The Symposium on “PIC/S GMP Annex 1 and Relevant GMP Inspections”

Case Studies and Points for Sterile Products

November 16, 2019

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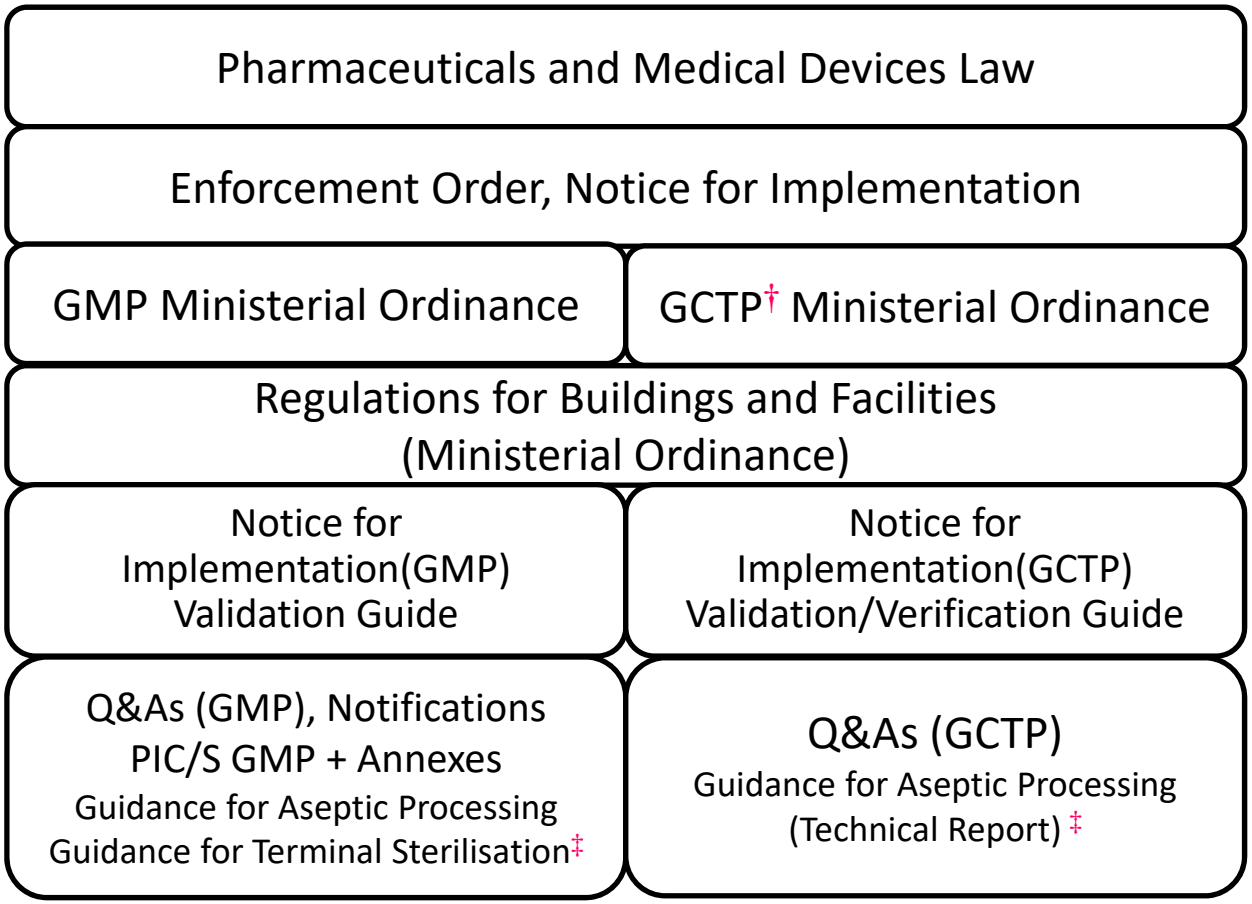
Case Studies and Points for Sterile Products

- The Legal System (related to GMP/ GCTP)
- Examples of Points and Case Studies
  1. Points for aseptic management
  2. Aseptic environment for API filling process
  3. Visual inspection of parenteral products
- Conclusion

Disclaimer:

This presentation is based on the presenter's experience and does not state PMDA's view.

