Rapid announcement of inspectional observations

< ORANGE* Letter >

Pharmaceuticals and Medical Devices Agency

* *Observed Regulatory Attention / Notification of GMP Elements*

Improper modification of records to align with Instructions

<< 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 modified to align with instructions.

< Background >

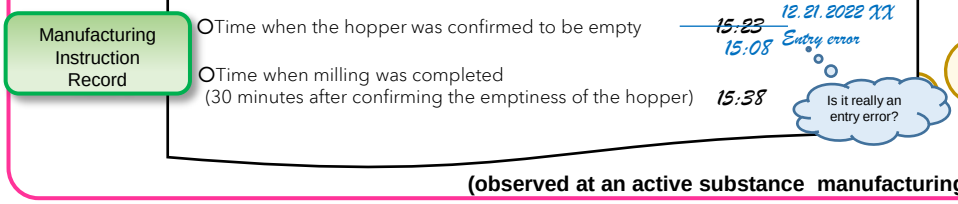
- GMP Ministerial Ordinance provides that manufacturing operations should be performed according to manufacturing instructions and that records should be retained.
- The manufacturing instruction of the manufacturing site for the milling process of the drug substance specifies that the mill should be stopped "30 minutes after" confirming the supply hopper is empty.
- The manufacturing instruction provides that the "time when the hopper was confirmed to be empty" and the "time when milling was completed" should be filled in the manufacturing record of the milling process.

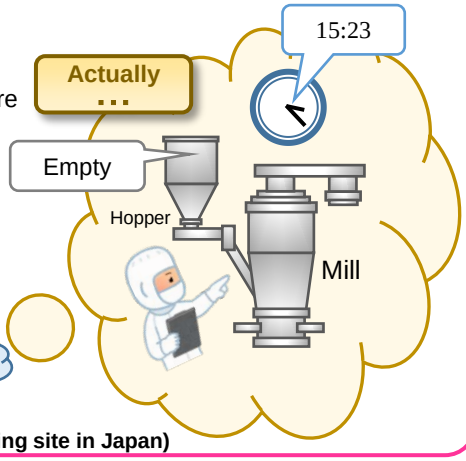
< Actually observed situation >

- An operator recorded the "time when the hopper was confirmed to be empty." Fifteen minutes after that, the operator "mistakenly" stopped the mill and recorded the "time when milling was completed." There are several other products for which the mill is stopped after "15 minutes," and the operator was confused with these operations.
- The operator noticed the deviation from manufacturing instructions, and crossed out the "time when the hopper was confirmed to be empty" entering a false reason of "entry error" and changed it to "30 minutes" before the "time when milling was completed."
- Similar inappropriate changes were also made for other lots; however, the responsible person did not detect any of them.

< Possible problem and risk >

- If there is a discrepancy between the instructions and the actual operations, there is no guarantee that the product is manufactured according to the specified manufacturing method. This discrepancy poses a significant risk that could impact the product quality.
- In the case of a quality defect, there is a risk that a proper 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 deviations?
- ☐ Have records been reviewed appropriately, including the validity of the reason for correction (whether unnatural correction can be detected)?

Honest reporting of mistakes is the first step to the next improvement activity!

- ✓ The basis of GMP is to truthfully record facts as they are. It is inappropriate to patch up records when 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 events have a low quality risk, they can lead to major deficiencies that have a significant impact on quality when accumulated.
- ✓ Instead of blaming the mistakes themselves, it is important to build a system and foster a corporate culture that encourages proper identification, a root cause investigation, and prevention of recurrence!