INTRODUCTION

Why Audit?
One of the first questions to be asked before conducting any audit is: Why? This question gives a constructive premise for the auditor who plans and conducts the audit. Quality and compliance audits have different purposes and the answer to the question of “Why?” will define the scope and the type of the audit.

GMP AND QUALITY SYSTEMS AUDIT
The aim of this type of audit is verification of the manufacturer’s quality and compliance systems. One must determine if these systems have been maintained or whether any changes in the management, shifts in the company’s business focus or product spread have created new problems.

Previous Audit’s Corrective Action Plan.
GMP audits will have no real value if the manufacturer and auditor have not agreed to a corrective action plan from the previous audit or have been working on them.

Some of the questions that the auditor would want answered for GMP audits are:

1. Has the manufacturer carried out all the corrective actions noted in the previous audit? If not, why not?
2. How many deviations or investigations have occurred since the corrective actions were implemented?
3. How many employee or process errors have occurred since the last few significant change-controls?
4. How many rejections have occurred? What is the scrap rate?
5. What is the employee turnover rate? Has the company lost any talent base?
6. How are the quality and compliance initiatives viewed within the company? Does it have top management support?
7. Has there been an increase in the workload or the capacity of the company’s production or testing activities?
8. Has there been any regulatory action against the company? How is the company managing it?
9. Has there been any change in ownership of the company?
10. How significant is the business, and what is the management’s attitude toward that business?

During the GMP audit 15-20% of the time has to be allotted for reviewing the corrective actions from the previous audit report.
Defining the roles and responsibilities: Not having a clear agreement on audit objective and role definition will cause several problems during the audit process. Auditor should strive to maintain control during auditing and refrain from going out of bounds.

It should be clearly established up front that the manufacturer is ultimately responsible for the business, its performance and compliance with the laws of the land.

However, it is auditors job to establish clear audit guidelines in the pre-audit letter. Some companies conduct a meeting to discuss these audit objectives and use the minutes of the meeting to plan the audit.

Focus: Maintaining focus during an audit is a challenging task. People tend to go off on tangents, moving to uncharted waters or toward small talk. While some off-tangent conversations are interesting, the auditor must maintain control by keeping the focus on the objectives at hand. Conversely, the auditor may want to spend some time off on a tangent, which may turn out to be an important area of cGMP compliance. In short, auditor must balance time and attention on an area depending on the overall audit objective.

Authority: Occasionally power struggles may arise during the audit. The manufacturer may want to steer auditor in one area, while auditor may want to spend some more time in another. If auditor has a valid reason to produce, auditor should do so politely while explaining reasons to the manufacturer. Conversely, auditor must make sure not to get carried away just because the item was on the checklist or because it is auditor’s area of interest.

Business paradigms: As an auditor, one must keep in mind the company’s business and should audit on the same basis. The auditor should discuss the rules and regulations that are followed for that particular field of manufacturing establishment.

Planning an Audit
To put it simply, no auditor wants to be at manufacturer’s site for any more time than is needed to complete the objectives of the audit. A lack of planning will result in wasted time and efforts on both sides. For example, if there are documents that the auditor can review ahead of time and if the manufacturer is willing to supply the same, auditor should try to review them at office, rather than spend time doing so during the audit.

Other things to plan are gathering and previewing the summary of all the problems encountered since the last audit. For example, auditor should try to review following items:

- Previous audit reports and the manufacturer’s response;
- A list of rejected lots and the investigations associated with them;
- All laboratory Out Of Specification (OOS) notices since the last audit. Auditor should include OOS notices related to facilities and processes, not just the batch-specific testing;
Suggestions for Corrective Actions

GMP & Quality System Audit with focus on reviewing Laboratory Records

- Change-Control summary;
- Adverse Event reports;
- Stability Failure reports;
- Scrap and waste reports;
- Last two FDA-483s or Warning Letters, if applicable;

Typically, the last few years’ annual product reports can supply the information listed above, however, it is usually beneficial to review the most current events.

