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PMDA

ORANGE Letter

< Rapid announcement of Inspectional Observations >

* *Observed Regulatory Attention / Notification of GMP Elements*

Development of a Risk-Based Validation Plan

≪ Related GMP Ministerial Ordinance** Clause: Article 13 ≫

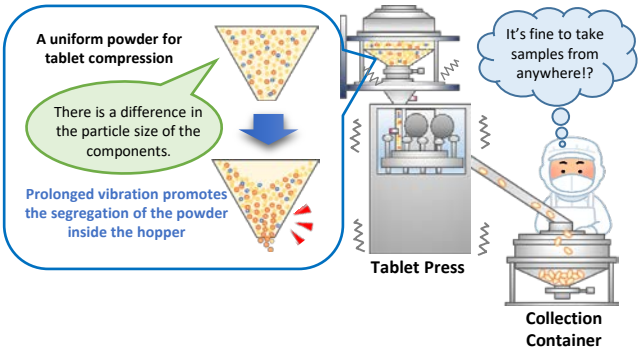
** GMP Ministerial Ordinance: Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (MHLW Ministerial Ordinance No. 179 dated December 24, 2004)

Observation

The risk assessment required during validation was insufficient.

＜Background＞

- GMP regulations require validation, including when initiating the manufacture of a new pharmaceutical product at a manufacturing site. In addition, based on validation results, if improvements in manufacturing management or quality control are deemed necessary, appropriate corrective actions must be taken.
- During commercial production, samples for release testing were taken from any single location within the lot.



＜Observed Situation＞

- During process validation (PV) of the tablet compression process, parameters such as content uniformity and formulation uniformity were evaluated at three stages:
  - the initial stage (start of compression),
  - the mid-stage (at approximately 50% completion), and
  - the final stage (at approximately 90% completion).

  As the acceptance criteria were met at these stages, the lot was concluded to be uniform.
- However, a validation plan based on risks associated with product characteristics, manufacturing process, and equipment features had not been established. Consequently, for the product in question (a low-dose formulation manufactured by direct compression), tablet uniformity was not evaluated during the final phase of compression (from approximately 90% completion to the end), despite the potential for segregation in this stage.

＜ Possible Problems and Risks ＞

- It is unclear whether tablets meeting the required quality are consistently produced the final stage of the compression process.
- Even if the uniformity of the compression blend is ensured, if uniformity of tablets within the lot after compression is not verified, there remains a risk that the quality of the entire lot cannot be assured.

（observed at a drug product manufacturing site in Japan and Overseas）

Check Points

- ☐ Before performing validation, is a risk assessment conducted, taking into account the product formulation, manufacturing process, equipment, and production scale, and are factors affecting uniformity identified and appropriately evaluated?
- ☐ Is an appropriate sampling plan (including sampling location, frequency, and methods) established to verify lot uniformity?

Have all the factors that may lead to non-uniformity been identified?

- ✓ In the manufacture of tablets, granules, and other powder-based products, factors such as powder characteristics (e.g., particle size and flowability), manufacturing processes, equipment-related factors (e.g., vibration), manufacturing time, production scale, and powder handling (e.g., transfer, feeding, and discharge) may promote segregation.
- ✓ Validation should be performed taking these factors into account. If any factors is found to adversely affect uniformity, it is important to ensure lot uniformity through appropriate measures such as equipment modification, process adjustment, or removal of non-uniform portions.
- ✓ Insufficient verification of lot uniformity may lead to issues such as specification deviations identified during stability monitoring. Reducing the risk of non-uniformity in solid dosage form manufacturing is directly linked to minimizing the risk of post-distribution quality issues requiring regulatory action.