Some Typical GMP Issues With Analytical Laboratories

Introduction

[This article was originally written with analytical laboratories in general in mind. It is here as a white paper in the PMF website because a number of the issues are also relevant to microbiology laboratories.]

Over many years of investigating GMP issues related to analytical laboratories, a number of common issues have been noted. The purpose of this white paper is to delineate a number of them. The paper is divided into various sections pertinent to GMP.

Sample Flow/Document Flow, OOS Investigations, Reference Standards

The general impression of sample control and flow to be achieved is that the system is in control. Analytical samples should not be scattered throughout numerous locations in the QC analytical laboratory. The following observations have been made repeatedly:

- The incoming sample area is inadequate in terms of size and capabilities for segregating samples.
- Samples appear to be handled differently based upon whether they are in-process samples, raw materials or finished products. This leads to inconsistent tracking.
- There is no SOP for how to log in samples.
- There are no login:logout books for samples going in and out of the sample cabinet, nor for other designated areas.
- QC login sheets do not indicate when a sample was actually taken by the analytical laboratory people.
- Cases are observed in which paperwork accompanying samples is separated from the samples.
- Determination of which technician will be responsible for what samples is determined during planning meetings. How that information is conveyed to technicians is not clear.
- It is not possible to track physical location of samples from just after receipt in the sample receiving area through the rest of the flow.
- Labels for storage areas in balance room can be easily rubbed off.
- Status labels (e.g. under analysis, completed, etc.) are not on samples.
- It is difficult to determine whether instructions found in analytical protocols are actually carried out with a given bottle of sample. Positive documentation can be

facilitated by including analytical steps (e.g. weigh out 150 mg; dissolve in 1 mL solvent) in data sheets.

- Many samples are located in "personal" drawers. Clearly unless one were to create logbooks for each drawer, this aspect demonstrates lack of sample control.
- The storage area (where retains, etc. are kept) does not have a logbook for all of its contents.
- Data sheets do not clearly separate observations from conclusions. For example, the observation section might contain "sample conforms" when in fact that statement is derived from data.
- Basic GMP observation: Too many blank spaces in quality control documents.
- Justification of sample quantities is not readily apparent. The documentation system is inadequate.
- There is no positive documentation that secondary samples were prepared correctly.
- There is no positive documentation of where samples were from time of receipt until secondary samples were prepared.
- There is no positive documentation of how secondary samples wound up in the actual analysis.
- The versions of SOPs actually used in the analysis (called from protocols which use generic SOP number without reference to specific versions) should be indicated in analytical reports.
- There are many instances where the lack of positive documentation would make an OOS investigation much more difficult.
- Calculations are often missing for derived data (e.g. percentages obtained from weights).
- There are data in the form of tapes (e.g. from balances) that are not readily cross-referenced from the body of the report, or in the reverse direction.
- The protocols for analytical procedures generally indicate what should occur if all is well, but not what to do if all is not well. For example, IR identification protocols indicate what peaks should be present, but they do not specify what to do if extra peaks, fewer peaks, retention time variances, etc. are observed. In general, a protocol should describe what to do if things are as expected, and what to do if they are not.
- There are summary reports packaged with raw data with the assumption that the packaged contents will not become separated. Should they become separated, rejoining the material is difficult due to lack of cross-references.

- Data is transcribed from hardcopies into Excel, but the transcription is not cross-checked by a second person for transcriptional errors.
- The SOP for OOS investigations needs to further emphasize the importance of thinking broadly about potential causes. For example, by thinking broadly about all of the aspects that could impact an analysis (e.g. the efficacy of a glassware washer), the results of the OOS investigation might be very different than if one were to think with tunnel vision.
- Remember to think broadly when a potential OOS occurs. Observed protocols for OOS analysis require the analyst involved plus possibly one other. A more team-oriented approach could be beneficial. For example, contamination issues may be short-circuited if someone thinks in terms of all aspects that can affect an analytical result, including ancillary elements such as glassware cleaning.
- Until an OOS investigation is completed, an analytical result may be an actual OOS result or possibly a lab error, not a genuine OOS. It might be advisable to refer to preliminary OOS results as "potential" OOS results.
- It is unclear how, or if, reference standard expiration dates are determined. Reliance on retests instead of expiration date determinations is evident. If retests are used, they should be the same as those used in the original certification of the standard, not a truncated, non-orthogonal ID only.
- The reference standard certification protocol does not indicate what to do if the material does NOT conform.
- Storage conditions need to be indicated on all vials for all conditions. Room temperature is a storage condition!
- There is the potential for confusion by having both active reference standards and what can be described as inventory control vials in the same storage unit.
- There should be a logbook for reference standards.
- The certification document for reference standards should indicate that the elemental analysis confirms the molecular formula, not the chemical structure.

Method Validation and Transfer, Retains Handling, Reagent and Supplies

- The accuracy parameter should be delineated properly in a validation protocol. There should be no confusion with specificity.
- Available software can perform peak comparisons (e.g. IR standard versus samples) instead of purely visual comparisons.

- Words such as “similar” in the validation protocol beg the question of what constitutes adequately “similar”. Spell this out. For example, is an assay result within 10% of the comparison method result? 20%?

- Add a statement in the validation protocol about what constitutes adequate peak separation.

- Be sure statement of method purpose is specific to the method. For example, if a method is designed to detect the total number of carbonyl functionalities, then say so. Mention could be made for purposes of clarification what a method is NOT intended to do. For example, a method designed to detect the total number of carbonyl groups is not intended to serve as an identification test. The results from such a method could be supportive of a more specific method, but the method itself serves only to detect carbonyl groups.