Scheduling the audit is another critical area. The schedule should leave auditor enough time to conduct the audit without becoming a burden on the manufacturer. One should try to provide at least a month’s notice so that the manufacturer is aware of the audit schedule and its objectives. A month gives the manufacturer enough time to plan for the audit and schedule the right personnel to be available for the auditor when the auditor gets there. (Another school of thought might say that too much advance notice allows the manufacturer to superficially “straighten out” the site. However, a good audit team should be capable of checking for systematic improvements and ignoring the superficial ones.)

Pre-Audit Assessment
Pre-Audit assessment is very critical in determining the audit’s overall purpose and scope. A review of all the items listed in the planning section will offer a good understanding of the product’s quality and compliance. Auditor must be careful not to form any strong opinions about the manufacturer during this pre-assessment. Sometimes those biases, good or bad, will defeat the purpose of the audit. In short, the pre-audit assessment while critical in planning, it is not meant to replace the audit.

Audit Standards
An appropriate set of standards is critical to conduct an effective audit. Use of the wrong standards or standards defined by vague and subjective interpretations can cause potentially explosive situations during an audit.

A typical list of standards include:
- Published government standards (e.g., Code of Federal Regulations);
- Corporate policy or requirements;
- Specifications;
- Industry standards and guidelines.

If the industry is manufacturing a drug, one has to use the drug standard. One should not impose medical device standards. Sometimes, auditor’s interpretation of standards may be necessary for particular product or because of company policy, but it may be more than what the industry is legally required to do. In these instances, identification of those requirements that are related has to be clarified to the industry, with an acknowledgement that the auditor is asking them for more than the industry is required to do.

Agenda
Auditor’s agenda is the blueprint of the audit objectives. It should include all the details
that the manufacturer should know to help prepare for the audit. The items in the agenda should be specific with timeframes assigned so that the manufacturer may have the responsible person in that area available.

Where possible, auditor should avoid going off-site for lunch, unless the audit team will use that time to discuss observations confidentially. Also, audits on Fridays and Mondays can be avoided. Typically those are the days when people take off, so important personnel may be absent. Additionally, Mondays are usually very hectic for most businesses. The manufacturer may need some time on Monday to get some of its real work done. Auditor is a guest of the manufacturer and the audit places a significant amount of strain on the manufacturer’s resources, so one has to choose the agenda items wisely.

**Selecting an Audit Team**

A typical audit team usually contains two to three people. More members would be cumbersome for both the auditor and the manufacturer to manage. The team must have a lead person. A lead is not necessarily the most senior person, however; it is more important that the lead has the skills to steer the audit towards its objective and organize all the activities.

Usually, the team will include a technical person, a compliance person and a quality systems person. The collective experience of the team must be complementary, not repetitive. A strong lab person can complement the skills of a strong technical person and a quality systems person. The personalities of the team members are very important. One must avoid people with combative and argumentative personalities in the team. Of course, this is not to say that one has to avoid “pleasantly persistent” people.

**Pre-audit Planning**

A pre-audit meeting may be necessary if the auditor thinks that manufacturer needs it. Usually this meeting is conducted a week in advance to confirm audit dates and objectives. A telephone conference is usually sufficient. The key objective of this meeting is to let the manufacturer know of any modification in audit objectives or request any items that the manufacturer could send ahead of time to make the audit run more efficiently.

**Conducting an Audit**

Audit roles and code of conduct: Etymologically, the word audit is related to the word listen. An auditor’s key role is to ask open-ended questions and listen to the response. Review of procedures, data and verification of actual activities at the workstations should supplement this “listening.” An audit is not meant to be unpleasant for either the auditor or the manufacturer. There is no reason why the audit can’t be a friendly, pleasant and effective activity. One need not carry an impassive or solemn face all the time during the audit. At the same time, audit is not a frivolously everyday activity. It should have the intensity it deserves but no more. At all costs, auditor must avoid turning the audit into an interrogation (or, worse yet, an inquisition).
One must remember that the auditor is representing his/her sponsor company during the audit and, as such, must follow all the rules that his/her company dictates in a professional work environment. Auditor must avoid participating in off-color jokes or being overly casual, while respecting the manufacturer’s property and always asking for permission before touching anything at the site. If the manufacturer has any visitor policy, auditor must observe it to the letter.

