Review Article

Quality Audit and Regulatory Compliance with Respect to Instruments-A Review

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ABSTRACT

Auditing is a vital function within a pharmaceutical company nowadays. Quality audit is a review and evaluation of all parts of a quality system with the specific purpose of improving it. Quality audit is the process of systematic examination of a quality system carried out by a quality auditor (or) an audit team. It is the one of the means to examine pharmacy programs and ensures that the procedures and reimbursement mechanisms comply with the contractual and regulatory requirements. It can be an integral part of compliance. In general, compliance means conforming to a rule, such as a specification, policy, standard or law. Regulatory compliance describes goal that the organizations aspire to achieve in their efforts to ensure that they are aware of and take steps to comply with relevant laws, policies, and regulations. Compliance in the pharmaceuticals is to meet the success, not only because it is required by law, but it is considered one that does not allow the mistakes.
INTRODUCTION:
The term ‘audit’ was defined in the 16th Century as “the official examination of the accounts with verification by reference to witness and vouchers”. Gradually, it came to be associated with ‘any systematic investigation or appraisal or procedures or operation for the purpose of determining conformity with prescribed procedures’ the audit in simple terms could be defined as the inspection of a process or a system to ensure that it meets the requirements of its intended use. In the pharmaceutical industry, audits are virtual means for assessing compliance with the established objectives defined in the quality system and thus paving the way for the continuous improvement program by providing feedback to management and the main objective is maintenance of the quality system and to determine whether the processes and products meeting the established parameters and specifications (or) not.[1]

International organization for standardization (ISO) defines the audits as "Systematic, independent and documented process for obtaining audit evidence and evaluating them objectively to determine the degree to which the verification criteria are met".

QUALITY AUDIT:
Quality audit is the process of systematic examination of a quality system carried out by an quality auditor (or) an audit team. It can be an integral part of compliance [2]. Audits are typically performed at predefined time intervals and to ensure that the institution has clearly defined system. The process of the quality system determines whether:

1. The documentation meets the defined quality objective of the organization.
2. The activities performed are in conformity with the documented system.
3. The quality system is effective with respect to documentation and its implementation, in meeting the defined quality objectives.
4. Statutory and safety requirements are being fulfilled [3]

Audit should be carried out to:
1. Determine conformity or non-conformity of quality system elements with specified requirements.
2. Determine the effectiveness of the implemented quality system in meeting the specified quality objective.
3. Afford an opportunity to improve the quality system

(Figure : 1)

Types of Quality Audit: There are three types of quality audits, namely, first party (internal), second party (external) and third party (extrinsic) audits. Let us understand each of these in details:

1) First Party Quality Audit (Internal Audit): when an organization conducts an audit on its own quality system using its own staff / external consultants, the audit is known as first party quality audit or internal quality audit. Important points are: Auditing staff must be trained for conducting this exercise and should not bias against the functional department being audited.

2) Second Party Quality Audit (External Audit): The second party quality audit is performed by the purchasing organization upon the supplier organization. The idea here is to have an assessment of the supplier’s processes in order to have confidence that the supplier would be able to supply goods or services of an agreed quality level on a sustained basis. Important point is these audits can be performed by the trained personnel of the purchasing organization or an outside agency hired by them.

3) Third Party Quality Audit (Extrinsic Audit): This audit is performed by the certification bodies (ISO registered bodies) on the applicant organization seeking such certification. If these, auditors, after conducting the quality audit on the organization with respect to a standard, find the organization to be worthy enough, the certification is granted to the organization. Third party audits normally results in the
disruption of day-to-day activities of the organization being audited during the duration of the audit. Apart from the registered certification bodies, the third part audit may also be conducted by some government departments dealing with environment and pollution, health and safety, atomic energy etc… [4-6].

DEVIANATIONS:
Deviations is a departure from approved procedure(or) established standard or specifications for example: when we have written procedure like Sop, Protocol, BMR etc. and someone work against this then it is called as deviations.

Deviations are divided in to two types:
1. Planned deviation
2. Unplanned deviation

1. Planned deviation: Planned deviations are those deviations from the procedure that are planned and we know before they occur. For example, calibration is not carried out as per schedule due to delay for various reasons then it is a planned deviation.

