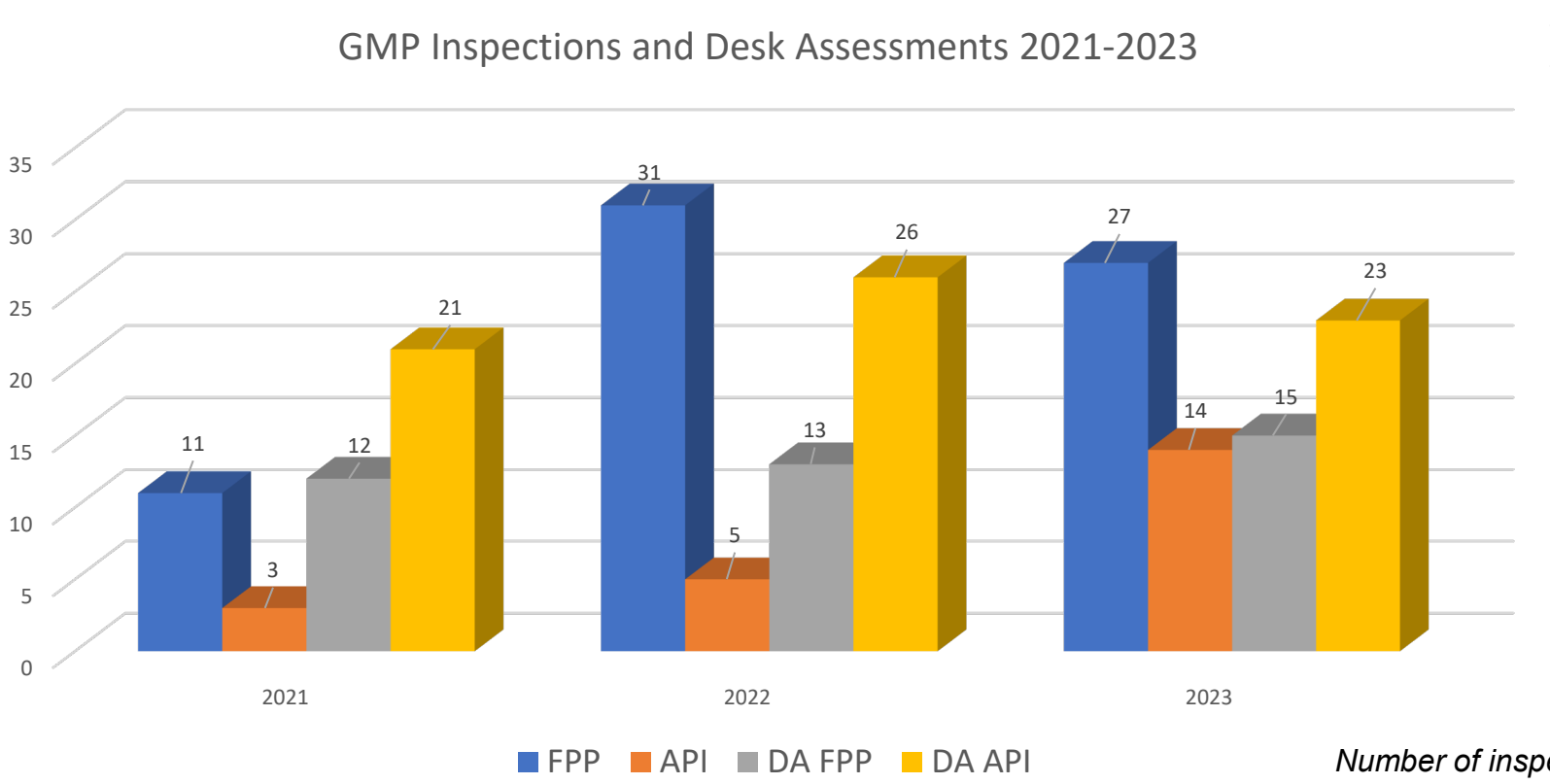
Inspection Trends of Pharmaceutical Manufacturing Sites APIs and FPPs

