APPENDIX II

EXAMPLE TEMPLATE FOR AN AUDIT SUMMARY REPORT

INTRODUCTION

At the completion of the audit, the findings need to be reviewed, organized, and presented in a coherent format that can be circulated and reviewed by management as well as other individuals within the organization. The output of this process is the audit summary report (ASR).

The audit summary report is a very valuable and useful document, not only from a what-it-costs standpoint, but also from a compliance and business efficiency standpoint. Specifically, if the audit is comprehensive and executed as delineated in the previous chapters, a significant number of labor-hours will be invested and the direct cost from labor alone can be substantial. However, if performed in a proper fashion, this investment in time and effort has value from a CGMP compliance perspective. Namely, you will have a detailed understanding of your current level of CGMP compliance and be able to show a regulatory agency what you know. From a business standpoint, the ASR lays the basis for the most systematic and efficient means to upgrade your level of compliance. Not to mention that noncompliance in general can be very expensive if it results in significant regulatory action.

Establishing a CGMP Laboratory Audit System. By David M. Bliesner

The process of organizing and reporting the results is a critical phase because it lays the ground work for developing a future corrective and preventive action plan. The greater the effort expended on determining how the data are to be reported, the more effective and straightforward the creation and implementation of the corrective and preventive action plan.

The final form of the audit summary report is determined by the details and logistics of the audit itself. However, the general structure of all audit summary reports should essentially be the same. The basic components of an audit summary report should include:

Header

The header should identify your facility name and location in addition to all of the personnel involved in the audit. A statement as to the confidential nature of the material included in the report should be made as well.

Background

The background section summarizes the purpose for performing the audit. For example, the audit may be in preparation for an FDA preapproval inspection (PAI), an upgrade of your existing quality systems, or a continuation of an existing audit program.

Approach

This section should describe all the subelements of the laboratory quality management system reviewed during the audit. As described in previous sections these elements include:

- 1.0 Laboratory managerial and administrative systems (MS)
- 2.0 Laboratory documentation practices and standard operating procedures (OP)
- 3.0 Laboratory equipment qualification and calibration (LE)
- 4.0 Laboratory facilities (LF)
- 5.0 Methods validation and technology transfer (MV)
- 6.0 Laboratory computer systems (LC)
- 7.0 Laboratory investigations (LI)

The approach section should also discuss the personnel who were involved in the audit, the mechanics of the audit (e.g., use of checklists), and how the

findings were documented (e.g., in a notebook with subsequent documentation on an official finding form, such as a LAF).

Description of Report Format

The body of the report includes sections discussing how the summaries of each of the subelement findings, which are contained within the report, are organized. Namely:

- A brief description of the subelement
- An overview of the current practice at the site or each subelement
- A listing of site documents reviewed
- Gaps in the subelement versus checklists or similar quality review documents
- Additional gaps not correlated to checklists or similar quality review documents
- Potential root causes for the gaps
- Potential corrective action needed to become compliant with CGMPs
- A summary matrix for the above steps, which can be used to creating the corrective action plan

The format of the report can be tailored to fit the individual site needs. However, it is strongly suggested that a summary matrix be included for each subelement. This format greatly enhances the generation of a corrective action plan.

Summary of Results

The summary or results section should capture the total number of findings discovered for all subelements during the audit. As with the individual subelement findings, the summary results should also be organized into a matrix.

Future Work

The future work section should review the steps required for the implementation of a complete audit, namely:

- Preparation phase
- Audit and Data Capture phase
- Reporting phase
- Corrective Action phase

- Verification phase
- Monitoring phase

Some explanation should be given as a need to continue with the Corrective Action phase, and the potential resources, which may be required to complete the full audit.

Laboratory Controls Subelement Sections (Report Body)

This section then presents the data for each subelement as described in the format section, namely:

- Description of subelement
- Current practice
- Site documents reviewed
- Gaps in the system versus audit checklist

The level of detail and breadth of discussion depends upon individual site organizational structure and level of compliance with CGMPs.

Attachments and appendices may be included enhancing the overall readability or usability of the report. Remember, the ASR is used as the basis for corrective and preventive actions and should therefore be as descriptive as possible.

With the previous suggestions in mind, an example report is shown. This report contains all the sections described here and can be modified to suit the needs of the individual organization. As with the checklists however; the example template report shown below is fairly comprehensive but may not be totally inclusive of all the sections required for a specific organization.

YOUR COMPANY QUALITY OPERATIONS LABORATORY

AUDIT SUMMARY REPORT

CONFIDENTIAL: This document is not to be distributed or copied except with the written permission of Your Company Products, LLC Quality Operations

Quality Management System: Laboratory Control System

Facility Name and Location: Dummy Products, LLC Quality Operations Laboratory Your Site Operations, Your Site, Your State, 99771

Auditors: J. Casey, R. Danny, J. Felix, J. Foosball, M. Gummy, A. Lavio, W. Link, R. Mettz, A. Quinones, U. Smith, J. Smyth, J. Smooter, E. Vazquez, D. Blistex, V. Dooby, R. Gillen, T. Johnson, B. McMillan, N. Ran

Background

As part of its continuing commitment to quality, Your Company Products, LLC has agreed to voluntary periodic CGMP inspections by the REGULATORY AGENCY. In order to prepare for an inspection, which was originally scheduled for mid-to-late April 2008, Your Company Operations (SITE) Site Management determined the need to conduct a series of self audits. These self audits were to serve two purposes. First, they would be used to prepare for the REGULATORY AGENCY visit. Specifically, a comprehensive review of internal systems would reveal any remaining potential deficiencies with respect to CGMPs and operations in general and allow sufficient time to address any shortcomings. Second, they would provide an excellent opportunity to instruct laboratory personnel with the help of quality assurance on the quality management systems-based audit approach, which was recently formally adopted by the REGULATORY AGENCY. Site management determined that at the beginning of these self audits that the Quality Operations Laboratory would serve as the starting point for this process. Audits of the additional Quality Management Systems (QMSs) would follow as time progressed. It should also be noted that the self-audit approach is meant to lay the groundwork for a formal on-going self-audit–corrective action program which will be spearheaded by the Quality Assurance Department.

