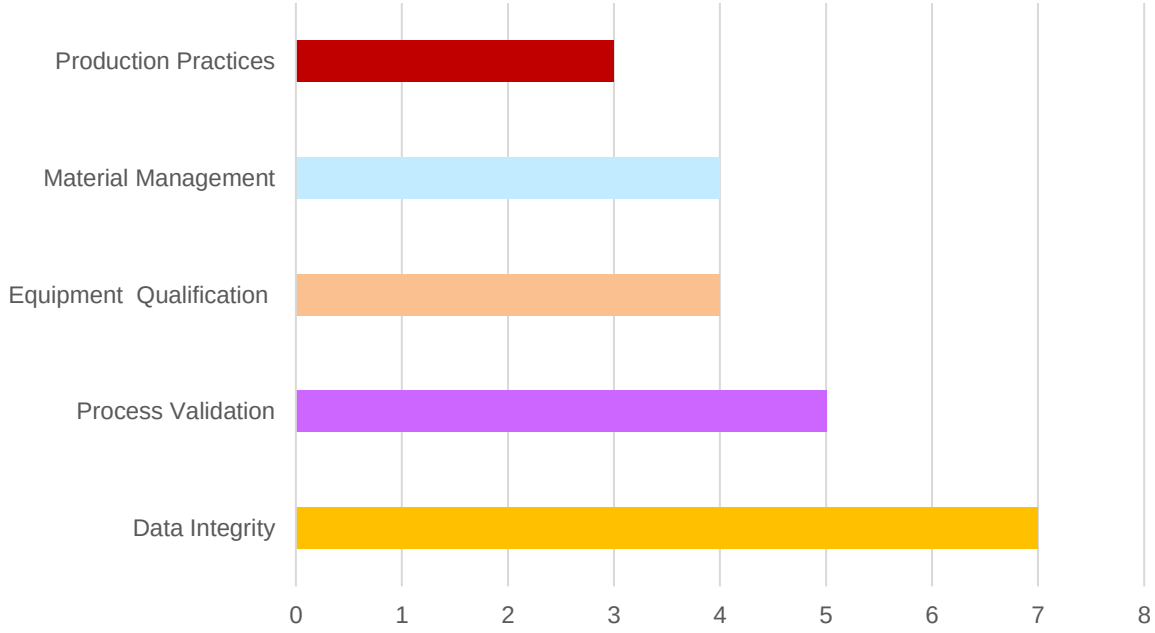
i. design of both the entire plant and processes, including the associated documentation;
ii. premises and equipment;
iii. personnel;
iv. Utilities
v. raw material controls, including in-process controls;
vi. product containers and closures;
vii. vendor approval, for example key component suppliers, sterilization of components and single-use systems (SUS), and critical service providers;
viii. management of outsourced activities and availability and transfer of critical information between parties, for example contract sterilization services;
ix. process risk management;
x. process validation;
xi. validation of sterilization processes;
xii. maintenance of equipment, utilities and premises (planned and unplanned maintenance);
xiii. cleaning and disinfection;
xiv. monitoring systems, including an assessment of the feasibility of the introduction of scientifically sound alternative methods that optimize the detection of environmental contamination;
xv. prevention mechanisms, including trend analysis, detailed investigation, root cause determination, corrective and preventive actions, and the need for comprehensive investigational tools;
xvi. continuous improvement

Critical and Major Observations for APIs 2023-2024

Top 5 critical and major observations for APIs in 2023



Top 5 critical and major observations for APIs in 2024



Data Integrity - An Example of a Major Observation

Existing controls to ensure data integrity requirements were found inadequate. Examples include but are not limited to the following:

a. No data integrity policy was available.
b. No data integrity risk assessment (DIRA) was performed for various equipment, instruments and systems which are used standalone.
c. Although an SOP for data integrity was available, the procedure did not address the data management system including senior management oversight, providing the appropriate working environment, adequate review of results, reporting of errors, unauthorized changes, omissions and undesirable results.
d. The date/time stamp for the analytical balance was not locked as observed during the inspection. Also, the IT administrator shared the password to DGM, QC/QA when on leave.
e. Privileges for manual integration of defined chromatographic parameters, and deletion/editing of files/folders were given to analysts.
f. Audit trails were not reviewed before a batch of an API was released

Summary

- Quality Risk Management and risk-based approaches are applied for planning and conducting inspections
- Sharing of information among authorities and harmonizing guidelines lead to better use of inspection resources and less regulatory burden for manufacturers.
- Contamination Control Strategy identified as a recurrent issue in sterile FPP inspections
- Data Integrity identified as key issue in API inspections
- Most of the manufacturing sites (APIs, FPPs) are found in India and China;
- Encouraging to see manufacturers from LMIC coming forward


GMP
Thank you for your attention