Rapid announcement of inspectional observations

< ORANGE* Letter >

Pharmaceuticals and Medical Devices Agency

** Observed Regulatory Attention / Notification of GMP Elements*

Risks associated with handling substances with unknown pharmacological activities and toxicities

<< Related GMP Ministerial Ordinance Clause: Article 9, 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

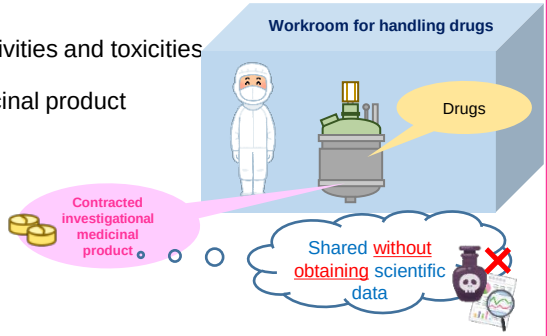
An investigational medicinal product with insufficient knowledge of pharmacological activities and toxicities was manufactured in a room where marketed drugs are manufactured.

< Background >

- In principle, the GMP Ministerial Ordinance prohibits manufacture of substances which are out of the scope of the GMP Ministerial Ordinance in the work room where pharmaceutical product is handled.
- Sharing of work room is accepted only in the following exceptional circumstances: ① limit of residual amount is set based on the scientific data (pharmacological and toxicological evaluation) and ② appropriate cross contamination prevention measures are implemented (verified residue removal processes or other cleaning steps are implemented).
- In this case, the manufacturer is a contract manufacturer, and manufactured contracted investigational medicinal products (investigational medicinal product is classified as a substance outside the scope of GMP Ministerial Ordinance) in the same equipment used for the manufacture of marketed drugs.

< Actually observed situation >

- The manufacturer did not obtain information on the pharmacological activities and toxicities of the investigational medicinal product from the contract giver yet.
- The manufacturer did not set a residual limit of the investigational medicinal product based on a scientific data.



< Possible problem and risk >

- In the absence of the knowledge of toxicity or other safety characteristics of substances sharing same facilities/equipment with a marketed product, there is a risk of contamination of the marketed product with the substances due to the lack of appropriate preventive measures for the cross contamination such as an appropriate setting of the limit for controlling residues.
- There is a risk of health hazards to the patients by the administration of the marketed product contaminated with the substance of the investigational medicinal product with insufficient knowledge of its toxicity.

(observed at an active substance manufacturing site in Japan)

Check Point

- ☐ When a manufacturer is going to introduce a new substance, does the manufacturer have enough information on the characteristics of the substance?
- ☐ Does the manufacturer implement appropriate cross contamination prevention measures? (establishment of cleaning procedures, contaminant-removing processes, etc.)
- ☐ Does the manufacturer understand the characteristics of all the products sharing the work rooms etc., and implement all the necessary measures to sufficiently remove the residues?

Be aware, that the uncontrolled risk may ultimately place the patients at risk!!

- ✓ Even in the case of contract manufacture, it is essential to take responsibilities for the efficacy, safety and quality of the product released from their site.
  Risk caused by insufficient information from the contract giver should not be transferred to the patient!
- ✓ It is important to take thorough measures to prevent contamination by unintentional substances.
- ✓ In particular, when work rooms or equipment are shared, it is essential to demonstrate that the risk of carry over of each product is adequately controlled, based on a scientific rationale.