Laboratory Operations Self Audit Approach

This quality management system (QMS) self audit reviewed all the current good manufacturing practices (CGMP) systems and practices in the Your Company Operations (SITE) Quality Operations Laboratory. In addition, many of the administrative systems and practices, which can ultimately impact compliance with CGMPs, were also evaluated. The Laboratory Quality Management System encompasses a variety of subelements

that cover all aspects of the laboratory. Because the laboratory is staffed as a semi-independent organization, many of the subelements overlap with the other QMSs. Examples include investigations, validation, facilities, training, etc. However, this audit focused on conditions as they exist in the laboratory and when processes connect to organizations outside the laboratory, seeks to assure that the interface is adequate to allow these interdepartmental processes to be conducted seamlessly. The subelements that comprise the Laboratory Operations QMS, which is also referred to as the Laboratory Control System, are:

- 1.0 Laboratory Managerial and Administrative Systems (MS)
- 2.0 Laboratory Documentation Practices and Standard Operating Procedures (OP)
- 3.0 Laboratory Equipment Qualification and Calibration (LE)
- 4.0 Laboratory Facilities (LF)
- 5.0 Methods Validation and Technology Transfer (MV)
- 6.0 Laboratory Computer Systems (LC)
- 7.0 Laboratory Investigations (LI)

The laboratory operations audit team was composed of representatives from SITE QA, the Quality Operations Laboratory, and supervised overall by the senior manager of the Your Company Quality Operations Laboratory. The audit team was divided into 7 subteams, which mirrored each of the subelements listed above. Each subteam was responsible for assessing its specific subelement in the QC laboratories versus the audit checklist for the laboratory. The audit checklist is a comprehensive and detailed document, which is used to systematically evaluate an organization's level of compliance with CGMPs. It represents numerous personnel-years of experience acquired by assisting companies to comply fully with CGMPs.

Deficiencies versus the audit checklist were documented on laboratory audit forms (LAFs). LAFs are considered the raw data captured during the review. LAFs are identified via a standard alpha number naming scheme. For example, **SITE-MS-1.2.2-001** is identified in the following fashion:

- **SITE** = Indicates the deficiency for Your Company Operations (SITE)
- **MS** = Indicates that this is related to the Laboratory Managerial and Administrative Systems (MS) as designated on the audit checklist
- **1.2.2** = Links directly to the audit checklist STEP 1.2.2 which asks "Are training requirements clearly documented in a SOP or similar guidance document including managers, supervisors, analysts and temporary staff?"
- **−001** = Indicates that this is the first finding for this STEP.

Narrative details of the finding are documented on the LAF form itself. Once captured, LAF data are entered into a database, which is used to support corrective and preventive actions (CAPAs), via a corrective action project plan (CAPP). Considerable effort has been made in design of this form to link and consolidate all LAF findings to other quality management systems, and previously documented findings, such as FDA 483 observations, and previously conducted site internal assessments. All LAFs are stored in separate binders corresponding to their subelements. Also included in the binders are a summary of the LAFs for that subelement and the completed audit checklist. The original LAFs (revision 0) have also been scanned or printed to Portable Document File format (*.pdf) and burned as a permanent record to CD-ROM disk.

It should be noted that items, which are not specifically covered by steps in the audit checklist are identified by an "Additional Items (9.0)" designation. For example, SITE-MS-9.1-001 is the first additional deficiency identified by an auditor for issues related to Managerial and Administrative Systems, but not specifically covered by a step number on the checklist. Details of the finding are documented on the LAF as before, and entered into the database. Details of the audit and LAF generation process are show in Appendix A of this report.

This Quality Management System applies to the entire Quality Operations Laboratory including the following sections: Immediate Release and Extended Release Laboratories, Analytical Technical Services, Stability, and Raw Materials. These five sections are located in nine major laboratories in a single building at the Your Company, Your Company Operations, Your Company, Your State, USA. Supervisors report to section managers who in turn report the Quality Operations Laboratory senior manager, who is the laboratory director. Testing responsibilities include: in-process testing, testing to support investigations and stability testing, and raw materials testing for all pharmaceutical solid dosage forms and products which are manufactured, used, or maintained at Your Company at Your Company Operations.

Report Format

The sections shown in the following text are summaries of each of the subelements assessed versus the audit checklist. The format includes: (1) A brief description of the subelement, (2) An overview of the current practice at SITE for each subelement, (3) A listing of site documents reviewed, (4) Gaps in the subelement versus the audit checklist and additional gaps not correlated to the checklist, (5) Potential root causes for the gaps, and (6) Potential corrective action to become compliant. Steps 4–6 are summarized in a matrix.

Summary of Results

The breadth and extent of the quality operations laboratory self audit were extensive. All laboratory personnel who provided information or were interviewed were forthcoming and enthusiastically engaged in the audit process. Moreover, they frequently demonstrated their knowledge of the importance of CGMPs and the need for continuous improvement.