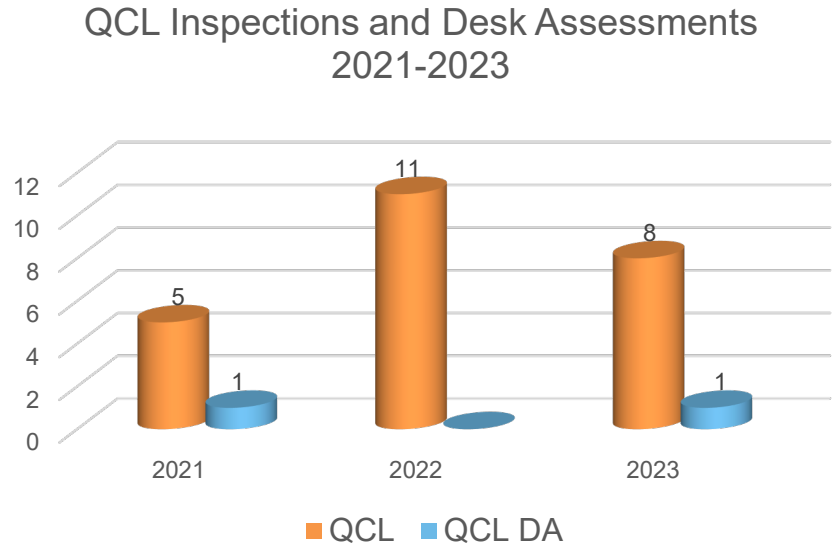
Dimitrios Catsoulacos
Technical Officer (Inspector)
Inspection services, Prequalification Unit
Regulation and Prequalification Department
Access to Medicines and Health Products Division
WORLD HEALTH ORGANIZATION