Auditor Approaches: Pros and Cons
There are a couple of approaches to conducting an audit. One may conduct a standard checklist audit or use the checklist as a reference document only. Checklists sure will have more advantages, but in the long run they tend to restrict the auditor to the items in the list. An effective auditor makes sure that all the critical areas are covered at least once, and is keenly aware of areas that may not be included in the checklist.

Checklist – Eight Major Areas
Whether auditor use a checklist or not, the following areas should be covered. Please note that this list is not all-inclusive and should not be treated as such.

Personnel & Organization:
People make an organization. Both auditor and manufacturer are dependent on their skills, knowledge and training. Some of the questions an auditor should ask about personnel are:

1. Do they have adequate personnel?
2. How do they hire their people?
3. Do they have a steady supply of employees?
4. Do they use temporary employees? If so, what is their role?
5. What sort of training (cGMP, GLP and job-specific) is provided? Is the training documented?
6. Can they read, write and speak the language they must use to do their job with?
7. How do they verify the personnel’s basic literacy in the language used?
8. Who has the authority to accept or reject the product?

Manufacturing and Packaging
1. Does the manufacturer have a master batch record system, which details all the critical manufacturing and packaging processes?
2. Does the manufacturer have adequate equipment of appropriate design? Is the equipment in a good state of repair?
3. Are the manufacturing and packaging areas of appropriate design and do they have adequate space?
4. Is the equipment maintained regularly?
5. Does the major equipment have a usage, cleaning and maintenance log?
6. Are the personnel in the manufacturing area following cGMPs?
7. Is the area classification, such as specific air pressures and air exchanges, monitored and maintained?
8. Are the gauges and instruments used to monitor the manufacturing and equipment process calibrated and traceable to NIST?
9. Is the equipment easy to clean?
10. Is there an overall system to report mechanical or process failures? Is QA involved in decision making?

Quality Control
1. Is the quality control unit independent of manufacturing operations?
2. Are all the lab procedures validated where applicable?
3. Is there an adequate system of sampling, testing and reporting test results?
4. What is the process of handing out of specification (OOS) reports?
5. Is the laboratory equipment suitable for the testing? Is it calibrated and in a good state of repair?
6. Are the laboratory systems (e.g. information system) validated?
7. Are the personnel qualified or certified before they perform a test?
8. Are the reagents and standards appropriately labeled and stored?
9. How does QC handle obsolete standards and reagents?
10. How are changes to test methods and equipment managed?
11. How are the results recorded? Does QC have an informal reporting? Is the data transcribed from scrap paper? Are the results validated or verified?
12. How long is the data stored?
13. Are there laboratory notebooks with numbered pages?
14. Does QC have a deviation procedure? How does QC determine and validate human or process errors?
15. Does QC have a final authority to accept or reject a lot?

Master Validation Program
1. Does the manufacturer have a Master Validation Program?
2. Does it include all the critical equipment, systems and processes in the company?
3. Does the manufacturer have a summary of the status of all the individual validation programs?
4. Does the manufacturer have the technical and compliance expertise in managing the master validation program?
5. Has the manufacturer validated its critical computer and PLC systems?