Due to the comprehensive nature of the audit, a good number of gaps were documented. Many of these gaps are not considered *critical*; they would not result in Form 483 observations. However, many of the *noncritical* gaps have to do with administrative systems and practices and can ultimately lead to degraded compliance with CGMPs. Therefore, many of the observed gaps should offer suggestions on "How can this be done better?" It should also be noted that the REGULATORY AGENCY or REGULATORY AGENCY auditors would never have such unfettered access to personnel and records, and would therefore be less likely to document as many findings as was done during this self audit. It should also be noted that several gaps may be related to the same root cause and thus the total number of unique gaps may be less than the number stated.

Table 1 below summarizes the gaps versus the subelements. Table 2 shows the correlation of critical (e.g., = potential 483) gaps and the noncritical gaps (e.g., = can be done better versus the subelements).

TABLE 1

Subelement	# of Checklist Item Gaps	# Non Checklist Gaps	Total # of Gaps	% of Total Gaps Found
1.0 Laboratory Managerial and Administrative Systems (MS)	20	32	52	19.5
2.0 Laboratory Documentation Practices and Standard Operating Procedures (OP)	25	78	103	38.6
3.0 Laboratory Equipment Qualification and Calibration (LE)	25	2	27	10.1
4.0 Laboratory Facilities (LF)	26	0	26	9.7
5.0 Methods Validation and Technology Transfer (MV)	2	35	37	13.9
6.0 Laboratory Computer Systems (LC)	9	0	9	3.4
7.0 Laboratory Investigations (LI)	10	3	13	4.9
Total =	**117**	**150**	**267**	**100**

TABLE 2

Subelement	Total # of Gaps	# of Critical Gaps*	# of Noncritical Gaps
1.0 Laboratory Managerial and Administrative Systems (MS)	52	14	38
2.0 Laboratory Documentation Practices and Standard Operating Procedures (OP)	103	14	89
3.0 Laboratory Equipment Qualification and Calibration (LE)	27	10	17
4.0 Laboratory Facilities (LF)	26	11	15
5.0 Methods Validation and Technology Transfer (MV)	37	3	34
6.0 Laboratory Computer Systems (LC)	9	4	5
7.0 Laboratory Investigations (LI)	3	0	3
Total =	**267**	**59**	**208**

*Critical = could potentially warrant a Form 483 observation from FDA.

Future Work

The completion of this report represents the completion of the first three steps in a complete self-audit process, which includes the following phases:

- Preparation phase
- Audit and Data Capture phase
- Reporting phase
- Corrective Action phase
- Verification phase
- Monitoring phase

To complete the process, this report should be used to create a comprehensive corrective action project plan (CAPP) which will be used to implement corrective and preventive actions (CAPAs). This should in turn be followed by implementation of a verification plan, which will be integrated to a monitoring plan that includes periodic reassessments and reporting of those results. Appendix B outlines the process from LAF generation to CAPP implementation in detail.

Laboratory Control System Subelement:	***1.0 Laboratory Managerial and Administrative Systems (MS)***
Auditor(s):	J. Felix, J. Smooter, D. Blistex

Description of the QMS Subelement 1.0 Laboratory Managerial and Administrative Systems (MS)

The Laboratory Managerial and Administrative Systems subelement has eight individual topics as defined in the audit checklist. These are: Organizational Structure and Roles and Responsibilities, Training, Tracking and Trending—Statistical Quality Control, Complaints, Laboratory Purchasing and Requisition, Laboratory Administration, Laboratory Chemicals, Solutions, Reagents, and Supplies, and Laboratory Reference Standards and Solutions. Each of these eight topics is addressed separately as part of the subelement discussion in the following sections.

Current Practice 1.1 Organizational Structure and Roles and Responsibilities

This review involved conducting interviews with supervisors, managers, and personnel within the Quality Operations Laboratory. In many cases the interviews are the result of a "follow the sample" approach to auditing. That is, personnel were asked to track a sample from receipt to final disposition.

The roles and responsibilities for each position in the Quality Operations Laboratory are defined by a combination of organizational charts, standard operating procedures, resumes, position descriptions, training qualifications, and yearly reviews. Section supervisors assign work responsibilities based on their understanding of the workload and knowledge, experience and abilities of the scientists to perform the analysis. Signature authority and responsibility are not clearly defined by SOPs. However, the supervisors and managers have sufficient knowledge of their tasks and authority to identify the occurrence of departures from the SOP. For example the supervisors can perform investigative testing of suspect samples to determine an assignable laboratory cause. The staff has turned over significantly over the last 2–3 years, and considerable effort has been made to bring the laboratory to a higher state of compliance with CGMPs. This has increased the workload significantly and results in a substantial number of the supervisors and managers working 10–15 hours of overtime on average per week.

Current Practice 1.2 Training

This review involved discussions with a newly assigned laboratory training manager. Since the Quality Operations Laboratory operates as a semi-independent entity, the training manager is responsible for coordinating, documenting, and in many cases preparing/conducting the majority of laboratory training. Technique and product specific training is conducted directly by this individual or by subject matter experts within the lab. Training is documented in several ways, including course attendance records, completed knowledge checks, and data and instrument outputs for hands-on procedure specific training. These documents are tracked via manual systems like the internally generated training

matrices for hands-on training and by the XTrain software package. These tools are used to create a training file (binder) for each person in the laboratory. These binders are stored at various locations within the lab, usually close to the primary work location of the individual. No one system compiles and tracks training documentation, which is currently a work topic for the training manager. This is part of the overall effort by the training manager to form a more coherent and effective training program for laboratory personnel, which will include generating a master training, schedule, formally codifying all training modules, and comprehensive use of XTrain to track all laboratory training.

