Rapid announcement of Inspectional observations

< ORANGE* Letter >

Pharmaceuticals and Medical Devices Agency

** Observed Regulatory Attention / Notification of GMP Elements*

Environmental monitoring in aseptic processing areas

<< Related GMP Ministerial Ordinance Clause: Article 24, Item (i) >>**

** 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

Contamination risk may be underestimated.

< Background >

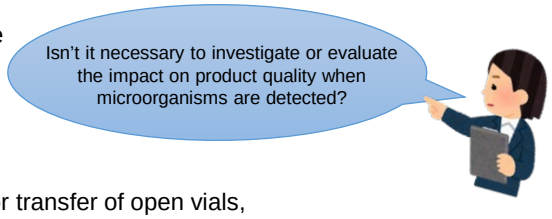
- GMP Ministerial Ordinance stipulates to appropriately control cleanliness of work areas for sterile pharmaceuticals by defining control levels of the work environment, according to the type, dosage form, characteristics and production processes, nature of operations performed in the work areas and so on.
- The manufacturer performs aseptic filling process of vial drug products using filter sterilization in an open clean booth (Grade A zone[Class 100, corresponding to ISO 5]).
- The manufacturer performed microbial monitoring using settle plates and contact plates(equipment and operators) at multiple locations. The measurement results for each monitoring item are evaluated by taking the average of the points in each item.
  The manufacturer determined the maximum permitted microbial contamination level in Grade A zone as "the average of each measurement item should be less than 1 CFU".



Grade A	Point	Results (CFU) Measured value	Mean Value	The maximum limit	Judgment
Settle plate	(1)	0	0.66	<1	Conforms
	(2)	1			
	(3)	1			
Contact plates (equipment)	(1)	0	0.66	<1	Conforms
	(2)	2			
	(3)	0			
Contact plates (operator A)	Left 5 fingers	0	0.5	<1	Conforms
	Right 5 fingers	1			
Contact plates (operator B)	Left 5 fingers	0	0	<1	Conforms
	Right 5 fingers	0			

< Actually observed situation >

- Despite the manufacturer detected microorganisms from multiple monitoring locations in the Grade A zone, no investigation, corrective action, etc. was conducted, because they considered the monitoring results to be within the limit.



< Possible problem and risk >

- If microorganisms are detected in a critical zone, such as lines for transfer of open vials, there is a risk that the sterility of the product cannot be assured because of a possibility of microbial contamination.
- Even though there is a problem in the qualification of equipment or operators, manufacturing may be continued at a high risk of contamination without identifying the cause and without taking appropriate CAPA.

(observed at a sterile product manufacturing site in Japan)

*** PIC/S: Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

Check Point

- ☐ Is there an appropriate evaluation approach to environmental monitoring for aseptic processing? (considering articles, sampling locations, timing and frequency, action level, etc.)
- ☐ Isn't the contamination risk underestimated by simply averaging the values of multiple monitoring locations?
- ☐ Is the impact on product quality evaluated when microorganisms are detected in a Grade A zone?

Environmental monitoring is the key to sterility assurance!

- ✓ It is important to carry out environmental monitoring appropriately, and evaluate the necessity of investigation of any event and its impact on product quality appropriately based on the results of proper environmental monitoring!
- ✓ The revised version of PIC/S*** Annex 1 sets the action limit of microorganisms in Grade A as 'no growth' and also specifies that "any growth of microorganisms in Grade A requires an investigation."
- ✓ In addition to the above, comprehensive activities such as maintenance of equipment and facility, qualification of personnel, validations concerning sterility assurance are directly linked to the development of the contamination control strategy (CCS).