Cross-Contamination Risks
1. How is the space utilized in the company? Is there adequate storage and manufacturing space?
2. Are there specific areas for holding unapproved and rejected material?
3. Is there a locator system for storing and retrieving material?
4. How is the printed packaging material stored? Is it segregated appropriately with limited access?
5. Are there cleaning procedures? Are they validated?
6. Are there line-clearance procedures?
7. Does the manufacturer stage or manufacture one lot at a time?
8. Are there cleaning and clearance logs for major equipment and lines?
9. Are the equipment and the lines properly identified as to their cleaning status?
10. Are the walls, ceilings and floors clean and free from potential contamination hazards?
11. Are the hoses cleaned and stored properly?
12. Are the clean equipment and utensils stored covered in a clean area?
13. Are there any dedicated equipment or utensils? Are they appropriately coded or identified?
14. Is there a sanitization program? Do they use appropriate cleaning agents that remove product or microbiological residues?
15. Is the employees’ dress properly designed and is the dress code observed in designated areas?
16. Are employee practices conducive to contamination prevention?

Documentation Practices and Control
1. Does the manufacturer have a Master Documentation system?
2. Does the manufacturer have all the appropriate procedures for all the critical functions?
3. Are the procedures up to date and consistent with cGMPs?
4. Are the procedures controlled, such that only one version is officially available at all workstations?
5. Are any informal instructions printed and used?
6. Are the forms controlled?
7. Does each procedure have a revision history?
8. Does the manufacturer inform the customer of any critical changes in the procedures?
9. Are the appropriate individuals or departments involved in developing, approving executing and training for all the procedures?
10. How are the obsolete procedures managed?

Change Control
1. Does the manufacturer have a formal change control procedure?
2. How are changes reported and implemented?
3. Are the changes documented?
4. Are the customers involved in reviewing and approving changes?
5. Does the supplier maintain a log of all change controls?
6. Who has the overall responsibility for managing the change controls? Is the Quality unit involved?
7. Is the Regulatory department involved in reviewing changes that impact the FDA-filed status of the product?
8. Are all the personnel trained in reporting all changes?
9. Are all the changes consistent with the cGMPs?
10. How do they manage customer-initiated changes?
Suggestions for Corrective Actions

Warehousing and Distribution

1. Does the manufacturer have adequate warehousing space to hold all the material?
2. Are all the material and locations adequately identified?
3. Is the warehouse free from clutter?
4. Is the storage space environmentally sensitive (e.g., light, temperature, humidity) material adequately controlled?
5. Are those areas monitored and mapped where applicable?
6. Are the ceilings, walls and floors free from debris?
7. Are the pallets and material neatly stacked? Are they free from debris?
8. Do they have an adequate pest control program for the site, including the warehouse?
9. How are unidentified materials managed?
10. Is the Quality unit involved in any material damage event?
11. What is the policy on usage of containers and pallets? If reusable, is there a cleaning program?

The Audit Kick-off Meeting

When auditor arrives at the manufacturer’s site, auditor first order of business should to get the hosts comfortable. An auditor can achieve this by pleasantly and professionally setting the right tone for the next couple of days, letting them know that auditor is not on a mission to find faults but to work with them in identifying any compliance or quality issues. Auditor should discuss the standards that will be used and ask for any questions that they may have.

Next, auditor should explain the agenda and the role of each of member of audit team. One has to find out if agenda items must be shifted because of the manufacturer’s schedule. Auditor should make sure to thank the manufacturer for finding the time and resources it is providing auditor and assure that the audit team will try to be as unobtrusive as possible.

The Audit Process

The Tour: One of the most important aspects of the audit is the plant tour. A typical tour starts with the receiving area and progresses all the way thorough the final release and testing. Auditor may choose to break down the tour in different segments and, if necessary, auditor can break up audit team to follow the pertinent manufacturer personnel. It may not be necessary for every member of audit team to visit every area, but the lead auditor may choose to do it all.

Asking Questions

Do’s and Don’ts: One has to ask a lot of open-ended questions, and make sure not to jump the gun in making qualitative statements about the responses. One of the best ways is to repeat answers in a paraphrase, to better verify understanding. One can ask for specific examples, such as a document or a log, to verify the answer. One should not interrupt when someone is answering. Auditor should be able to bring out an atmopsher where in it facilitates for a more positive answer for the compliance issues in the auditing. When speaking, the auditor has to keep his/her tone low, but speak clearly and should not
inflect words with cynicism or frustration. Auditor must never lose temper! If auditor strongly disagrees, he/she can just take a step back and make notes and say something like, “I'll need to revisit this issue later and verify my understanding of the standard.” Auditor has to always refer to a known standard where possible.