Current Practice 1.3 Tracking and Trending-Statistical Quality Control

These duties are not the responsibility of the Quality Operations Laboratory and are performed by the Quality Management Group, which falls under the auspices of the Quality Assurance Unit. Therefore, an audit of this system was not performed at this time, but will be included in future, expanded audits of the additional Quality Management System (QMS).

Current Practice 1.4 Complaints

Complaints are received at the Tahiti Regulatory Department and forwarded to the SITE Regulatory Department as necessary. The Quality Operations Laboratory is responsible for conducting only the required testing determined by SITE Regulatory. Testing is requested and initiated by the SITE Regulatory Department via issuance of Attachment II (a form) found in YLP 05-011 *Complaint Investigation Report*. The laboratory uses this form and follows YLP 02-055 *Investigating Customer Complaint Samples* to generate the results and forward it back the Regulatory Department. The lab is not involved in any decision making process, only data generation and reporting as delineated in these procedures.

Current Practice 1.5 Laboratory Purchasing and Requisition

This review involved discussion with the analytical services supervisor who has recently been placed in charge of laboratory purchasing and requisitions. Previous to this, it had primarily been the responsibility of the stock room supervisor and instrumentation supervisor, with final signature approval performed by the senior manager of the laboratory. To obtain supplies, laboratory personnel request needed laboratory supplies from the laboratory stockroom supervisor. The stockroom supervisor then completes a purchase order, obtains the analytical services manager's or the senior manager's authorization and then forwards the requisition to the purchasing function. Levels of signature authority are not clearly defined in writing. There is no indication if the proper grade of reagents is taken into account during the requisition process. Although QA has a list of qualified vendors, the laboratory does not and may not take this into consideration when making requisitions. Monitoring of expenditures and budget generation and review has primarily been the responsibility of the senior manager but is shifting to the analytical services supervisor. None of these individuals has received significant formal training on theses topics.

Current Practice 1.6 Laboratory Administration

This review involved interviews with the senior laboratory manager, analytical services manager, training manager, and the instrumentation supervisor using a prepared questionnaire and the audit checklist. To this point most of primary administrative tasks for the laboratory were spread out among the managers, and instrumentation supervisor. Due to work schedules and volume many of the issues addressed in the audit checklist were never addressed in a coordinated, definitive fashion. Because of this the senior manager has recently suggested the creation of a formal position within the laboratory where a single individual will be responsible for most of the diverse administrative issues such as budget management, overseeing stockroom operations, capital expenditures, managing external contracts, etc.

Current Practice 1.7 Laboratory Chemicals, Solutions, Reagents and Supplies

This review involved touring the laboratories, reviewing existing SOPs and answering questions on the audit checklist related to laboratory chemicals, solutions, reagents and supplies. SOPs YLP 02-013 *Maintaining Volumetric and Reference Standard* Solutions and YLP 02-014 *Storage of Reactive Solutions in the Laboratory* give fairly comprehensive instructions with respect to the handling of chemicals, reagents and solutions. When coupled with the USP, EP, and product specific procedures (PSD) they provide sufficient guidance to comply with current industry standards. A spot check of labeling of solutions and reagent in the laboratory confirmed this to be generally true.

Current Practice 1.8 Laboratory References Standards and Solutions

This review involved using the audit checklist and discussions with personnel responsible for receipt, labeling, handling, and recertification of reference standards and materials in the Quality Operations Laboratory. The Central Reference Standard Group in Tahiti has the primary responsibility for reference standards at Your Company. Details of these responsibilities are addressed in the LEVEL II 22,414 *Reference Standards*. Currently there is no Level III SOP addressing reference standards at SITE and the LEVEL II has not been implemented at SITE. Consequently there are shortcomings in the reference standard program at SITE. In house reference standards are received from Tahiti, and compendial standards are ordered and received directly from the source. Once received, all standards are logged and secured with lock and key; however, they are not stored in environmentally controlled environments. In addition, certificates of analysis are not handled as controlled documents. In general, reference standards are not handled in accordance with current industry standards. This area represents one of the greater challenges in the Quality Operations Laboratory.

Site Documents Reviewed

- Blank copy of Your Company professional/managerial performance appraisal
- Chromatography module
- Dissolution test module

- Human Resources organizational charts
- Individual training records (Various Binders)
- Interoffice memorandum *Analyst Qualifications and the Site Training Function Responsibilities, 26 Nov 2007*
- YLP-02-108
- Quality Operations Laboratory Your Company operation products
- Quality Operations Laboratory basic training module
- Quality Operations organizational charts
- Spectrophotometery module
- Training attendance records (Various)
- Training matrices, all sections

Gaps in the System versus the Audit Checklist

The following matrix correlates potential gaps uncovered during the self audit and links them to specific line times in the audit checklist. In addition to the gap, the matrix also indicates if the gap represents part of the system that is in sustainable compliance (e.g., No = a Critical finding which potentially could result in a Form 483 finding if discovered by the REGULATORY AGENCY), what the potential root cause may be for the gap, and some suggestions for potential corrective action to make the system become compliant. If the auditor did not make suggestions as to the root cause or potential corrective action to become compliant, the statement "None offered" is included in the space.

In addition to the findings correlated directly to the audit checklist, additional gaps are included in the matrix. In some circumstances the description serves as the gap and therefore the gap block may state "Same as description."

