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GXP Talk: Questions 52 and 53

Jerry Lanese

Timothy J. Fields

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“GXP Talk” discusses issues identified by readers of the journal and provides current good practice to resolve those issues.

We encourage readers to ask questions about compliance issues that are challenging to their firms or to industry. We also encourage readers to respond with opinions as to how to resolve the question or issues presented, identifying current good practice, or sharing with us current good practice in use in your firm. We invite members of regulatory agencies and industry to take part in this initiative.

We will keep the names and contact information of all who write to us confidential and will not publish them unless specifically requested to do so. Questions and responses may be directed to either or both experts at the following addresses:

Jerry Lanese, Ph.D.:jerry@lanesegroup.com

Tim Fields: timfields213@comcast.net

You may also respond to Jerry and Tim via the comments section below.

This article is a continuing series in which representatives of the industry and regulatory agencies have an opportunity to express opinions on current GXP issues.

Thank you for your responses to questions 52 and 53 posed in the Spring 2012 issue of the Journal of GXP Compliance. The questions are repeated below together with responses.

QUESTION 52

Q: In the annual product review, if a lot is manufactured, but not released, do we include the reason?

A: The United States current good manufacturing practices (cGMPs) state that the annual product evaluations should include a representative number of batches, whether approved or rejected, as well as records, where appropriate, associated with the batch (1). Any investigation and the subsequent conclusions are a critical part of the batch related records.

The European Union GMPs and the guidance supporting the Canadian GMPs both have similar wording that state the requirement that the product quality review and annual product quality review (respectively) include a review of all batches that failed to meet specifications and all critical deviations/non-conformances and related investigations (2, 3). These regulations are newer than the US GMPs and should be seriously considered in interpreting what is the “c” in cGMPs

Beyond these stated requirements, the purpose of the annual product review is to “determine the need for changes in drug product specifications or manufacturing or control procedures.” The investigation that led to the decision to not release a batch of product and the organization’s reason for not releasing the batch would be very critical in determining if any changes should be made to the process or controls, and vital for identifying opportunities for improvement.

To summarize, the logic for not releasing a batch should and must be included in the annual product review.

QUESTION 53

Q: Can pharmaceutical firms be forced to change outdated equipment used in manufacturing?

A: The simple answer is no, however, there may be situations that warrant the need to replace outdated equipment used in manufacturing. It is important to always remember the “c” in cGMPs stands for current.

Equipment must be maintained in a good state of repair so as to not adversely affect the product. If the equipment is outdated and is no longer functioning correctly then a regulatory agency could cite this as a GMP observation and force corrective actions to be implemented, such as replacing the equipment.

Equipment must be calibrated to ensure that it provides correct, accurate, and reliable measurements. If the equipment can no longer be calibrated to meet the required precision and accuracy for the measurements that it is intended to monitor, or the measurements are not considered reliable, this could lead to an adverse observation. The resulting corrective action will be to replace the faulty equipment.

Equipment must be cleaned and cleanable. Over time equipment surfaces may become pitted or scratched resulting in product clinging in these areas or microorganisms growing in these pits. These present problems with the ability to adequately clean the equipment. There is also the potential for rust to build up unless the equipment is stainless steel. Inability to adequately clean old equipment due to pitting or the appearance of rust can certainly lead to regulatory observations, which again can result in the corrective action of replacing the equipment.

Equipment must not be reactive, additive, or absorptive so as to affect the product quality. Over time, equipment may begin to leak lubricants or coolants due to wear and tear particularly around the gears or moving parts. Leakage of these fluids into product or product contact areas can become a concern if they impact the product quality, especially the product purity. A regulatory observation may, again, lead to the corrective action of replacing the equipment.

A good preventative maintenance program and calibration program can help maintain the equipment in good working condition and mitigate the risks of using outdated equipment. As long as the equipment continues to function correctly, is not adversely impacting product quality or safety, and is cleanable, then it can continue to be used.

REFERENCES

1. FDA, 211 Code of Federal Regulations 211.180(e), Federal Registrar, available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.180
2. EMA, EU GMP; 1.5
3. “C.02.011; I51”, Good Manufacturing Practices (GMP) Guidelines, Health Canada GXP