**Making Observations**

When making observations that are verified by some evidence such as a document or a process, one has to do so gently. Say, for example, that auditor believe that such a practice is not consistent with cGMPs, a known standard, or auditor manufacturer’s documented procedure. Make notes and let auditor know the manufacturer that it will be included in auditor’s report. One should not argue or haggle if the manufacturer disagrees; one has to quickly go on to the next topic.

**Verifying Observations**

When verifying, auditor hast to look for strongly documented evidence. For example, if the manufacturer’s procedure requires that an equipment cleaning process be documented immediately after it is cleaned, one hast to look for a specific entry that verifies this practice. Try to get the manufacturer to understand auditor’s evidence and always provide an opportunity to explain any discrepancies. Auditor should not make statements based on superficial observations. Auditor is not there to nit-pick, but rather to make systematic observations. One should not document any unverified observations.

**Classifying Observations**

Typically there are three types of observations: critical, major and minor. A critical observation must be strong enough to be corrected immediately. An example would be lack of temperature monitoring for a stability chamber. A critical observation will most likely have impact on marketed products. A major observation is reserved for an unacceptable practice that may have an impact but is not as significant as a critical observation. A minor observation is about a practice that has no significant impact on the product quality or its compliance status. However, if auditor has several minor observations, they may reflect a major or a critical underlying systematic problem.

**Establishing Perspective**

As each observation is made, one should not rush to classify them immediately, unless they are glaringly obvious. Typically, audit team should discuss these during breaks or lunch, to get a regulatory perspective. It may be necessary to have a conference call with auditor’s senior management to get their perspective, but don’t call them for each and every observation.

**Handling Disagreements**

As an auditor, auditor need not welcome disagreements; however, auditor must assure that manufacturer understands auditor’s particular observation. If the manufacturer disagrees, the auditor must try hard to define what the disagreement is about. Many times, the manufacturer may have a point. At times, the manufacturer may not be clear on
what auditor is referring to. Auditor must tactfully weed out the emotional aspects of the argument and relate himself/herself and manufacturer toward the standard. It may very well be that auditor’s observation is an exception. If so, allow manufacturer to demonstrate that assertion. If auditor decides to make such an observation, auditor must balance it by noting that it was an exception rather than the rule.

**Managing Time and Maintaining Focus**

Time is a critical resource for auditor and manufacturer. Auditor can use it wisely, with proper planning and placing finite time brackets around audit areas. Unless an observation is critical or major, auditor need not hold court at manufacturer’s site. If a particular observation takes excessive time, one should not hesitate to note that clearly and politely, and then move onto the next topic.

**Daily Summaries**

It is generally a good idea to recap a day’s work with manufacturer. This is the time to summarize the day’s findings. One has to confirm requirements for the next day and get an understanding of manufacturer’s position. Again, auditor should not use this time to specifically discuss any particular observation in detail, unless it is critical. This is typically a verbal session, so auditor need not give anything in writing to the manufacturer unless specifically requested.

**Audit Closure Meeting**

It is very critical for entire audit team and the manufacturer’s senior management to attend the audit closure meetings. Typically, the audit team should meet and have all the observations tabulated and agreed to before the closure meeting. It is appropriate for the lead auditor to start this meeting by thanking all the manufacturer’s personnel for their help and hospitality during this audit. The audit team must set the tone in reiterating that the audit is meant as a tool to monitor company’s quality and compliance systems and not as an all-inclusive survey of all areas. If there are any positive things to be said about the plant or their systems, they should be said before discussing the observations. Remember: tactfulness is key. Allow the manufacturer to save face. Think of those problems in terms of opportunities.