Gaps in the System: Laboratory Subelement 1.0 Laboratory Managerial and Administrative Systems (MS)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action to Become Compliant
1.1.6 What is the ratio of supervision to analyst? (8:1 recommended)	The agreed target ratio of analyst to supervisor is 8:1. That ratio has not yet been achieved in the stability area.		Some laboratory personnel have recently left the company due to a major hiring initiative from another local firm.	Evaluate the root cause of departure. Reevaluate the current compensation system. Make sure to include noncash incentives as part of the evaluation.
1.1.9 Are signature authority, responsibility, and accountabilities appropriately and clearly defined?	The Quality Operations Laboratory does not have a memorandum or similar document, which delineates signature authority for laboratory managers, supervisors, or other personnel.	No	Many of the administrative tasks assigned to managers and supervisors are not part of their formal job descriptions and done on-the-side in conjunction with their regular duties.	Create a document which clearly defines signature authority. Create a position within the laboratory where the individual is responsible for the general administrative functions such as training, supply requisition (e.g., stockroom), equipment maintenance and calibration, etc. Then assign this individual the responsibility for creating, submitting, reviewing, and monitoring the training budget by interacting with the managers and supervisors. This person

(*Continued*)

Gaps in the System: Laboratory Subelement 1.0 Laboratory Managerial and Administrative Systems (MS) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action to Become Compliant
				will have most of the signature responsibilities in the laboratory.
1.1.10 Do systems exist to enhance communications, understanding, and working relationships between the laboratory and quality assurance personnel?	Systems do not currently exist to enhance communications, understanding, and working relationships between the laboratory and QA personnel. In general, QA is not involved in the over site of day-to-day operations of the laboratory.	No	None offered.	Laboratory management needs to perform an analysis of where QA personnel can add the most value within the Quality Operations Laboratory organization. Once the analysis is complete, discussions need to be initiated with QA to determine the best path forward.
1.1.11 Does a personnel performance system exist which tracks laboratory personnel strengths and weaknesses and establishes corrective action procedures to mitigate weaknesses?	The Personnel Performance Evaluation System as currently used by the laboratory may not be effective in identifying employee strengths and weaknesses, identifying avenues for continuous improvement, and providing continuous and timely feedback on performance.		Existing performance evaluation system is not metrics based.	To augment the existing system, initiate a complimentary performance metrics based system to evaluate performance in the laboratory.

1.1.12 Does a master testing schedule or similar document(s) exist to insure smooth workflow, and minimize laboratory personnel over commitment?	The laboratory does not currently have a master testing schedule to insure smooth workflow and minimize laboratory personnel over commitment.		Communications between the laboratory, manufacturing, and technical services needs to be improved.	Design and development of proper communication systems between these groups and supervise their implementation.
1.2.2 Are training requirements clearly documented in an SOP (including managers, supervisors, analysts, and temporary Staff)?	There is currently no SOP in place to address revisions of training curricula, or clearly define training requirements for all personnel including managers, supervisors, analysts, and temporary staff.	No	Training supervisor is a recently created position. In addition, a specific written path forward to develop department training objectives has not been created.	As part of the CAPP, a performance matrix needs to be created and executed for the training supervisor. This matrix should include the creation of an SOP to address the issues highlighted here.
9.1 The laboratory training supervisor is not involved in the interview and hiring process of laboratory personnel.	Same as description		There is currently no formalized system in place which addresses all of the components required to properly search for, interview, hire, train, and evaluate personnel.	The process for hiring new personnel within the Quality Operations Laboratory needs to be reevaluated to include not only steps for assessing the needs of the department, but also what the impact of hiring the individual has on the workflow and resources needed to add this individual to the

(*Continued*)

Gaps in the System: Laboratory Subelement 1.0 Laboratory Managerial and Administrative Systems (MS) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action to Become Compliant
				department roles. An equivalent system of DQ/IQ/OQ/PQ and maintenance and calibration, which is used in purchasing, qualifying, and installing equipment needs to be developed and implemented for personnel.
9.2 Initial SOP training and training on revisions to SOPs has limited effectiveness.	Same as description		Current system for SOP training and SOP revisions training is based on an augmented "read-understand-test" scenario. Studies have shown this is perhaps the least effective means of training.	Design and develop a multifaceted approach to SOP training, which includes classroom, video, self-instruction, and bench-chemist led instruction.
9.3 The laboratory training Supervisor does not have full access to the XTrain computer software system.	Same as description		Training responsibilities for the QC Laboratory are currently split between the Regulatory Department and	Arrange with the Regulatory Department for the QC training supervisor and general administrative

		the laboratory training supervisor. However, accountability, authority, and responsibility are not clearly delineated leading to potential shortcomings, such as access to XTrain.	manager to assume total accountability, authority, and responsibility for the laboratory training program to include access to the XTrain system.
9.4 Training for raw material methods and USP methods are not currently tracked by the XTrain system or the augmenting paper system. They are contained in training grids, which is a third way that training is tracked.	Same as description	Same as 9.3	Same as 9.3
9.5 Records in the XTrain system are difficult to access in a timely manner.	Same as description	XTrain resides on a corporate computer server located in the Mainland USA. Therefore, large-scale data transfer, which is required to query and review files, takes a significant amount of time.	Work with the owners of the corporate computer server and IT to determine if speed can be improved. If it is not possible, determine whether a copy of XTrain can reside locally at SITE.