The Legal System (GMP/ GCTP)



† GCTP: Good Gene, Cellular and Tissue-based Products Manufacturing Practice

‡ See the last page of this slide deck: “References”

System Inspection

1. Quality
2. Premises and equipment
3. Materials handling and storage
4. Production
   - i. General (Non-sterile)
   - ii. Sterile
   - iii. Biological
   - iv. Radioactive
5. Packaging and labeling
6. Laboratory control

薬食監麻発０２１６第７号
平成２４年２月１６日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局監視指導・麻薬対策課長

ＧＭＰ調査要領の制定について

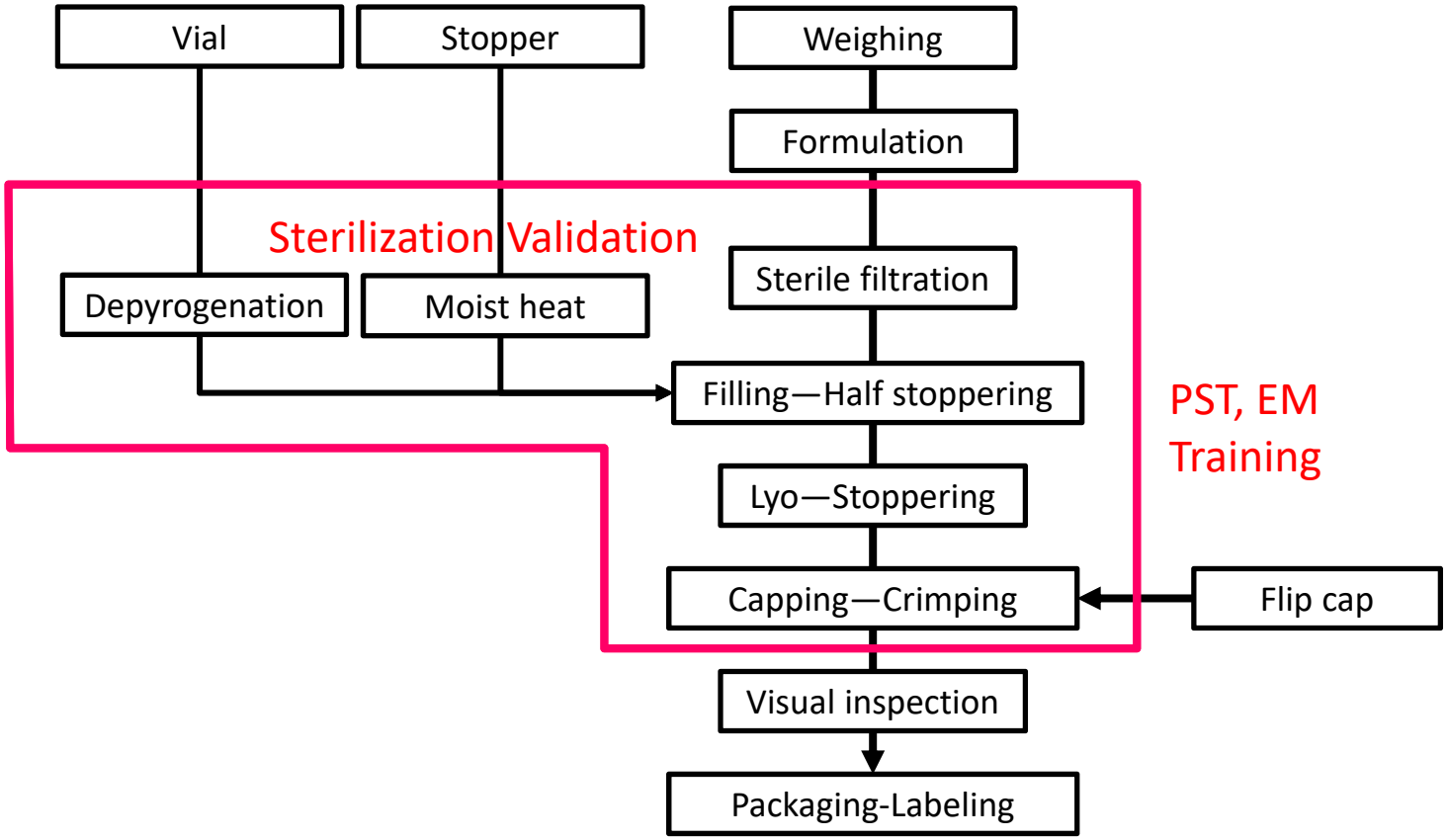
ＧＭＰ調査要領については、「ＧＭＰ／ＱＭＳ調査要領について」（平成１７年１１月３０日付け薬食監麻発第１１３０００２号厚生労働省医薬食品局監視指導・麻薬対策課長通知。以下「ＧＭＰ／ＱＭＳ調査要領通知」という。）により、すべての調査権者間に共通の調査体制、業務の根拠及び業務の要領を示し、国内における調査権者間のＧＭＰ関連業務の標準化を図ってきたところである。

