FDA Form 483: Observations of CCTV Data Review, Sterile Parts Cleaning Not Performed with Electronic Records, Second Person Missing Records of Intervention

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Observation 3

Batch production and control records do not include complete info1mation relating to the production and control of each batch.

1. Production personnel used the "Check List for Verification of Product Contact Parts for Line-xxx to document the xxx stopper xxx bowl (IVFSM-001/S0l 7) and the cap xxx bowl (IVCPM-001/S006) were removed, washed, and xxx before being used in the Grade A xxx for the aseptic filling of xxx Injection batches xxx and xxx Injection batch xxx (all U.S. batches). Review of CCTV showed the stopper bowl and cap bowl were not removed from the xxx during the disassembling step. Production personnel confirmed they had not performed the bowl disassembly, washing, or sterilization between these batches.
2. Per SOP EP3-PR-SOP-048-00. Block xxx Line xxx are cleaned xxx of xxx filling activity. The e-log cleaning records document specific times the xxx were cleaned for xxx of the aseptically filled batches xxx and xxx and xxx Review of CCTV recordings showed none of the xxx were cleaned. Production personnel confirmed they did not clean any of the xxx Grade A xxx associated with these batches.
3. E-log cleaning records documented cleaning activities including mopping disinfection, xxx rinse, and sanitization for the Block xxx Line xxx vial filling & stoppering machine (PN-IVFSM-001), and vial sealing machine (PN-IVCPM-001). Review of CCTV recordings associated with aseptically filled batches xxx and xxx showed most of these cleaning activities were not performed. Production personnel confirmed they did not follow the cleaning SOP for Line xxx cleaning and they made up the time spent for each cleaning activity documented in the e-log.
4. Review of the intervention records showed production personnel did not document all interventions or document interventions accurately. Production personnel inside the aseptic filling room do not have records. Intervention records are supposed to be documented by a production operator located outside of the production room continuously watching live activities from the CCTV camera. Production operators stated they may stop watching to perform weight checks or to take bathroom breaks, with no alternative person recording while they are not present. Review of recordings identified the following batches had interventions that were not recorded:

   Note:

   1. It is okay for the intervention to be recorded by the 2nd operator. As described in the MHRA's DI guide " *The use of scribes to record activity on behalf of another operator can be considered where justified, for example: • The act of contemporaneous recording compromises the product or activity e.g. documenting line interventions by sterile operators.*" It is reasonable to consider using a scribe to record an activity on behalf of another operator, e.g., if the action (recorded at the same time) would damage the product (or activity), e.g., if the production line intervention of a sterile operator is recorded.
   2. The design of (so-called) personnel to view the monitoring records is actually not necessary for (this) to ensure sterility, such as (similarly) having someone monitor the EMS in a certain room.

- First, in terms of design, it is necessary to consider how many people are invested, how many pairs of eyes, how many hands, (when continuous production, it is inevitable that it is necessary to record, when 1 person records, where can the eyes still look at the screen in order to ensure that 360 has no blind views, there are so many cameras, and even need to go to the bathroom), in order to ensure that the data (uninterrupted) is accurately recorded.
- The second is to make sure that how many people are put in to audit this part of the record (really) is recorded accurately. In my daily experience, the more complex the process and the more people involved, the harder it is to ensure that the process is robust and the more likely it is to have problems.

a. xxx batch xxx (US market). There were 24 interventions not recorded. This included xxx new interventions that would have required a product non-conformance investigation. xxx is the maximum permitted times for intervention (C1l), clearing of jammed xxx stoppers. The intervention recorde only documents xxx occurrences, but the intervention occurred approximately 13 more times that were not documented. This would have exceeded the permitted number of interventions and required a product non-conformance investigation.
   Note: Removal of (clogged) rubber stopper is a corrective intervention, (excessive) intervention (maybe) affect the laminar flow environment, close to the limit, and it is best to have some assessment.
b. xxx Injectable Suspension xxx Vial batch xxx (US Market) had 21 interventions that were not recorded. This included six instances of clearing of jammed vials with L xxx PN-GPO05, which is a new intervention that would require a product non-conformance investigation.
c. xxx Injection xxx mg/mL batch xxx and batch xxx (US market) had a total of 97 interventions not recorded in filling and xxx record.
d. xxx Injection USP xxx mg/vial, batches xxx and xxx (US market). had a total of 167 interventions not recorded in filling and xxx record.
e. xxx Injection batch xxx (US market) had 12 interventions that were not recorded.
f. xxx Injection batch xxx (US market) had 7 interventions that were not recorded.

Observation 8

Changes to written procedures are not drafted, reviewed and approved by the appropriate organizational unit.

