Rapid announcement of Inspectional observations

< ORANGE* Letter >

Pharmaceuticals and Medical Devices Agency

** Observed **R**egulatory **A**ttention / **N**otification of **G**MP **E**lements*

Handling of stability monitoring results

<< Related GMP Ministerial Ordinance Clause: Article 11, Paragraph (2) and Article 21, Paragraph (2) >>**

** 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

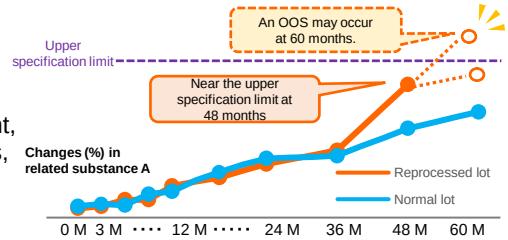
Adverse trends of stability monitoring were overlooked, and no action was taken.

< Background >

- The GMP Ministerial Ordinance stipulates the following requirements regarding stability monitoring.
  - (1) Select the lot and the package form of the drug to be placed in the stability monitoring, based on the results of the assessment of identified risks to the product quality.
  - (2) Select stability test items among the product specifications related to the characteristics of the product vulnerability during storage, or characteristics considered to have an impact on efficacy or safety of the product in the event of out of specification test results.
  - (3) When out of specification test results are obtained or suspected during the stability test, prompt actions should be taken including notification and supplying information necessary for product recall to the marketing authorization holder of the product.
- The manufacturer placed the "reprocessed" lot of the drug substance with a retest period of 5 years into the stability monitoring.
- It is known that the value(related substance A) of impurity tends to increase with time from the beginning.

< Actually observed situation >

- The test result of related substance A reached near the upper limit of the specification at 48 months. Unlike the usual trend, there was a rapid increase in related substance A in the past 12 months.
- The manufacturer neither conducted cause investigation, risk assessment, communication with the marketing authorization holder, nor other actions, because the test results were within the specification.



< Possible problem and risk >

- There is a potential risk that the drug substance does not conform to the specification throughout the assigned re-test period because deterioration of the quality due to the factors besides the temporal change could not be denied.
- There is a risk that the drug products containing out of specification drug substance might be distributed and used by the patients if no actions are taken until OOS events occur.

(observed at foreign drug substance manufacturing site)

Points to be Checked

- ☐ Does the procedure specify not only confirming test results but also evaluating and examining any adverse trends?
- ☐ Is cause investigation conducted when a potential future OOS result is obtained?
- ☐ When adverse trend is detected, is there a system in place to manage it and to promptly notify it to the marketing authorization holder?

Recognizing signs of unusual changes will help protect patients!!

- ✓ Recently, there have been several product recalls due to the deviation of the test results from specifications before the expiration date or retest period.
- ✓ If an adverse trend is observed in a stability monitoring lot, it is necessary to evaluate it's impact on the quality not only of the lot but also of other relevant lots, such as those manufactured at the same time period and those manufactured by the same process. Additionally, it is important to address such situations proactively, that may include checking trends ahead of the planned time schedule of the next test, before an OOS occurs!
- ✓ Such activities contribute to a stable supply of the product to the market by identifying the products which may be affected by the above situation.