今般、医薬品査察協議会及び医薬品査察協同スキーム（以下、「ＰＩＣ／Ｓ」）にお

- GMP Inspection Manual, No. 0216-7, 16 Feb. 2012

Example-1: Points for Aseptic Management

A case of lyophilized product



Example-1

Points for Aseptic Management-1

PST (Process simulation)	- Whether site follows Annex 1 or JP 17 (see the slide after next) - Worst case scenario (model product or conditions) - Concept for setting intervention (representing routine manufacturing, worst case and non-routine, how to define them in protocols or standard operation procedures) - Frequency of the test (once a half year) - Are all operators (e.g. filling) included at least once a year? - Operators training and qualification (procedure and records) - Subjected process including Lyo (how to modify) - How to handle units which are not incubated - How to investigate if site gets positive results - EM data ⇒ see below
EM (Environment monitoring)	- Cleanliness classification (design concept) - Whether site follows Annex 1 to define criteria for viable and non-viable monitoring - Method and frequency of viable monitoring and data/ trend - How to investigate when positive data obtained: for viable/ non-viable
Equipment design-1	- Air flow (by e.g. smoke studies) at each intervention (routine/ non-routine) of PST

cont. to the next

Example-1

Points for Aseptic Management-2

Equipment design-2	- Capping station ➢ Quality of air in capping station and data ➢ Material handling before capping including 100% check by height sensor or other appropriate methods ➢ Human intervention (121 of Annex 1)
Moist heat	- Heat distribution and penetration studies and results ➢ Loading patterns representing maximum and minimum ➢ Frequency
Depyrogenation Tunnel	- Heat distribution and penetration studies with challenge test and results ➢ Any worst case scenario (e.g. speed) ➢ Frequency
Sterile filter	- Initial validation and re-validation at change (if applicable) ➢ Challenge test protocol and data ➢ Bioburden data - Routine integrity test ➢ Method and rationale for criteria ➢ Procedure when test failure
Gowning	- Cleaning (method and supplier management) - Gowning procedure and operators training/ qualification ⇒ operators behavior

Example-1 (for reference)

Criteria for PST by JP 17

Media Fill Test (Process Simulation), General Information

Table 1 Initial performance qualification

Minimum number of simulations	Number of units filled per simulation	Contaminated units in any of the three simulations	Action
3	< 5000	≧ 1	Investigation, corrective measures, restart validation
3	5000 – 10000	1	Investigation, consideration of repeat of one media fill
		> 1	Investigation, corrective measures, restart validation
3	> 10000	1	Investigation
		> 1	Investigation, corrective measures, restart validation