2. Unplanned deviation: Any deviation which are occurred in an unplanned manner due to system failure or equipment breakdown or manual error shall be termed as unplanned deviation. Unplanned deviations may be critical, major and minor.
   a) Critical deviations: Sops are not followed during analysis.
   b) Major deviations: Permission is not taken from QA, samples wrongly printed with price.
   c) Minor deviations: The materials are received in damaged form.
OUT OF SPECIFICATIONS:
OOS: The test results that fall outside the specifications (or) acceptance criteria. OOS result should be identified either as an mistakes from the laboratory error (or) the mistakes from the manufacturing process.

PROCEDURE FOR “OOS”:
1. When the OOS result is found, analyst should inform laboratory supervisor immediately.
2. Before start the OOS investigation, analyst should inform the quality manager by using the Out of Specification Report to record and number the OOS.
3. Investigation should be conducted by the analyst and laboratory supervisor by using the Out of Specification Check List.
4. Laboratory supervisor assigns an analyst to perform the test.
5. Details of the retest procedure should be written by the analyst or assigned person and then approved by laboratory supervisor.
6. The analyst or assigned person should perform the test by using the approved procedure.
7. The analyst or assigned person prepares the test report for approval by laboratory supervisor.
8. In case that the cause of OOS could be identified (If conclusion can be done), the report should be approved by laboratory supervisor.
9. When the retest has already been performed and the cause of OOS result cannot be identified (If conclusion cannot be done), laboratory supervisor should inform technical management team.
10. Technical management team considers and evaluates the investigating result and all the data for conclusion and report.
When the OOS report is complete, it should be kept in the sample report and the copy should be sent to the quality manager. The OOS will be recorded in the List of Out of Specification by the quality manager.[7]

**CALIBRATION:**
Calibration is the act of ensuring that a method or instrument used in measurement will produce accurate results or not. Calibration is performed by using the primary reference standard.

**Calibration of Instrument is important as:**
To determine the regular performance checks of instruments.
It ensures that the testing performed on the respective instrument give the accurate results and meets the standards of GMP and GLP.

**CALIBRATION FOR GC-MS INSTRUMENT:**
Tuning is the heart of GC/MS operation, where the tuning is done to ensure optimal response and accurate mass to charge ratio. Tuning is the procedure, whereby parameters are changed on a variety of analyzer components in order to know the sensitivity of the system to different parts of the mass spectrum. Typically, this is done by changing the voltage and/or other settings on one or more components of the analyzer.

All quadrupole mass spectrometers are tuned with a compound of known mass spectrum (PFTBA - perfluoro tributyl-amine for our instruments) to insure that the instrument is operational and has a similar response to other instruments. All instruments are tuned prior to use each day batches are initiated. The autotune program adjusts the many parameters of the source, mass filter, and detector to give a consistent response to the tuning compound over the entire mass range, with excellent sensitivity and accurate mass assignment. Thus, the resulting spectra are consistent from instrument to instrument and from day to day. This also allows mass spectral libraries to be used for searching unknown peaks and confirming known peaks. The autotune program uses three ions from the PFTBA spectrum for its tuning: m/z 69, 219 and 502. The program also uses the abundance of the naturally-occurring C13 isotopes at 70, 220, and 503 as a check of tuning.

**Procedure for Auto Tuning:**
1. Double click MSTOP icon in windows. This will load the instrument panel.
2. On upper left pull-down menu, click on “Instrument”.
3. Move down menu and highlight “Perform MS autotune”.
4. In Select Tune Type pop-up box select “Autotune”.

[Note: Autotune is selected from the three options (Autotune, Standard, Quick tune) because it is the most comprehensive tune. Standard tune sets standard response values over the mass range. Quick tune only adjusts EM voltage and peak width; there are no lens corrections made, which is not sufficient for our purposes. Autotune maximizes instrument sensitivity over the entire mass range and makes corrections as needed. This is most suited for our purposes.]
5. Click on OK. Autotune will proceed until completion and print out an autotune report.

