Rapid announcement of inspectional observations

< ORANGE* Letter >

Pharmaceuticals and Medical Devices Agency

** Observed Regulatory Attention / Notification of GMP Elements*

Overlooked risks to the quality of products due to insufficient CAPA

<< Related GMP Ministerial Ordinance Clause: Article 11, Paragraph 1, Item 8 >>**

** 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

Impact of an OOS event on other lots was not evaluated sufficiently.

< Background >

- GMP Ministerial Ordinance requires to investigate the root cause of an out of specification (OOS) test result, and to take necessary corrective action and preventive action (CAPA).
- The OOS management procedures of the manufacturing site requires investigation of the possibility of laboratory errors by the Quality Control Unit upon the occurrence of OOS, and in case of the identification of the laboratory errors, the initial OOS result is invalidated and retest is conducted.

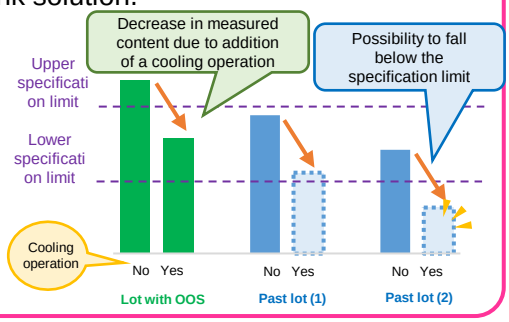
< Actually observed situation >

- An OOS result exceeding the upper limit of the specification was obtained when assay test of active substance X was conducted by titration according to Japanese Pharmacopoeia.
- Omission of cooling after preparing blank solution was identified as the root cause. The blank solution preparation method was changed, and retest was conducted. Then, acceptable result was obtained and the initial result was invalidated. Therefore, the lot was judged to meet the specification. As a corrective action, test procedure was revised to provide cooling step after blank solution preparation.
- Measured values shifted to lower side as the result of adding cooling step to the blank solution preparation, but the manufacturer didn't evaluate the effect of the revised blank solution preparation to the test results of other lots tested without cooling of prepared blank solution.

< Possible problem and risk >

- The test results obtained by the previous test procedure could have been overestimated, and there is a possibility that unidentified OOS results were present in the past.
- There could have been a release of non-complying drug substance from the site which had affected quality of the products.

(observed at an active substance manufacturing site in Japan)



Check Point

- ☐ Did the site identify the root causes of the OOS by the investigation? (Check if the identified causes are truly root causes.)
- ☐ Did the site implement adequate CAPA, based on the identified root causes?
- ☐ Did the site evaluate the impact of OOS on possibly affected lots or products besides the lots subjected to the test?

Appropriate OOS management is the basis of the consistent Quality Assurance of the products in the market.

- ✓ When OOS occurs, conducting a logical cause investigation based on appropriate risk analysis and implementing CAPA are essential. When the OOS relates to the test procedure, consideration should be given to other lots tested by the same test method.
- ✓ If the above steps are inappropriately conducted, lots to be rejected as out of specification are released to the market, and expose the patients at risk.
- ✓ To avoid occurrence of OOS test results, it is important to establish appropriate test procedures at the time of analytical technology transfer to the manufacturing site, taking the factors affecting the testing procedure into consideration, even the test method is established in the pharmacopoeia.