1. Change Control, APL-FU4-CC-21-0673 for xxx Injection, xxx mg/ xxx mL, implemented visual inspection for color change, in the filled and sealed vials. xxx sterilization. As part of recall investigation, APLUnit 04/INV/651/20-00, for this same product, which included color change from clear to xxx (indicative of xxx degradation), you performed a review of your control sample visual inspection results. Per this review, color change was not observed in any vials until the xxx Yet based on this review, you chose xxx as your inspection time point when reviewing the batch for color change prior to batch release.

The following are examples of complaints submitted for color change from clear to xxx which were received following the implement of the aforementioned change control:

a. APL/FU4/2022-USA-PCM-00141
b. APL/FU4/2022-USA-PCM-00152
c. APL/FU4/2022-USA-PCM-00158

2. Prior to June 30. 2022. CCTV recording review for aseptic manufacturing operations was part of the batch record review and disposition decision for each batch. Change control APL-FU4-CC-22-0128 eliminated this review for each batch with no documented justification · evaluation of historical data, or assessment of the impact of this change.

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Note: This is (probably) a big reason why this company has this 26-page DI observations. Completely abandon 1 effective precaution. No one is looking at the CCTV, (probably) this company originally wanted to ensure sterility, it was to (minimize) the way when people enter and exit the sterile area, all the supervisors used to check the CCTV (based on the above intervention operation is recorded by CCTV, guess that QA estimates rarely go to the sterile area), but once canceled, and there is no reason to cancel this step, it is very dangerous. Is a process that does not trigger (any) quality events, removal. In fact, the correlation is huge. For (any) process change, we should look at it as a whole and evaluate it carefully, not that (a certain leader) wants to change, we will change, it is completely meaningless. To know that there is a process that can be run, and the existence of each step is meaningful.

3. Change control CCP-EP-COA-23-0023 further implemented changes to the CCTV recording process by changing procedure COA-SOP-GEN-026 on May 4. 2023. that reduced the amount of time video recordings of production activities is saved to permit review from xxx to xxx The justification stated: “For better compliance, but no explanation could be provided to explain how this change would result in better compliance.

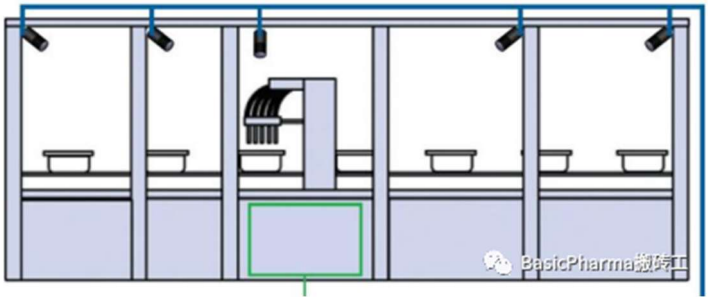
   Note:

   - First, one is the camera: if you want to meet the (aseptic production) high-definition without blind views, the amount of data in 1 hour is close to 1G, at least 10 probes can ensure that there are no blind views from the outside of the A and B level areas, and the data (generated) is big. To be honest, this change of this company is excusable, but it is indeed not easy to do, so it is not impossible to initiate.
   - Second, the assessment is insufficient: in principle, reducing the frequency of retention does not guarantee better compliance. There is no shame in making the original intention clear and evaluating the measures. If you want to increase the frequency and scope of inspections, it is actually desirable.

Topic 1. About CCTV is based on the latest version of EU GMP annex1

EU sterile annex requires monitoring from outside the A and B zones without blind views (see below).
4.17 Facilities should be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.

Since even fully transparent floor-to-ceiling windows may still have blind views for supervision, or (as much as possible) avoid human interference, it is better to be supervised by cameras, and the following Fig 1 is an example of good supervision (see ISPE Remote Observation Technologies in the Pharmaceutical Manufacturing Space).



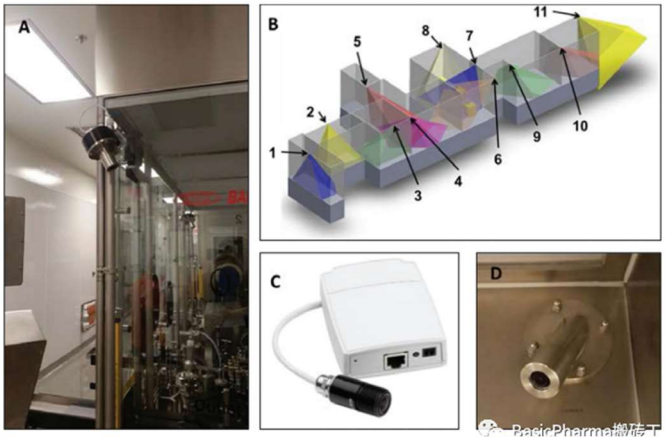


Fig 1. The network connection of the remote visualization camera system is realized on the

business network, completely isolated from the automation residing on the manufacturing network, and part of the design (environment, airflow, etc.)