**AUTOTUNE ACCEPTANCE CRITERIA:**

1. The m/z 69 is usually the base peak (100%). After a new or freshly cleaned source is installed, the m/z 219 peak may become the base peak for autotune. This is acceptable. If the m/z 219 peak becomes the base peak, the m/z 69 peak must be greater than 70% of the m/z 219 peak.
2. The m/z 219 must be greater than 40% of the m/z 69 peak (except when 219 is the base peak. 3. The m/z 502 must be greater than 2.5% of the m/z 69 peak.

**Note:** Any values greater than the target values of 100%, 40%, 2.5% constitute acceptable ratios.

4. Isotope ratios should be ± 20% of target values (1.08 ± 0.216 for m/z 70, 4.32 ± 0.864 for m/z 220 and 10.09 ± 2.01 for m/z 503

**Additional considerations for a proper tune are:**

a. EM volts should vary no more than ± 150 volts of the previous tune. A larger variation than this indicates that the source may need maintenance.

b. Filament emission should be set at default of 34.6 μA.

c. Electron energy should be set at default of 70 EV.

d. DC polarity should be as the factory recommends, and Ion Polarity should be positive.

e. Fore line pressure should be around 50-60 mTorr for diffusion pump instruments. For turbo pump instruments, turbospeed should be 100%.

f. Ion Focus volts should vary around 80 (60-100). A larger voltage than this could indicate that the source needs maintenance.

Gain, offset, entrance lens, x-ray, mass gain, and mass offset values should vary by no more than 20%. Any variance greater than this could indicate that the source needs maintenance. Criteria 1 through 5 must be met for the tune to be accepted and specimens run. If any of these criteria are not met, the autotune must be repeated. Occasionally, the subsequent tune will be better or the tune will return to previous values. The system is ready to run when the tune is acceptable.

Two consecutive autotune fails require system maintenance before any specimens are run. Criteria a through g are transient values. Changes in these variables greater than those stated above do not necessarily constitute a failed tune. These parameters must be viewed overall and, in the case of extreme changes, a decision on tune acceptability is made. In addition, after the profile scan is run, evaluate the symmetry of the peaks used for the autotune. Any peak splitting could be a sign that the source is in need of cleaning. If peak splitting is more than 10%, the system should not be used until source maintenance and/or cleaning is completed. Consult with the supervisor or a manager if in doubt.

You should run Autotune if any of the following conditions exist:

- It has been 30 days since your last Autotune
- You have changed columns
- You have changed the column flow in your analytical run by more than 10% (i.e. you go from 1.0 mL/min to 1.2 mL/min)
- You have vented the MSD
- You have had the MSD serviced for any reason
- You are having problems passing BFB/DFTPP [8-11]

**REGULATORY COMPLIANCE OF INSTRUMENTS:**

In general, compliance means conforming to a rule, such as a specification, policy, standard or law. Regulatory compliance describes goal that the organizations aspire to achieve in their efforts to ensure that they are aware of and take steps to comply with relevant laws, policies, and regulations. Compliance in the pharmaceuticals is to meet the success, not only because it is required by law, but it is considered one that does not allow the mistakes. [13-15]

**GOOD LABORATORY PRACTICES (GLP):** In general instrument calibration is part of compliance.

**According to the GLP:**

There must be written operating procedure for each instrument.

The instruments should be located in adequate place in a separate room under controlled temperature.

The calibration and maintenance service record must be kept must be done periodically.

The surroundings must be clean [16-17].
21CFR PART 11
According to the 21CFR part 11, a system having audit trail should include the following;
1. Records should be protected maintained in electronic form.
2. Access to the system should be limited to the authorized persons only.
3. The system should record the date and time of used entries and action, modifications and deletion of records in the system. The records should be shown during the review of system [18-20].

CONCLUSION:
Audits should be conducted at planned intervals to evaluate effective implementation and maintenance of the quality system and to determine whether the processes and products meeting the established parameters and specifications (or) not. The Audit should be performed by a well-trained and thoroughly prepared auditor can be highly beneficial by identifying areas for genuine improvement. So, the organizations should follow some steps in order to comply with relevant laws, policies and regulations. Compliance in the pharmaceuticals is to meet the success, not only because it is required by law, but it is considered one that does not allow the mistakes and to maintain the quality of the instruments.

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