Lastly, auditor should let the manufacturer know that the observations may be corrected if it turns out that auditor misunderstood any of its processes. But auditor’s main objective is to say what auditor think, clearly and professionally.

If there are agreements about auditor’s observations, auditor may ask the manufacturer to provide a tentative corrective action plan and a timeline. Don’t get the manufacturer to commit to a rigid schedule unless there is a critical observation on the list.

If there is a disagreement, auditor should say that auditor beg to differ and that auditor would be willing to take the manufacturer’s objections to the compliance management and let them know about the outcome. One should not engage in long arguments. Let the manufacturer know about audit report format and schedule and assure them that there will be no surprises in the report.
The Audit Report
The Audit Report must mirror audit closure meeting. Some auditors write up their audit report in a plaintext format before the closure meeting and use that to discuss the observations at the meeting.

The audit report language should be professional and deal with the facts. It should not contain any unsubstantiated opinions or any disagreements. It should include a classification for each of auditor’s observations.

Where there are multiple observations relating to one system, it is better to categorize them under one heading: e.g., Documentation System or Validation Program, rather than make several individual observations.

Follow-ups
No audit is really complete unless auditor receives a response from the manufacturer and auditor’s company follows up on all the corrective action items. If the corrective action suggested by manufacturer is not adequate, auditor must schedule a meeting of senior management and get their agreement to an alternative plan. This meeting should be followed by a teleconference with manufacturer to discuss auditor’s position.

It is not wrong to ask manufacturers for detailed descriptions of what to expect from their corrective action plan. The auditor must be open to their suggestions, since they are sometimes the process experts. Auditor need not push for a pet solution, if the team agrees to the manufacturer’s plan.

Once the corrective action plan is agreed to, auditor may choose to send periodic letters requesting the status of the plan. However, letters should be reserved to discuss critical and major items only, so as not to dilute their impact.

An audit program can be a powerful tool in managing a manufacturer’s quality and compliance systems. However as with any tool, it is only as good as its user. A poorly managed audit program will result in a waste of resources at both ends and may possibly ruin relationships between an audit sponsor and the manufacturers.

Corrective and Preventive Action
Corrective Action - action taken to eliminate the cause of an existing nonconformity, noncompliance, defect or other undesirable situation in order to prevent reoccurrence. The corrective action required may take two forms to address the situation:

(i) immediate or adaptive corrective action: will correct or address the current noncompliance. They are actions taken to reduce or eliminate a noncompliance’s effect;

(ii) (permanent) corrective action: will ensure that the required steps are taken to see to the noncompliance does not recur. They are actions taken to eliminate the cause(s) of a noncompliance.
**Preventive Action** - action taken to eliminate the causes of a potential nonconformity, noncompliance, defect or other undesirable situation in order to prevent occurrence. Preventive actions are actions taken to reduce the probability that a potential problem will occur. Preventive actions may also include contingent actions taken to reduce the seriousness of a future problem if it should occur.

The following information is a composite of the ISO 9001 standards

14. CORRECTIVE AND PREVENTIVE ACTION

14.1 General
The supplier shall establish and maintain documented procedures for implementing corrective and preventive action.

Any corrective and preventive action taken to eliminate the causes of actual or potential nonconformities shall be to degree appropriate to the magnitude of problems and commensurate with the risks encountered.

The supplier shall implement and record any changes to the documented procedures resulting from corrective and preventive action.

14.2 Corrective action
The procedures for corrective action shall include:

a) the effective handling of customer complaints and reports of product nonconformities;

b) investigation of the cause of nonconformities relating to product, process and quality system, and recording the results of the investigation;

c) determination of the corrective action needed to eliminate the cause of nonconformities;

d) application of controls to ensure that corrective action is taken and that it is effective.