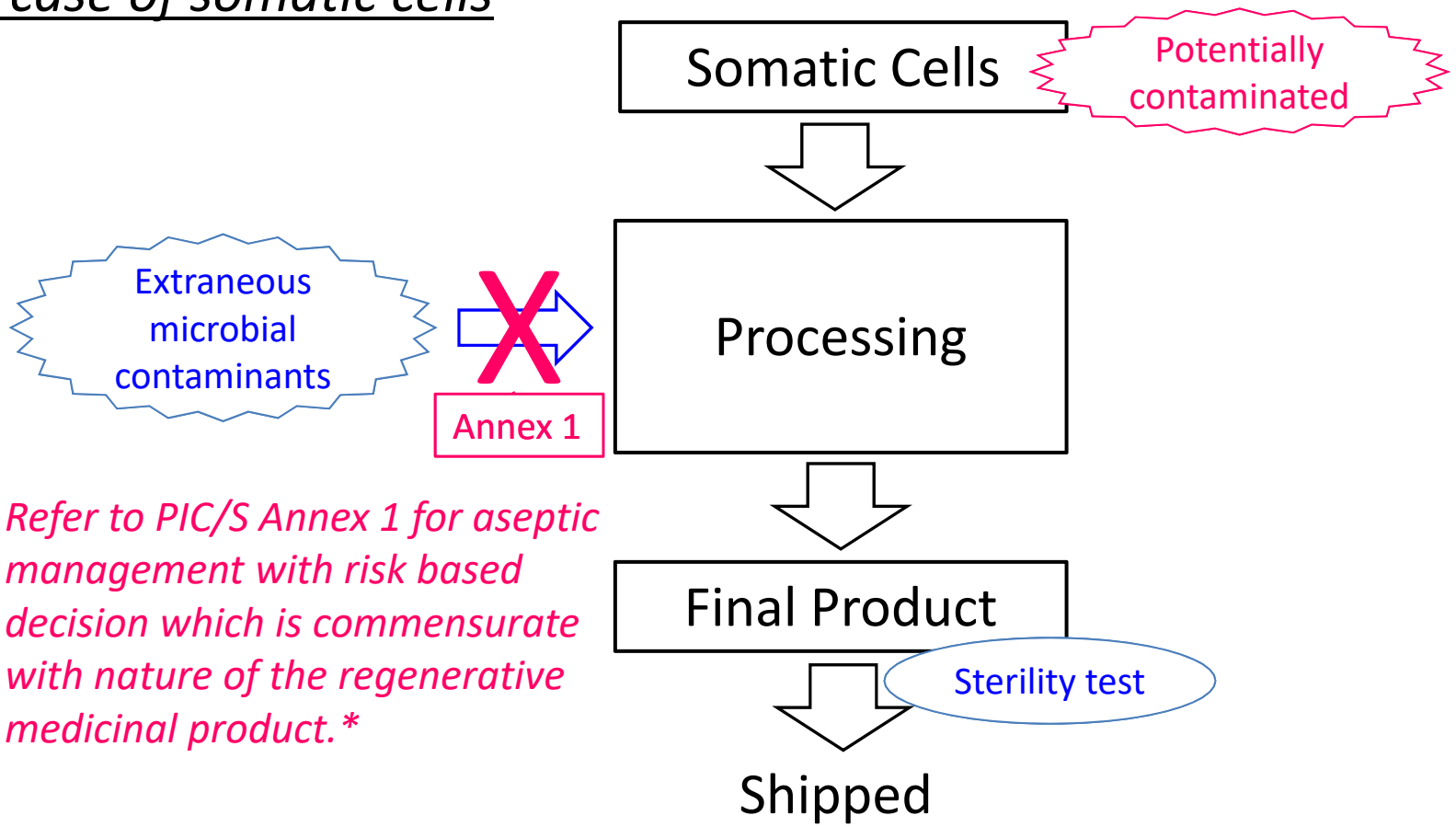
Table 2 Periodic performance requalification

Minimum number of simulations	Number of units filled per simulation	Contaminated units	Action
Every half year	< 5000	1	Investigation, revalidation
	5000 – 10000	1	Investigation, consideration of repeat media fill
		> 1	Investigation, corrective measures, revalidation
	> 10000	1	Investigation
		> 1	Investigation, corrective measures, revalidation

Example-1 (additional)

Aseptic Management on Regenerative Medicinal Product

A case of somatic cells



*Refer to PIC/S Annex 1 for aseptic management with risk based decision which is commensurate with nature of the regenerative medicinal product.**

*PIC/S Annex 2A (Draft) and "A Guidance for Aseptic Manufacturing Process of Regenerative Medicinal Products" (Draft Technical Report)

Example-2: Aseptic Environment

API of small molecule

- Filling process of the API
  - A tank to bottles
  - Aseptic “core”: Grade A supported with horizontal LAF by a portable HEPA unit
  - Filling room (background of the aseptic core): Grade B (air supplied from the ceiling)

Note

- The sterilization and aseptic processing of sterile APIs: should be performed in accordance with GMP guidelines for drug (medicinal) products as defined by local authorities. (Q7)