Laboratory Control System Subelement:	***2.0 Laboratory Documentation Practices and Standard Operating Procedures (OP)***
Auditor(s):	J. Foosball, M. Gummy, A. Quinones, D. Blistex

Description of the QMS Subelement 2.0 Laboratory Documentation Practices and Standard Operating Procedures (OP)

The Laboratory Documentation Practices and Standard Operating Procedures subelement has nine individual topics as defined in the audit checklist. These are: SOPs–General, SOPs–Specific Procedures, Laboratory Test Procedures, Laboratory Data and Results, Security of Data, Distribution of Results, Chromatography, In-Process Testing, and Assignment of Retest/Expiry Dates. Each of these nine topics is addressed separately as part of the subelement discussion in the following sections.

The review for the entire Laboratory Documentation Practices and Standard Operating Procedures subelement involved an in-depth interview with the laboratory documentation supervisor. In addition to using the audit checklist the supervisor was asked to explain, in detail, the major and minor facets of his/her job and to process diagram workflow in circumstances where it was appropriate.

Current Practice 2.1 SOPs—General

This section review focused on ascertaining whether the laboratory has: (1) The proper documents on hand to complete the tasks and provide guidance, (2) These documents are clearly written and used appropriately by laboratory personnel, and (3) The proper systems for creating, revising, and storing these documents are in place. In general it was found that the status of document control was sufficient but that the quality of documents was in some cases lacking. It was discovered that many procedures were difficult to follow as written and in some cases had errors which could adversely affect results. Although the documents are controlled appropriately, much of this system is manual and very labor intensive.

Current Practice 2.2 SOPs—Specific Procedures

This section review focused on ascertaining whether specific procedures related for common laboratory operations were in place. In most cases procedures were in place; however, SOPs on computer validation, glassware cleaning, and document review were not.

Current Practice 2.3 Laboratory Test Procedures

This section review focused on reviewing specification documents, product testing procedures, and instrument use procedures and control of these documents. As with the general observations, the instrument procedures often lacked sufficient detail

making them difficult to use as written. Also, the creation and revision process for these documents is via manual system and is cumbersome and inefficient.

Current Practice 2.4 Laboratory Data and Results

This section review focused on ascertaining whether laboratory data and results are properly captured, processed, reviewed, and stored for later retrieval. In general, the laboratory has good systems for addressing these issues. Data are captured via instrument outputs and/or bound notebook entry. Calculations are preformed by software algorithms or by manual means. Regardless, all data are reviewed and signed off by a data verifier. Some issues do exist with respect to standardized integration/reintegration procedures for HPLC and GC chromatograms.

Current Practice 2.5 Security of Data

This section overlaps with the section described above for data and results in general. With the diversity of the tasks performed in the laboratory (e.g., finished product testing on one end and methods validation on the other) there are different means and locations for the storage of data. Finished product data are stored in the SITE's central archive. Although very secure, access to these data is very restricted making it difficult for someone to easily retrieve them. Methods validation data are at the other extreme and maintained in the laboratory area in standard locked filing cabinets. Open access, to just about anyone in the laboratory, is available during the work day and strict check in and out procedures are not followed. These records are also susceptible to water (from the overhead sprinkler system) and fire damage. Overall there is no disaster recovery system in place and no offsite data and records storage facility exists.

Current Practice 2.6 Distribution of Results

Much of the audit checklist review for this section focuses on the use of LIMS in the laboratory. SITE Quality Operations is not currently using a LIMS system so most of these questions are not applicable. Transcribed data that are captured via instrument output and transcribed to paper are properly reviewed by a second party.

Current Practice 2.7 Chromatography

This section addresses the proper use of system suitability for HPLC and GC chromatographic runs. The SITE Quality Operations Laboratory establishes appropriate system suitability for each of their chromatographic runs.

Current Practice 2.8 In-Processing Testing

All in-process testing is performed by the In-Process Quality Testing Laboratory.

Current Practice 2.9 Assignment of and Retest/Expiry Dates

All issues related to retesting and expiry is addressed by the Product Disposition Department.

Site Documents Reviewed

- C-141 Mesh Analysis, Potassium Chloride
- CV-064
- F-137 P-Dip Friability
- K-191
- YLP-02-002
- YLP-02-004
- L128 Theosux Loss on Drying
- MV-02-111
- MV-02-112
- Notebook YLP-2470 pp. 38
- Notebook YLP-2474
- Notebook YLP-2484 pp. 50
- Notebook YLP-2506 pp. 86
- Notebook YLP-2510 pp. 4-11
- Notebook YLP-2512 pp. 80-83
- Notebook YLP-2513 pp.139-147, 140-147
- P-226 P-Dip Chloride Identification
- PSD ??? V3 Chicken Soup Determination of Degradation Products
- PSD 2852 V8 Veggie Soup Content Uniformity
- PSD 2852 V8 Veggie Soup Description
- PSD 2885 V8 Veggie Soup Dissolution
- PSD 30503 Identification, TLC Micronized Loratadine
- PSD 4703 V3 Chicken Soup Description
- PSD 4703 V3 V3 Chicken Soup Description
- STP-591 Rowboat Moisture Content
- STP-688 Moisture in Vanilla
- USP <461> Nitrogen Content (in Cross Povidone)
- USP <578> P-Dip Disintegration
- USP <905> Rowboat Content Uniformity
- LEVEL II 22,409

Gaps in the System versus the Audit Checklist

The following matrix correlates potential gaps uncovered during the self audit and links them to specific line times in the audit checklist. In addition to the gap, the matrix also indicates if the gap represents part of the system that is in sustainable compliance

(e.g., No = a Critical finding which potentially could result in a Form 483 finding, if discovered by the REGULATORY AGENCY), what the potential root cause may be for the gap and some suggestions for potential corrective action to make the system become compliant. If the auditors did not make suggestions as to the root cause or potential corrective action to become compliant, the statement "None offered" in included in the space.