- Clearly state what is to be accomplished by examination of data as part of linearity assessments. What should an analyst be looking for?

- State what should be done with linear regression results. For example, when looking at y-intercept values, how much difference from 0 is analytically meaningful? Remember that statistical significance does not necessary imply scientific meaningfulness.

- The word “minimum” appears a number of times in various method validation protocols. The term suggests that there may be circumstances when more than the minimum should be used. How does the analyst identify situations where the “minimums” are not adequate?

- Validation reports should cross-reference all supporting data. Reports generated following methods that have undergone validation need to clearly cross-reference the relevant validation reports and their associated data.

- It is important in a validation report to clearly identify conditions under which the validation studies were performed (a portion of intermediate precision and robustness). For example, if all of the validation studies were done in a room with relatively subdued light at no more than 25C, indicate this in the report. Then, should one consider using the method in a cooler or hotter environment, perhaps exposed to bright sunlight, it would be apparent that further validation studies are necessary to prove these alternative conditions would alter results.

- Labels on retains should include storage conditions and expiration dates, quantity and any quantities removed.

- If a protocol discusses a logbook for the retains, all of the columns in the logbook should be described. Some examinations of the retains logbooks show a column or columns with labels that are not described in the protocol. Because the column might include important data such as dates and quantities removed from retains, the use of this column should be described in the protocol.

- Many supplies, such as flask stoppers, beakers, pipettes, etc. are often located in common repositories where it would be simple to inadvertently cross-contaminate a number of such supplies when removing one from the common supply. Dedicated supplies (i.e. supplies for use with only one chemical analysis) would greatly reduce this risk.

Equipment Qualification

- General comments regarding qualification: Consider the worst cases and validate against them. As an example, a glassware washer is considered below.

    - Ensure that ranges for all of the critical cleaning parameters are established.
    - Include length of time glassware can sit with dried material on it.
    - Include worst-case chemicals in terms of cleaning difficulty.
    - Include the maximum amount of these chemicals that can reasonably be expected.
    - Ensure that percent recovery of spiked material meets requirements.
    - Include acceptable time ranges for the various critical steps (e.g., how long must glassware be pre-rinsed in acidified water).
    - Ensure that worst-case glassware washer load patterns are established.
    - Ensure that positive documentation will be prepared by operators providing evidence that the times used, concentrations used, load patterns, etc. have indeed been satisfied.

- It may be necessary to bring on board more staff dedicated to method validation such that all necessary validation ranges can be established for all the necessary validation projects in an acceptable time period.

Stability

- There should be a statistical justification for the number of samples placed in stability program.
- There should be clear descriptions in logbook entries for stability samples.
- Leave no blanks in quality documents!
- There should be no unofficial documents in stability chamber rooms.
- There should be an automatic backup electrical system.
- Calibration labels should indicate what provided dates are for, and who did what (signatures should be accompanied by printed names).
- Many environments capture temperatures via remote temperature reporting probes entered into what may or may not be CFR 11-compliant software. Given the time and expense in collecting such data, ensure that the data are used. Cases have been

observed where operators look at those data once a day and make entries into a logbook as to whether the reported data is as expected, or deviates from expected. Audible alarms were generated if conditions were out of specification for 30 minutes or greater, yet the remote sensors reported conditions every 3 minutes. The concept of mean kinetic temperature tells us that 25 minutes (for example) out of every hour out of specification could be deleterious. Systems should be developed to make better use of the reported data. QA should look at those reported data for trends.

- Finished stability reports should be placed in fireproof cabinets (as should finished QC reports).

Instrument Maintenance/Qualification

- Protocols containing forms should provide complete instructions for filling out the attached forms.
- The qualification program for laboratory instrumentation should be based on an impact assessment approach that should define which kinds of lab equipment needs qualification and which activities must performed (e.g. HPLC are critical instruments which require whole IQ, OQ and PQ).

Analyst Training

- Copies of resumes for each analyst can be placed in training file, not just in HR.
- Much training is done online. Most of this has no evaluation. The trainee just signs electronically that they have read the document. No real assurance that the document has been read with comprehension. There should be a training system in place in which genuine comprehension is assured.
- If PowerPoint presentations are used, they should not be merely read verbatim by the trainer to the trainees. They can be effectively used to induce discussion, not merely to read to the trainees.
- All training should include some form of evaluation with established passing grades. If it is important enough to take time for training, it is important enough to establish adequate comprehension.
- Training should be provided at appropriate times. There is training that should be included as part of on-boarding, and training that should come later when the need arises. Cramming all the training into a tight time frame just to get it out of the way is not effective.
- Recommend that training be done with the use of a checklist approach. This can facilitate training along with provide positive documentation that each required step of the training was provided. This could be along the lines of:

Trainee understands how to attach column to HPLC pump.

Yes _____ No_____

Trainer initials: _____ Date: _____

- Recommend that when a trainee claims that they have read a paper document that the electronic evidence confirm this.
- Situations have been observed where there was a document for each trainee in which the date of initial training (for example, on a particular method) was indicated, followed later by a column indicating the most recent time in which the trainee performed the method. This was used to justify pushing back the retraining beyond the predetermined date. This practice not be followed. If retraining is supposed to occur every two years, ensure that it is done. Other wise, bad habits may creep in, eventually resulting in bad data.