Topic 2. Does CCTV need to be validated?

As for whether CCTV needs to be validated, it is also a topic worth interesting and discussing, and the GMP control of CCTV of macromolecule/vaccine companies Part1, here cites 2 documents of PDA and ISPE.

2.1. PDA Good Practices for PDA Document and Data Management

Q8: Retention of closed circuit television(CCTV)

Context:

Firms are unclear what is required for retention of closed circuit television (CCTV) footage.

Issue: For how long does a firm needto retain CCTV footage?

Clarification: CCTV footage from cameras that do not serve a GMP purpose, such as security cameras, should be handled in accordance with applicable firm procedures and retention policies. In general, there is not a GMP requirement to use CCTV. If CCTV footage is serving a GMP purpose, such as for batch release, then the footage should be retained as GMP documentation because it is part of the raw data supporting the disposition of the batch. It is not a GMP requirement to record aseptic process simulation/media fills, nor is retention of such videos required, unless the video is used as the primary documentation of a GMP operation (activity) that is not documented by other means (such as significant activities that are not documented on the batch record or control records for the process simulation batch). Please note, however, that it is a CGMP expectation to make a video of a smoke study validation. This video is the raw data supporting the qualification of a controlled environment, and the video should be retained as a GMP record. Aspects of local data privacy requirements also need to be considered in defining local procedures.

2.2. ISPE Remote Observation Technologies in the Pharmaceutical Manufacturing Space

Remote Observation Technologies in the Pharmaceutical Manufacturing Space Page 5
A Concept Paper

4 Compliant Data Handling and Storage

In addition to live streaming to relevant employees across a company's global network, embedded cameras present another opportunity with respect to data storage considerations. Long-term data storage is for the most part not pragmatic when costs are considered; however short-term data storage, perhaps over a matter of days, is eminently feasible. In a manner very similar to contemporary dashboard camera solutions for road vehicles, video could be stored for a short time in an effort to capture adverse events, particularly equipment malfunctions. This could assist enormously in subsequent root-cause investigations, especially if the video coverage of a given line is suitably comprehensive.

FDA 21 CFR Part 11 [1] compliant video storage solutions are technically feasible; however, if the video is intended only for system troubleshooting and is not used for drug product lot release, we believe such a solution can be implemented without being considered an integral part of the validated production platform.

2.3 Conclusion

PDA Opinion: FDA may select (these) records as supporting evidence for GMP observations, but it does not mean that (these) records are GMP records. According to the PDA, expanding the scope of GMP records (unlimited) will put a (large) burden on the quality department to review GMP records, and how to control (these) records is also a difficult problem to solve. Normally, the PDA considers that (this type) security surveillance video is not a GMP requirement, unless the video is (direct) evidence

of (some) GMP operation, and the process of (these) operations can only be recorded by video, for example, the PDA mentions one exception, the smoke study of the HVAC system, if the video is required to prove the gas flow pattern, the video needs to be retained. Correct? Enterprises should establish a good system, use CCTV as a tool, do not over quality, reasonable use (to ensure that they have resources, no additional resources), to ensure product quality and improve the overall quality system. This is what ISPE means, and it is only defined as a valid record when it is defined as a record (for batch release).

3.Summary

The FDA and the new EU GMP annex 1 requirements should be (expected) to converge, after all, the US is a participant in PICS Annex 1 (which is also EU GMP annex 1) (see below, excerpted from ISPE Pharmaceutical Engineering 09/10 issue, 2023 ISPE Aseptic Conference Regulatory Panel 2023 ISPE Aseptic Conference Regulatory Panel).

How will the FDA use Annex 1 in its final version?

Annex 1 is aligned and in harmony with the FDA's guidance for aseptic processing from 2004. The FDA has been involved in the development of the final version of Annex 1 via PIC/S (Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme). The FDA's guidance has different topics and details in it that are additive to Annex 1, but they are compatible. The FDA's guidance was written to last for a long time without being overly prescriptive. We describe the principles that facilitate voluntary compliance by the industry. Although local policies are in general alignment with PIC/S guidelines, there are some aspects that are additive in the EU, Australian, and other PIC/S member local guidelines on various topics.

Source: FDA Form 483: CCTV 數據審核的觀察項，無菌部件清潔未執行卻有電子紀錄，第 2 人對干預記錄缺失 (qq.com)