Overview

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

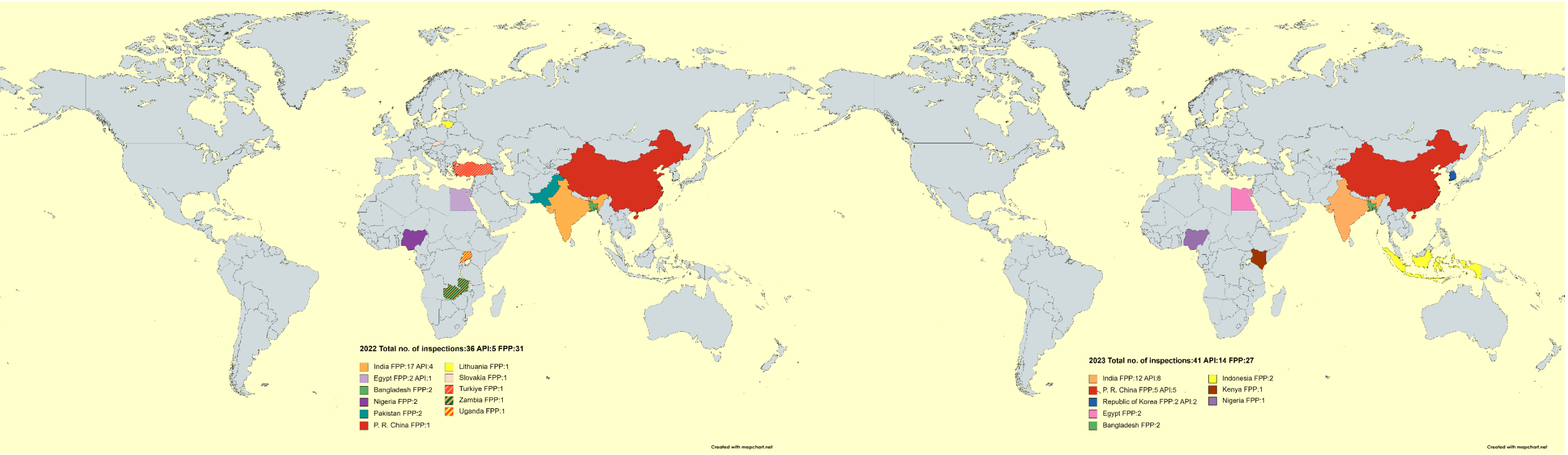
GMP Inspections and Desk Assessments





Number of inspections and desk assessments in 2023 is not finalized

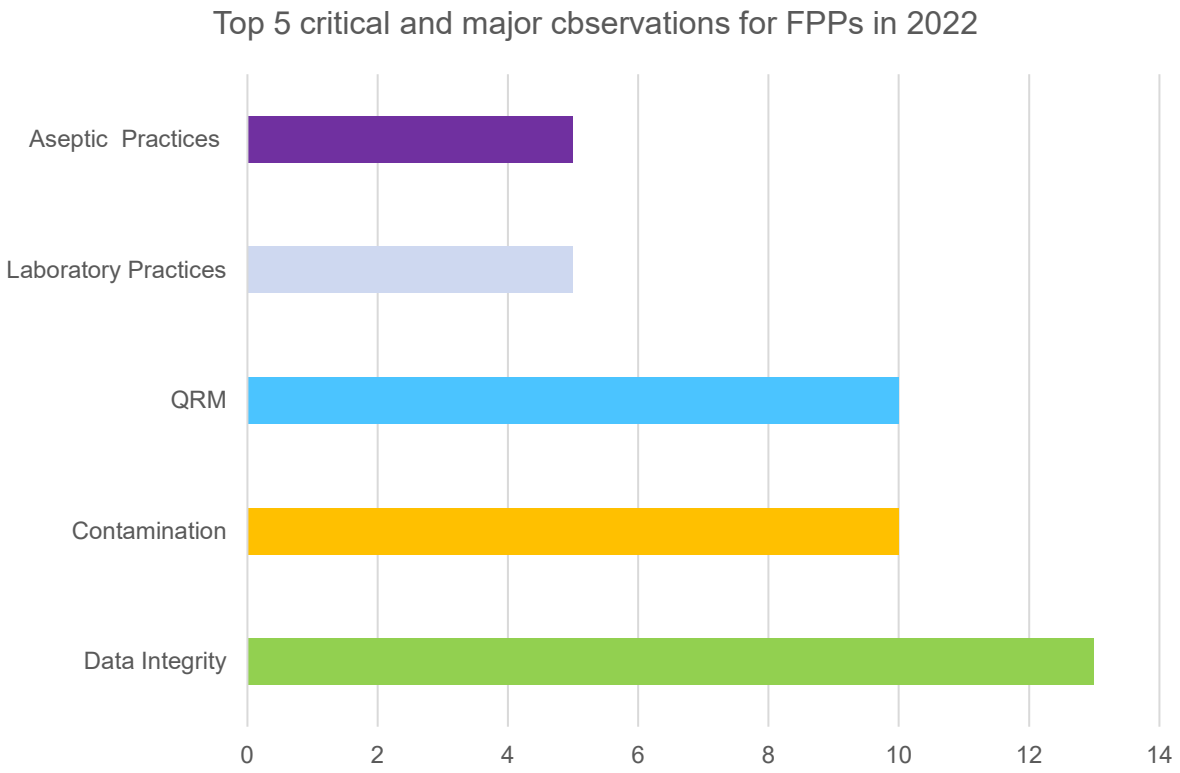
Geographical Distribution of GMP inspections

