No.10 October 2023

ORANGE Letter

< Rapid announcement of Inspectional Observations >

* *Observed Regulatory Attention / Notification of GMP Elements*

Communication within the Organization (From the Manufacturing Floor to Management)

≪ Related GMP Ministerial Ordinance** Clause: Article 3-3 ≫

** GMP Ministerial Ordinance: Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (MHLW Ministerial Ordinance No. 179 dated December 24, 2004)

Observation

The actual conditions on the manufacturing floor were not accurately reported.

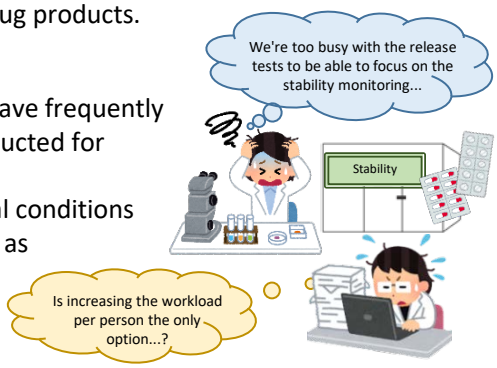
＜Background＞

- The GMP Ministerial Ordinance stipulates the following requirements for the pharmaceutical quality system (PQS):
  - ① To establish an effective PQS.
  - ② To allocate the necessary resources[1)] to establish the Quality Policy, which serves as the fundamental policy for ensuring product quality, and to achieve the Quality Objectives established at the manufacturing site based on the policy.
  - ③ To periodically review the PQS and take necessary actions based on the results.
- The manufacturing site manufactures more than 50 non-sterile drug products.

1) refers to those to be utilized for manufacturing control and quality control at the manufacturing site, such as individual knowledge and skill, technique, equipment, etc.

＜Observed situation＞

- Due to chronic staff shortages, delays in the stability monitoring have frequently occurred. In addition, product quality reviews have not been conducted for more than three years for over 30 products.
- The responsible manufacturing manager failed to report the actual conditions to management. As a result, fundamental corrective actions, such as increasing staffing levels and reviewing workload distribution, were not implemented, and the PQS has continuously failed to function effectively over an extended period.



＜Possible problems and risks＞

- When information is not properly communicated from the manufacturing floor to management, indicating that the PQS is not functioning effectively, responses to identified issues may be delayed. Consequently, even in the event of significant product quality issues, there is a risk of delayed detection, inadequate corrective actions, and the release of products that do not meet quality requirements.

（observed at a drug product manufacturing site in Japan）

Check Points

- ☐ Is the workload concentrated on specific individuals, leading to delays in required activities or compromising the PQS?
- ☐ Has the organization established a system for appropriate personnel allocation and work efficiency, ensuring that no undue burden is placed on the manufacturing floor?
- ☐ Are the conditions at the manufacturing site, identified issues, and proposed improvement measures appropriately communicated to management through management review and other measures?

Are the actual conditions at the manufacturing floor being reported to management?

- ✓ It is important to engage in proactive communication with management by providing necessary input from the manufacturing site in a timely manner. A culture should be fostered in which the actual conditions on the shop floor—including both positive and negative aspects—can be reported openly and accurately.
- ✓ Urgent issues should be escalated immediately, while other issues should be prioritized based on their criticality. A structured mechanism should be established—led by manufacturing management and the quality unit—to ensure that such information is consistently and reliably reported to management, for example through management reviews.
- ✓ In addition, the PQS should be routinely monitored to ensure that it is functioning effectively. If the manufacturing site can proactively propose improvements to management, this is expected to shorten the time required for problem resolution.