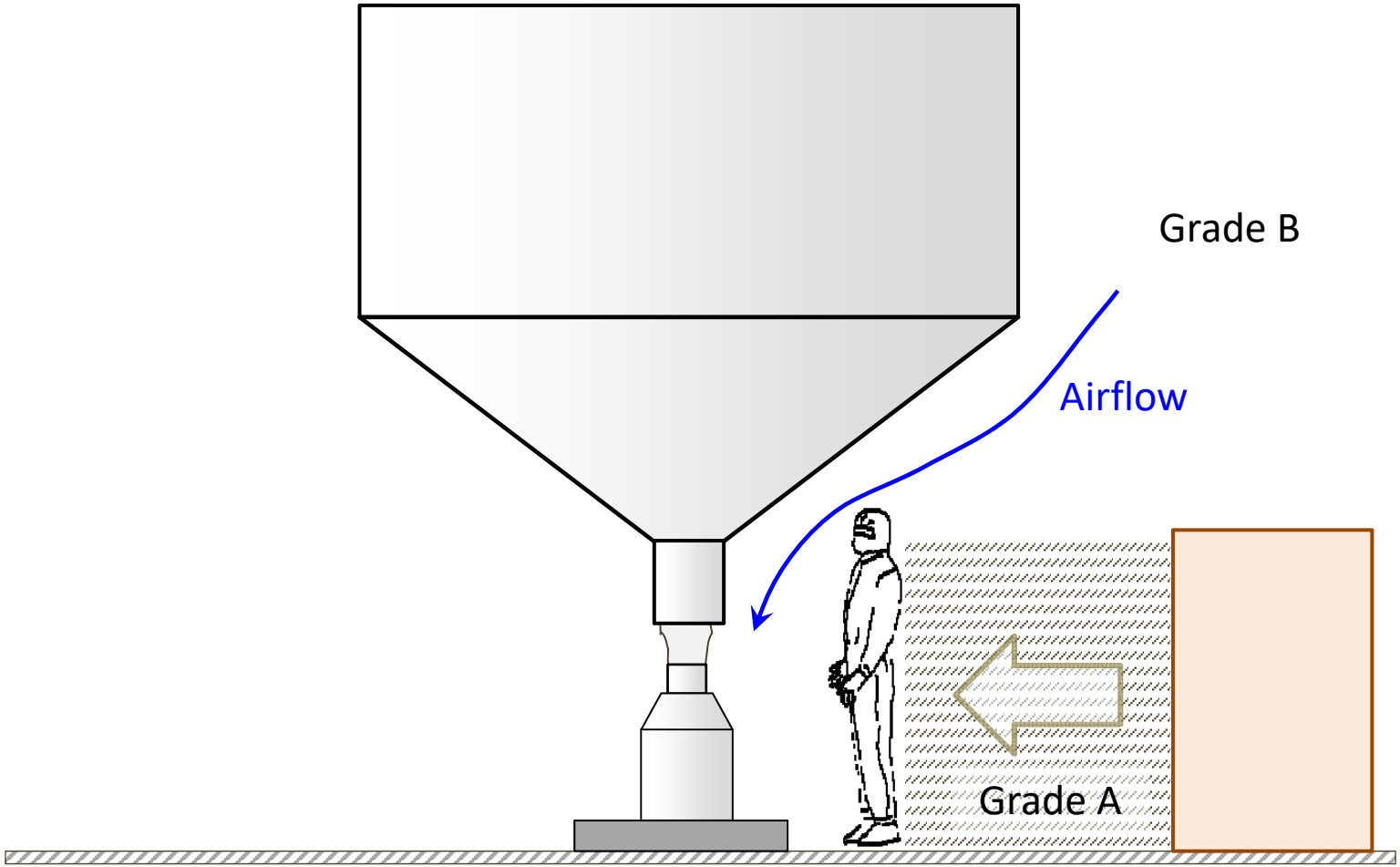
Example-2

Issues

- Findings
  - A smoke study showed that an operator blocked horizontal airflow then the air from ceiling goes to the open bottle via the operator's forehead. (Fig. 1)
  - Position of the portable HEPA filter unit was not clearly defined to ensure Grade A space around the filling port. (Fig. 2)
- CAPA
  - To improve operation procedure including operators' behavior. ⇒ Additional smoke study
  - To define position of the HEPA unit clearly.