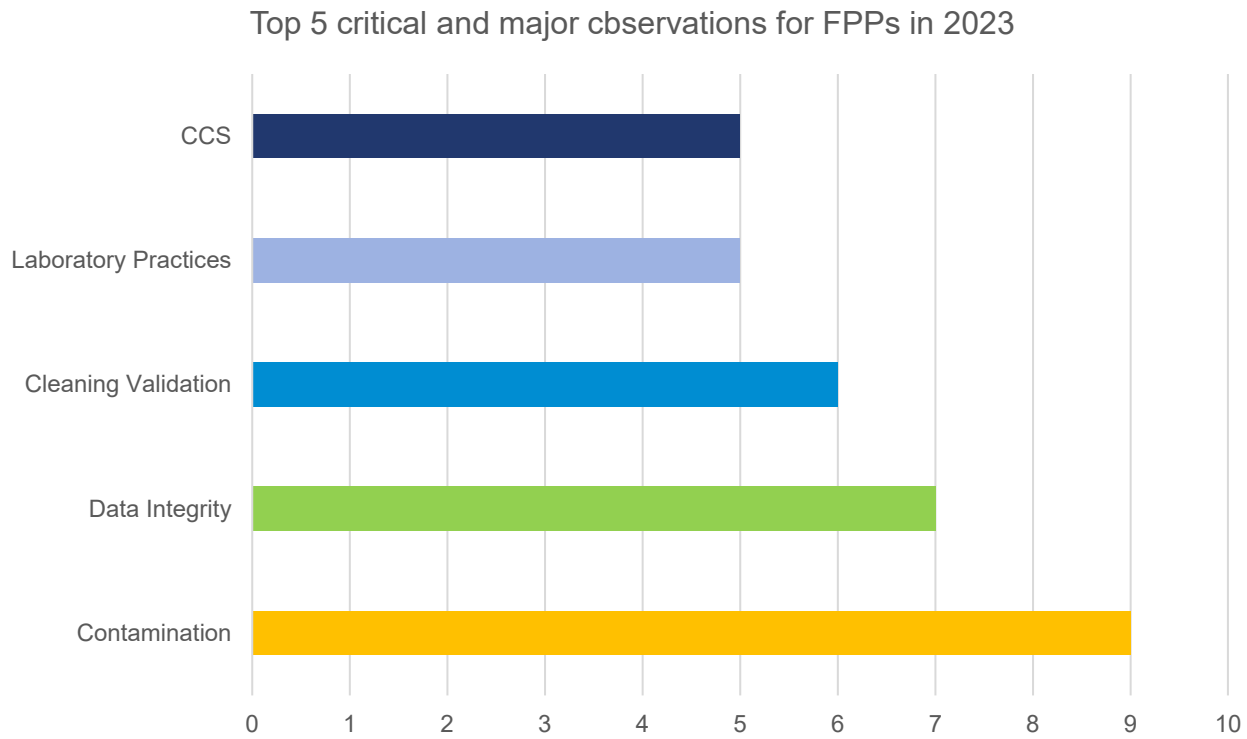


2022

2023

Critical and Major Observations for FPPs 2022-2023





Number of inspections in 2023 is not finalized

Examples of Critical and Major Observations - FPP

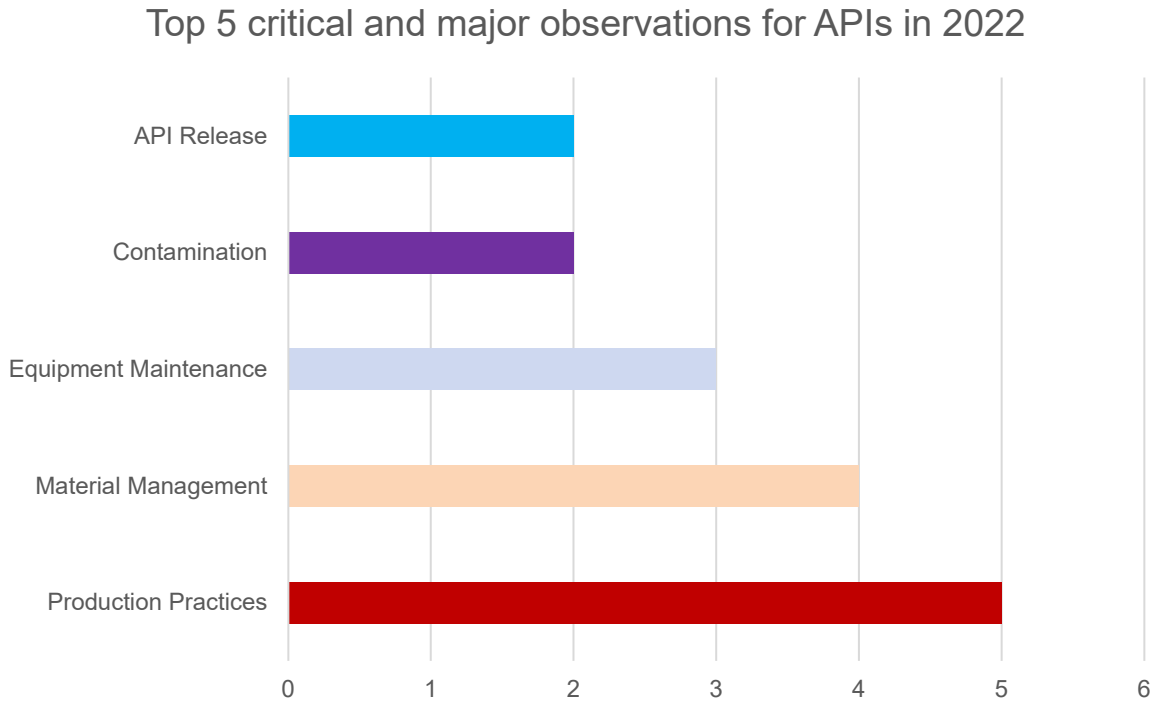
Data governance and related measures were found inadequate to minimize the potential risk to data integrity as noted from the following examples:

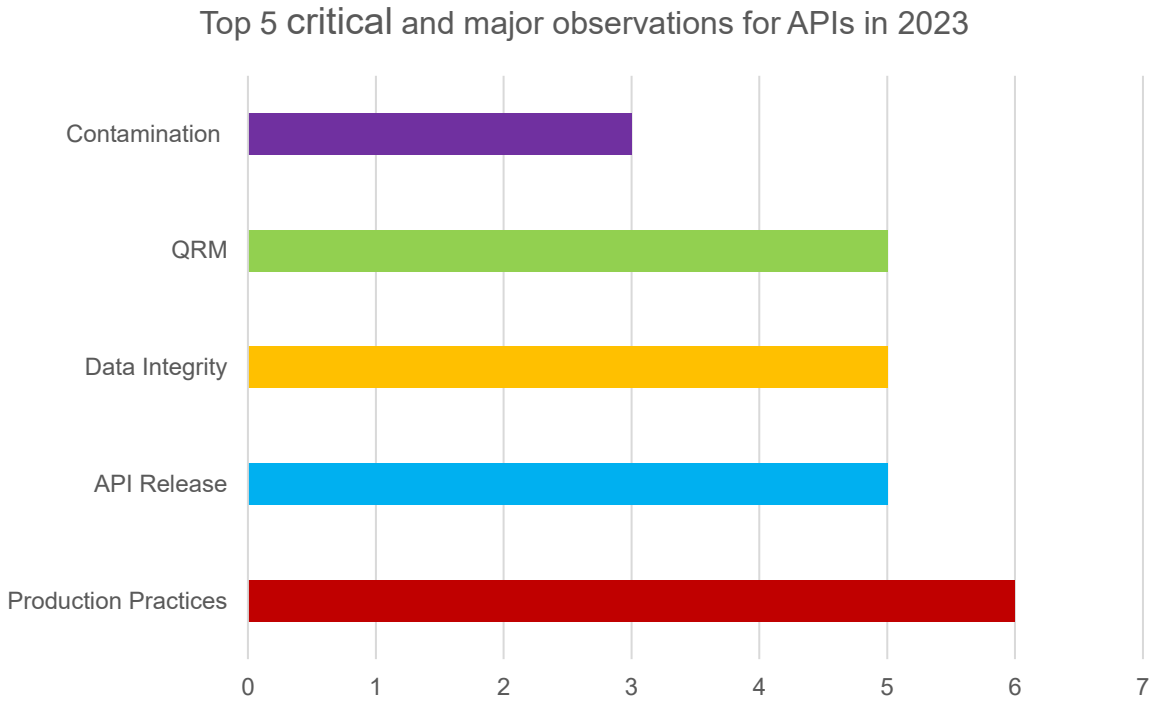
a. No written policy was available on data integrity which inferred that senior management was not accountable for the implementation of systems and procedures to minimize the potential risk to data integrity and to identify the residual risk using risk management principles.
b. Since senior management was not responsible for the establishment, implementation, and control of an effective data governance system, data governance did not ensure the application of ALCOA+ principles.
c. No data integrity risk assessment (DIRA) was carried out to identify and assess areas of risk.
d. Upon review of the access privileges on the Empower 3 system, it was noted that 7 user types were identified against the 4 user types described in the SOP.
e. It was also noted that not all audit trail functions were enabled.

The material and personnel flow at the dispensary as well as its design and construction were inadequate and could lead to contamination or cross-contamination. More specifically:

a. There were no material and personnel airlocks for entry and exit at the dispensary.
b. The same entry and exit doors were used for personnel and material
c. There was no door interlocking system. Entry and exit doors could be opened simultaneously.
d. The differential pressure between the dispensary and adjacent rooms was not monitored and the differential pressure cascade was not ensured. DP gauges in the dispensary were measuring DP between the dispensary and the external environment.

Critical and Major Observations for APIs 2022-2023





Number of inspections in 2023 is not finalized

Examples of Critical and Major Observations - API

Production practices were deficient in that:

a. The dust generation rooms for drying, milling and sieving operation in Workshop X were not equipped with any dust extraction system

b. The two dryers used for the API Y were connected by horizontal water pipes used for cleaning purposes. The potential risk of water remaining in the pipes was not addressed and controlled.

c. The three crystallization tanks in Grade D area, were connected by a common horizontal pipe, the potential contamination/cross contamination risk for materials remaining in the shared pipe were not assessed and mitigated.

d. Several tanks used for spare parts washing and cleaning purpose were not equipped with a draining system.

The following issues were identified regarding product release:

a. The checklist used for batch approval by QA included only two tick boxes (N/A vs Verified) per section checked. There was no tick box or field to report and comment on open investigations, deviations, or OOS results

b. The checklist did not include a section on evaluation of on-going changes affecting the batch/product

c. The same checklist could be used to document the release of several batches of the same product. This approach was not justified since reporting details for each batch could not be captured in one checklist

d. API batches intended for the local market were released by the authorized person/ legal pharmacist. Intermediates and finished product batches intended for overseas markets were released by the QA Head. The qualifications of these persons did not align with their job descriptions.

Summary

- Quality Risk Management and risk-based approach 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.
- Data Integrity and Contamination identified as key issues in FPP inspections
- Product Release and Production Practices identified as key issues in API inspections
- Most of the manufacturing sites (APIs, FPPs) are located in India and China;
- Encouraging to see manufacturers from developing countries coming forward