14.3 Preventive action
The procedures for preventive action shall include:

a. the use of appropriate sources of information such as processes and work operations which affect product quality, concessions, audit results, quality records service reports and customer complaints to detect, analyze and eliminate potential causes of nonconformities;

b. determination of the steps needed to deal with any problems requiring preventive action;

c. initiation of preventive action and application of controls to ensure that it is effective;

d. ensuring that relevant information on actions taken is submitted for management review.
GUIDELINES
Causes of detected (or potential) nonconformities should be promptly identified so that corrective action may be taken and recurrence (or occurrence) may be prevented. These causes may include the following:

- Failures, malfunctions or nonconformities in incoming materials, processes, tools, equipment or facilities in which products are processed, stored or handled, including the equipment and systems therein;
- Inadequate or non-existent procedures and documentation;
- Non-compliance with procedures;
- Inadequate process control;
- Poor scheduling;
- Lack of training;
- Inadequate working conditions;
- Inadequate resources (human or material);
- Inherent process variability.

The conditions resulting from these causes may be revealed by analysis of the following:

- Inspections and test records;
- Nonconformity records;
- Observations during process monitoring;
- Audit observations;
- Field, service or purchaser complaints;
- Regulatory authority or customer observations;
- Observations and reports by personnel;
- Sub-contract problems;
- Management review results;
- Inherent process variability.

Note: Corrective action is not necessarily required for every occurrence of a nonconformance, but periodic analysis of patterns of nonconformance should be considered to uncover opportunities for process improvement.

Procedures should be developed by the supplier to establish responsibility for taking corrective action and how this action will be carried out and the verification of the corrective action.

It is useful to implement procedures to deal with nonconformities discovered in product that has already been shipped as satisfactory. Such procedures can include:

- Investigations to establish whether the nonconformity is an isolated or a chronic problem;
- Actions to be taken, if necessary.
INSPECTION TRENDS
Below given are some of the trends observed during FDA’s inspections.

1. Any firm incorrectly identified in the application – Applications submitted to the FDA have named contractors that the company intended to use, but actually never did.

2. Incorrect analysis listed in the application – Changes are often made to an application just before filing. Some companies failed to ensure that those changes were incorporated into the laboratory procedures, by the time the FDA came to inspect.

3. No inter laboratory qualification – Inter laboratory qualification is required when any method is transferred from one lab to another. This includes transfer from a QC lab at one site to a QC lab at another, transfer from an R&D to QC lab, from R&D to a contract lab. Any time that method is moved from one laboratory to another it must undergo an inter-laboratory qualification.

4. Deficient methodology for related compounds where the method was unable to separate the toxic degradant. One of the FDA’s favorite topics in impurity and degradation product testing. The FDA turns down applications for inadequate methodologies for detecting impurities. It is also necessary to have a method that can quantitate degradant at whatever level is appropriate, down in the 0.1% range.

5. Lack of stability indicating method. The FDA requires stability indicating methods. (These methods may not be solely using HPLC). Stability testing protocols must comply. A common observation by the FDA is that although a stability protocol says to test at three, six, nine and twelve months, testing on a three month sample is actually done much later, say at five months. Therefore, the laboratory is not in-compliance with its own protocol. Companies need to set internal corporate guidelines on how close to those dates, testing must occur.

6. Stability storage conditions and monitoring were inadequate. The FDA requires that during stability testing, storage temperature is monitored and controlled. Modern pharmaceutical companies should be moving to adopt ICH conditions, which means monitoring and controlling temperature and humidity.

7. Processed data results came from re-integrated chromatograms, but the original raw data files were missing. In general, FDA inspectors prefer not to see re-integrated chromatograms. However, for low level impurities this is not always possible. If it is necessary to re-integrate, the original chromatogram must be saved.

8. Inadequate laboratory re-test procedures. Another common observation by the FDA is that there are inadequate laboratory re-test procedures. If a test fails, a procedure must be in place to describe what constitutes that appropriate re-test, whether re-sampling is required, re-injection or re-preparation of the sample.