In addition to the findings correlated directly to the audit checklist, additional gaps are included in the matrix. In some circumstances the description serves as the gap and therefore the gap block may state "Same as description."

Gaps in the System: Laboratory Subelement 2.0 Laboratory Documentation Practices and Standard Operating Procedures (OP)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
2.1.3 Are the SOPs current, clearly written, and accessible to all appropriate personnel?	Many SOPs and standard test procedures are not clearly written and therefore difficult to understand and follow.		None offered.	Perform a detailed, logical, prioritized wholesale review of existing SOPs within the laboratory. Consider clarity and language consistency in the review.
2.1.4 Is there a system for periodic review of all SOPs to assure that they are consistent with current company and industry practices?	Although there is a system in place, it is manual and very difficult to manage efficiently.		There are too many SOPs in use to manually track and review.	Begin using Wise Crack or similar software to organize and track periodic review of SOPs.
2.1.6 Is there a system for controlling the issuance and revision of all SOPs?	The system for controlling the issuance and revision of all SOPs is not fully documented in an SOP.	No	None offered.	Revise existing SOPs covering change control in the laboratory and include all steps which are currently performed but not documented.
2.1.7 Are policies and manuals used that supplement the SOPs? (e.g., Level I and II guidance documents)?	Policies and manuals do exist such as the ASQ and SQA documents, but they are not accessible or current.		None offered.	Revise existing SOPs covering change control in the laboratory and include all steps which are

				currently performed but not documented.
2.1.9 Are all SOPs reviewed and updated at least every year?	There is currently no automated system to track the mandatory 1-year SOP review requirement.	No	None offered. SOPs should be reviewed at least once a year.	Revise existing SOPs covering change control in the laboratory and include all steps, which are currently performed but not documented. Formalize and organize, using software tools when possible, the 1-year review period.
2.2.1 Are there specific standard operating procedures covering: change control?	There is currently no laboratory procedure which, address the change authorization process.	No	None offered.	Create a document which delineates the change authorization process for the laboratory.
2.2.8 Are there specific standard operating procedures covering: Policy for identification and reporting new impurities and/or higher levels of previously known impurities?	There are no SOPs addressing discovery of new impurities and/or higher levels of known impurities such as what is seen in Chicken Soup.	No	None offered.	Create a document which delineates how to address new impurities and/or higher levels of known impurities when they appear during stability studies.

(*Continued*)

Gaps in the System: Laboratory Subelement 2.0 Laboratory Documentation Practices and Standard Operating Procedures (OP) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
9.17 Data recording practices are different for the Analytical and In-Process laboratories (controlled data sheets vs. notebooks). Practices should be harmonized.	Same as description		The In-Process Laboratories often function independently from the other labs within the QO laboratory operation. This may lead to differences in practices between the Chemistry and the In-Process labs.	None offered.
9.18 No system exists to generate Standard Test Procedures within a reasonable period of time following completion of methods validation activities. For example, the Stickmud Traces method has been validated since (MV 69-007) 1999, but there is still no written procedure.	Same as description		Current change authorization procedure is inefficient and needs to be revised.	Perform a detailed, process diagram-based evaluation of the CA procedures. Modify to improve efficiency.

Laboratory Control System Subelement:	***3.0 Laboratory Equipment Qualification and Calibration (LE)***
Auditor(s):	J. Felix, A. Lavio, J. Smyth, N. Ran

Description of the QMS Subelement 3.0 Laboratory Equipment Qualification and Calibration (LE)

The Laboratory Equipment Qualification and Calibration subelement has three individual topics as defined in the audit checklist. These are: Laboratory Equipment Procedures—General, Laboratory Equipment Procedures—Specific, and Laboratory Equipment Procedures—Computer Controlled. Each of these topics are addressed separately as part of the subelement discussion in following sections.

Current Practice 3.1 Laboratory Equipment Procedures—General

This section addressed basic aspects of the laboratory equipment qualification, calibration, and maintenance program. Some of the review items included verification of master equipment lists, procedures for maintenance and calibration, equipment-use logs, and labeling of equipment. Overall the Quality Operations Laboratory has the rudimentary components of this system in place although the personnel are overburdened with other aspects of their jobs. This leads to a degraded state of compliance with their own procedures and industry practice in general.

Current Practice 3.2 Laboratory Equipment Procedures—Specific

This section reviewed aspects of equipment IQ, OQ, PQ, calibration and maintenance for specific pieces of equipment one would find in a typical analytical laboratory. Equipment records reviewed included pH meters, balances, thermometers, UV spectrophotometers, dissolutions baths, HPLCs, and GCs. As stated here, the Quality Operations Laboratory has the rudimentary components of this system in place although the personnel are overburdened with other aspects of their jobs. This leads to a degraded state of compliance with their own procedures and industry practice in general.

Current Practice 3.3 Laboratory Equipment Procedures—Computer Controlled

This section reviewed specific aspects of equipment IQ, OQ and PQ, related to computer-controlled equipment and the appropriateness of software validation. As with the reference standards handling, in general, equipment qualification of computer controlled devices is not handled in accordance with current industry standards. This area also represents one of the greater challenges in the Quality Operations Laboratory.