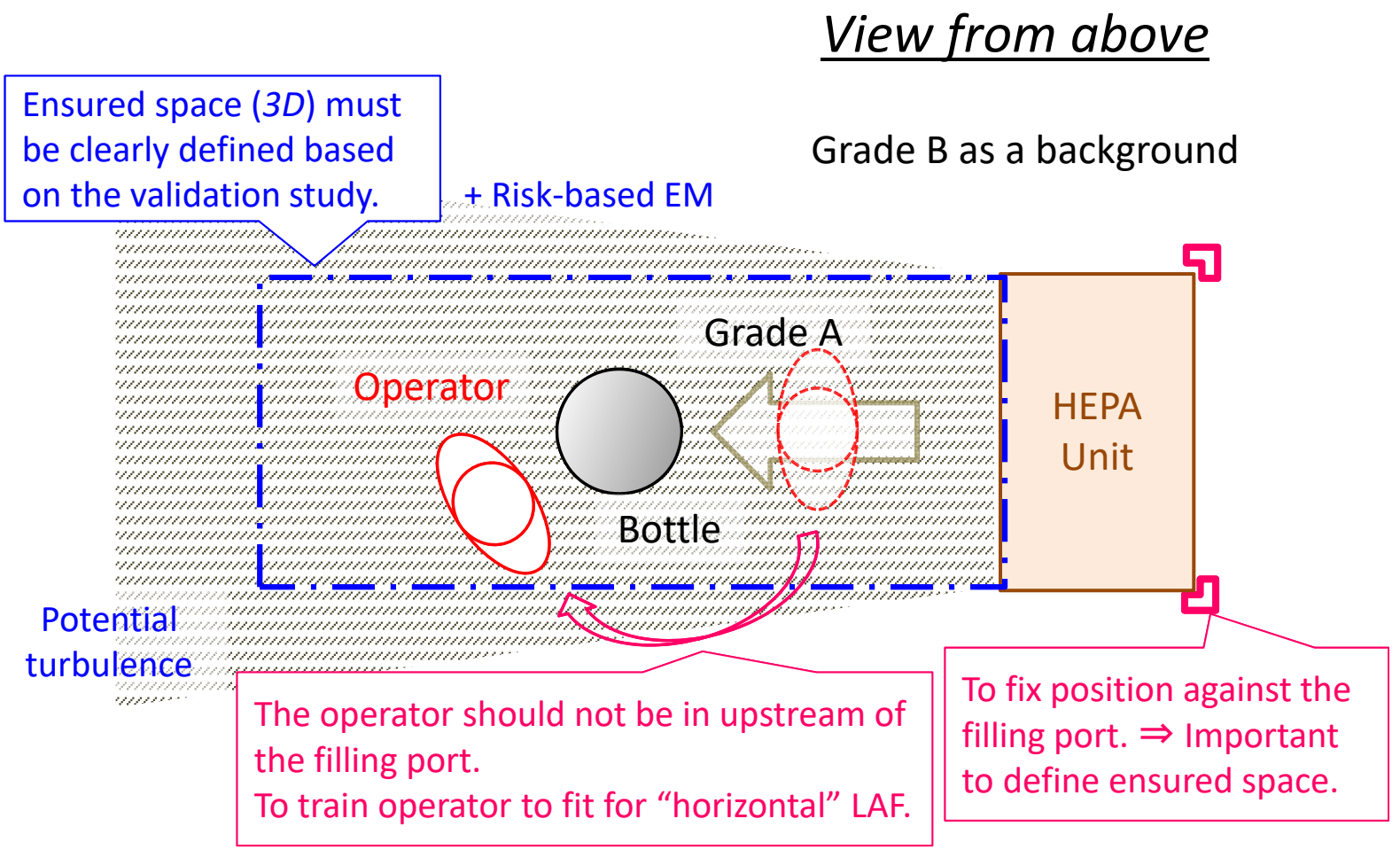
Example-2

Fig. 1



Example-2

Fig. 2



Example-3: Visual Inspection of Parenterals

- Vaccine injectable (lyophilized product)
  - Foreign matters of dark brown ⇒ analyzed result showed heavy metals (lead, tin), approx. 100 um in size
  - Rejects: a little over 0.1% in max per batch
  - Major issue of this case = CAPA prolonged
    - Inspection section got trend of the foreign matters: late in 2017 ⇒ “dark brown matters”
    - It took a few months to raise deviation and analyzing the foreign matters ⇒ “heavy metals”
    - It took totally more than one year to start CAPA (2019～)
  - Major causes
    - Insufficient risk assessment about the contamination.
      Root cause: the matters came from an utensil for Lyo loading
    - No action was initiated according to the OOT procedure at detection of the trend. = insufficient communication between production and quality units
    - Insufficient communication between managers of deviation and CAPA

Example-3

Consultation Document on Annex 1 - Finishing of Sterile Products -

8.26 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. QRM principles should be used for determination of defect classification and criticality. Factors to consider include, but are not limited, to the potential impact to the patient of the defect and the route of administration. Different defect types should be categorized and batch performance analyzed. Batches with unusual levels of defects, when compared to routine defect levels for the process, should lead to investigation and consideration of partial or the whole rejection of the batch concerned. A defect library should be generated and maintained which captures all known defects. The defect library can be used as a training tool for production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling of acceptable containers as it indicates a failure of the original inspection process.

8.27 When inspection is done manually, it should be done under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately validated. Operators performing the inspection should undergo robust visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate sample sets and taking into consideration worst case scenarios (e.g. inspection time, line speed (where the product is transferred to the operator by a conveyor system), component size or fatigue at the end of shift) and should include consideration of eyesight checks. Operator distractions should be removed and frequent breaks of appropriate duration from inspection should be taken.

8.28 Where automated methods of inspection are used, the process should be validated to detect known defects with sensitivity equal to or better than manual inspection methods and the performance of the equipment checked prior to start up and at regular intervals.