9. Use of loose paper for collection data. This is a recurring problem in the industry. Analysts like to use a loose paper to record their primary data before transcribing it to their lab books. This is a training issue, companies need to keep emphasizing to their analysts that loose paper is not to be used to record data.
10. Out-of-specification results were discarded without an investigation. Once an out-of-spec result is obtained, even if it is known why, it is necessary to perform an investigation. The investigation doesn’t have to be lengthy; “Analyst dropped the glass on the floor” can be investigation, if the cause was known.

11. The manufacturing process for clinical batches are significantly different from the commercial process and/or the manufacturing equipment was different. Though not strictly related to the laboratory procedures, if these problems occur, lab tests will tend to give failed results. If the manufacturing process for clinical batches is significantly different from the commercial process, the rate of degradation that the clinical product undergoes may not conform to the original. It can have an impact on the impurity profile of the drug substance, and/or it can impact the physical property of the drug substance.

12. Stability batches were not manufactured at the proposed manufacturing site - Stability batches should be manufactured at the proposed commercial site. This is specific for pharmaceutical and chemical materials, or the drug substance itself.

13. The synthesis method for the bulk pharmaceutical compound differed from the original synthesis. As before, differences could lead to impurity profiles changes and/or physical parameter changes. The latter, can be just as important as the impurity profile.

14. Polymorphs between bio-batch and commercial production are different; equivalency was not demonstrated. If it is known that polymorphs are present in the drug substance, an adequate investigation must be performed. If there’s a change between the bio-batch and that available for commercial production, work must be done to show equivalency, otherwise some bio-feasibility studies will be required.

Suggestions
Below given are few suggestions that can be used for QC laboratory. In no instance it is exhaustive and more suggestions that can enhance and improve the process in complying with the Code of Federal Regulations is always beneficial.

1. Each laboratory staff member must record data relevant to the analysis work in laboratory record books issued for recording experimental data.
2. The records should be presented at least monthly for review by the supervisor or incharge of the QC Lab.
3. The review should ensure that all records of laboratory are recorded appropriately with a date, title, an introduction (if appropriate), clearly laid out results, appropriate interpretation/conclusions and actions. Where a laboratory book is used by more than one individual, each piece of recorded work should be initialed.
4. On completion, the review should be recorded on a laboratory record book review log sheet, which can be fixed in the front of each laboratory record book.
5. QC sampling of raw materials should be conducted in closed and controlled warehouse.
6. Components received with a Certificate of Analysis should be subjected to specific identity tests, and the supplier’s analytical test results should be verified at established intervals.
7. Bulk intermediates should be adequately packaged and stored to ensure their suitability for use in further manufacturing.
8. Time limits and yields should be established for critical processing steps.
9. Validation protocols should address equipment, critical process parameters/ranges, sampling, data to collect, number of validation runs, criteria for acceptable results.
10. Batch records should be complete and should reflect actual operations.
11. All activities should not be recorded prior to their actual completion.
12. Lots have to be released only after successful review of the batch production records.
13. Changes to process and equipment parameters in batch records should be addressed by change control system.
14. All laboratory and manufacturing equipment use and maintenance records should be maintained.
15. Product annual reviews should be conducted and should be adequate.
16. Only validated test methods have to be used.
17. System suitability tests have to be performed.
18. Any usage of secondary reference standards should have comparative data against official USP standards.
19. Any retest done should be supported by a proper investigation report, which justifies the retest.
20. All the laboratory data should be reviewed by a second person.
21. Serious or persistent non-compliance information, against correct laboratory record keeping should be reported by the supervisor or the incharge of the QC Lab in writing to the QA personnel.
22. The QA should evaluate the reason for non-compliance and necessary action has to be taken immediately and prevent from any future occurrences.
23. When a laboratory record book is full or is to cease being used, the reviewer should authorize its removal from use and record this action in the comments column of the review log sheet. The laboratory record book is kept with the appropriate laboratory for archiving.

References:
3. www.iso.ch