Rapid announcement of inspectional observations

< ORANGE* Letter >

Pharmaceuticals and Medical Devices Agency

** Observed Regulatory Attention / Notification of GMP Elements*

Improper recording

<< Related GMP Ministerial Ordinance Clause: Article 10, items 3 and 4 >>**

** 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 Records were not contemporaneous

< Background >

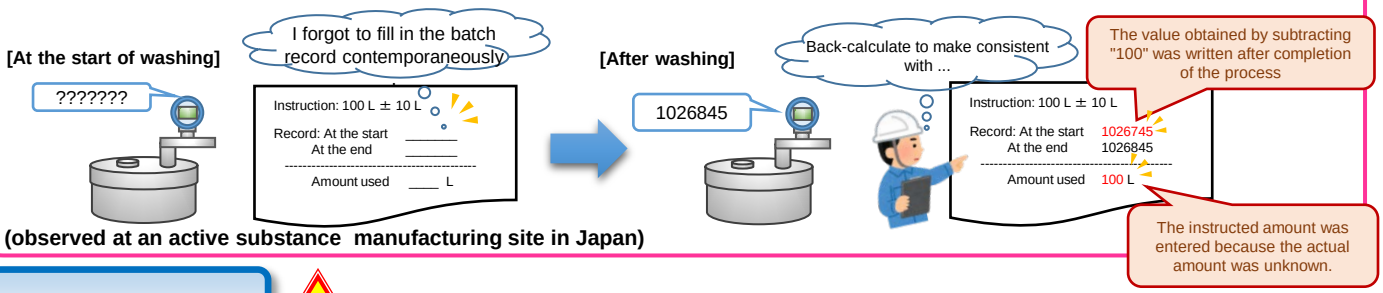
- GMP Ministerial Ordinance provides that manufacturing operations should be performed according to manufacturing instructions and that records should be retained.
- The manufacturing instruction of the manufacturing site for drug substance crystal washing process requires confirmation and recording that the actually used washing solvent complies with the instructed amount.
- The manufacturing instruction provides that the actual amount used should be calculated by subtracting the "value at the start of washing" from the "value after washing" using the integrating flowmeter.
- The instructed amount of washing solvent can be automatically charged in using a metering flowmeter.

< Actually observed situation >

- At the start of the washing process, the operator forgot to check the display of the integrating flowmeter and failed to document it in the manufacturing record.
- Since the “displayed value at the start of washing" was not recorded, and it was not possible to calculate the actual amount used, the operator documented the instructed amount as the used amount. In addition, the operator computed and documented the “value at the start of washing” based on the instructed amount.
- The facts that the “value at the start of washing” was not checked nor recorded, and that the recorded value was calculated from the instructed amount, were not reported to the responsible person, nor they were recorded in the manufacturing record.

< Possible problem and risk >

- Records that do not reflect actual operations cannot assure that the products are manufactured using the established manufacturing methods, and there is a risk of having a critical impact on the product quality.
- In the case of a quality defect, there is a risk that adequate root cause investigation cannot be conducted.



(observed at an active substance manufacturing site in Japan)

Check point

- ☐ Is the work environment transparent and open enough to reporting human errors honestly?
- ☐ Is there a system in place to handle operations differ from the instructions as deviation?
- ☐ Have the rules for correcting/adding records been appropriately specified?

Free communication of mistakes is the first step to improve the quality system!

- ✓ The basics of GMP is to record truthful representation of facts. It is falsification to enter plausible record when some mistakes occur.
- ✓ If an improper record is found, not only will the credibility of the record itself be lost, but also the credibility of all records at the manufacturing site.
- ✓ Even if individual event has a low quality risk, they can lead to major deficiencies that have a significant impact on quality when accumulated to a systemic failure.
- ✓ Instead of blaming the mistakes themselves, it is important to build a system and foster a corporate culture that encourages proper identification, and root cause investigation of issues, and prevention of their recurrence!