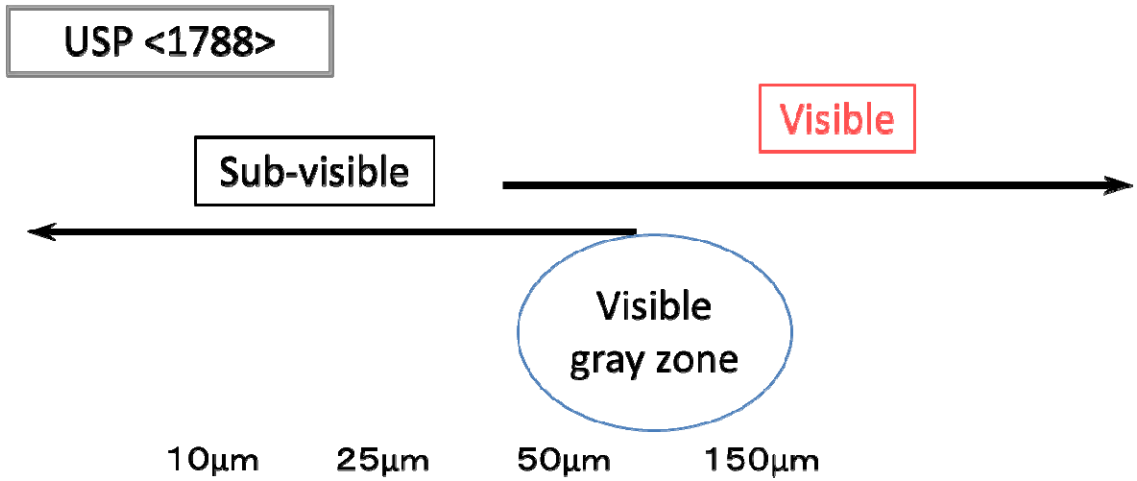
8.29 Results of the inspection should be recorded and defect types and levels trended. Reject rates for the various defect types should also be trended. Investigations should be performed as appropriate to address adverse trends or discovery of new defect types. Impact to product on the market should be assessed as part of this investigation.

Blue: included in current Annex 1 (Clause 124), Red: additional ideas

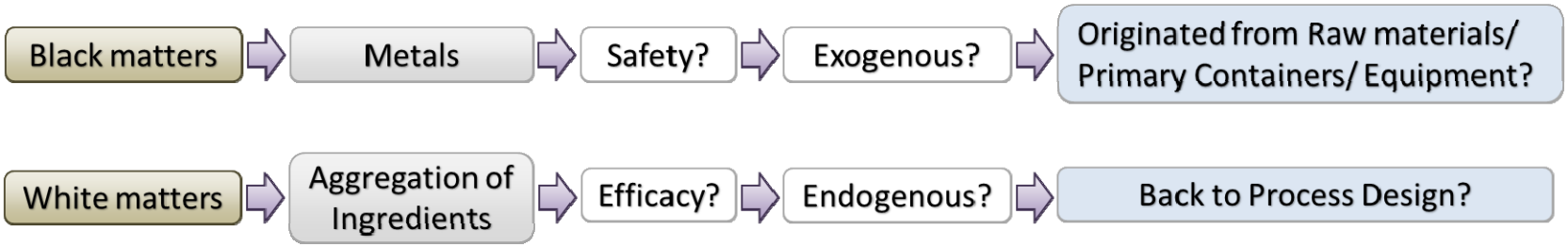
Example-3

Technical Aspects of Foreign Matters in Parenterals

Size:

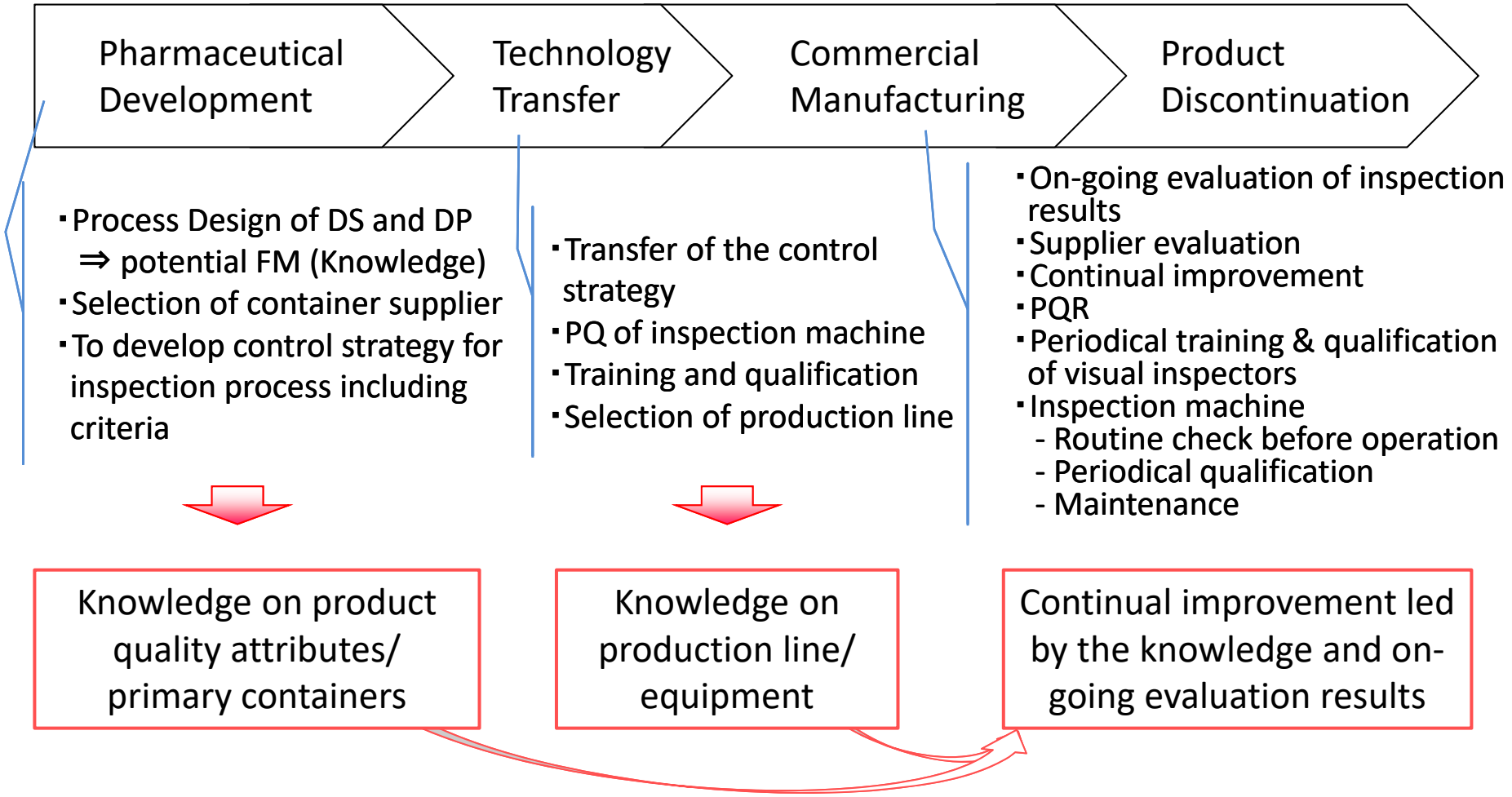


Type/ component ⇒ *An Example of CAPA strategy*



Example-3

Comprehensive Management throughout Product Lifecycle



DS: Drug substance, DP: Drug product, FM: Foreign matters, PQR: Product quality review

Conclusion: General Points for Inspection for Sterile Drugs

Philosophy	- **Consistent aseptic management with systematic control strategy by technical and procedural control measures**
Site Tour	- Premises (Cleanliness, air differential, air-lock, HVAC) - EM (Equipment, data handling system: viable/ non-viable) - Water systems (WFI loop and use points, dead-legs) - Filling line (Isolator/ RABS, Operators' behavior) - Containment - Flow line vs. mix-ups controls
Doc. Review	- Bio trend of WFI etc. - EM trend (viable/ non-viable) - PV (process qualification, periodical re-validation for sterilization) - Periodical PST - Sterile filters (validation: initial/ change, routine integrity test) - Cleaning validation (cross-contamination, microbes, endotoxin, DHT/ CHT) - Visual inspection (PQ/ maintenance of machine, operators qualification and training)

*Major points of inspection for sterile drugs are listed on this slide, but are not limited to these items.

References

- Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing
（無菌操作法による無菌医薬品の製造に関する指針）, 20 Apr. 2011
- Guidance on the Manufacture of Sterile Pharmaceutical Products Produced by Terminal Sterilization
（最終滅菌法による無菌医薬品の製造に関する指針）, 9 Nov. 2012
- Manufacture of Advanced Therapy Medicinal Products for Human Use (Draft), Annex 2A, PIC/S, PS/INF 25/2019
- A Guidance for Aseptic Manufacturing Process of Regenerative Medicinal Products (Draft), 2019（再生医療等製品の無菌製造法に関する指針（案））⇒ 検討中 (under discussion and not yet available)