Site Documents Reviewed

- YLP 11-028 *Lab Hood Verification*
- YLP 11-*122 Operation, Qualification and Calibration of Balances*
- YLP 011-149 *Operation of the Autosampler System For Total Organic Carbon (TOC) Analyzer Sievers, Model 800*
- YLP 011-174 *Operation of the Amsco SV-120*
- YLP 02-002 *Laboratory Safety Procedures*
- YLP 02-007 *Analytical Laboratory Investigations Including Out-of-Specification Results*
- YLP 02-016 *Requalification of Reference Standards*
- YLP 02-105 *Verification of Calibration Certificates Issued by an Outside Contractor*

Gaps in the System versus the Audit Checklist

The following matrix correlates potential gaps uncovered during the Self Audit and links them to specific line times in the Audit Checklist. In addition to the gap, the matrix also indicates if the gap represents part of the system that is in sustainable compliance (e.g., No = a Critical finding which potentially could result in a Form 483 finding, if discovered by FDA), what the potential root cause may be for the gap, and some suggestions for potential corrective action to make the system become compliant. If the auditors did not make suggestions as to the root cause or potential corrective action to become compliant, the statement "None offered" is included in the space.

In addition to the findings correlated directly to the audit checklist, additional gaps are included in the matrix. In some circumstances the description serves as the gap and therefore the gap block may state "Same as description."

Gaps in the System: Laboratory Subelement 3.0 Laboratory Equipment Qualification and Calibration (LE)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
3.1.1 Are the laboratories equipped with all of the necessary instruments for the analytical testing to be performed?	Many instruments are awaiting IQ/OQ/PQ, and are therefore not in use. Work around situations are present in the lab area.		There is a lack of adequate laboratory resources for performing IQ/OQ/PQ. There may be a lack of adequate GMP training on equipment related issues.	Conduct an inventory of equipment available in the labs and compare this inventory with the needs of the lab. Also, QA should be more actively involved in auditing the labs and associated areas to verify that (1) CGMPs are practiced and (2) Equipment qualifications are completed in a timely manner.
3.1.3 Is there a master equipment list available and is it properly maintained?	Test equipment and lab facilities (hoods) are not included in any equipment list. More than one (1) master equipment list exists. 1. There should be only one version of the master equipment list. 2. Master equipment list should include all analytical instrumentation, laboratory	No	Calibration/metrology program description SOP does not describe how to document and track analytical lab equipment and associated test standards.	Perform an equipment inventory in the labs and in the metrology area. Work with metrology to update and correct the master equipment list. Eliminate all other existing lists. Update associated SOPs with instruction for a single master equipment list.

(*Continued*)

Gaps in the System: Laboratory Subelement 3.0 Laboratory Equipment Qualification and Calibration (LE) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
	facilities equipment, and all test equipment and standard reference materials (SRMs). 3. Master equipment list must also indicate status (active/ inactive equipment).			
3.1.6 Are calibration/ service vendors qualified and are their training records available?	Contractors/vendors are not consistently trained to pertinent company SOPs. For example: 1. There is no indication that the site SOP is followed for calibration of AA by the Pooky-Elmer service personnel or if they have been trained on the SOP 2. There are no training records for Pooky-Elmer personnel.	No	No QA audit of the vendors has been conducted.	Obtain contractor training records and/or train contractors in SP SOPs; update contractor files. Implement an SOP if necessary.
3.1.9 Does each piece of equipment have a logbook or file, which documents instrument	Logbooks were available for the laboratory equipment, but entries were inconsistent. This problem prevailed throughout.	No	Ineffective logbook entry and usage training.	Review logbook entry practices throughout the laboratory. Retrain personnel as necessary.

maintenance, calibration and repair histories?	1. AAA-4 contained no distinct entry indicating the performance of PM. 2. IR-8 had no log-in or log-out indicated in logbook. 3. HPLC-25 was out of service, but the associated logbook had no entry to indicate the out-of-service status 4. Differing formats for time entries have been entered into logbooks. 5. Logbook XX-8 had a yellow sticky note with writing on it adhered to one of its pages. All information should be recorded directly onto the logbook page; other sources for notes are not to be used. This logbook also contained out of sequence dating. 6. The logbook for Dissolution Bath 1 was missing the entry for the calibration of the thermistor. 7. For the Star Ion Analyzer, calibration prior to use is required. The calibration has

(*Continued*)

Gaps in the System: Laboratory Subelement 3.0 Laboratory Equipment Qualification and Calibration (LE) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
	not been noted in the associated logbook. 8. HPLC 52 had no entry for calibration. 9. TCB-1 showed no record of use logbook available.			
3.1.12 Has IQ/OQ/PQ been performed and properly documented for all equipment?	Instruments are not in use because IQ/OQ/PQ has not yet been completed. For example, no balance printers have been qualified.		Lack of effective IQ/OQ/PQ strategy.	Mandate a timeline for completion of IQ/OQ/PQ and salvage of lab equipment. Conduct internal audits to verify adherence to this timeline.
3.1.17 Is there an SOP, which requires that instrument failing calibration be removed from service?	YLP 666 should be used for out-of-service labeling. Also, some equipment labeled as out-of-service was still being used. For example: 1. The out-of-service label affixed to HPLC-32 was not the correct form. A piece of paper with “out-of-service” written on it was used to label the HPLC system as out-of-service.		Ineffective or inadequate SOP and GMP training for this subject.	Retrain personnel on associated SOPs and provide refresher GMP training in this area. Confirm that SOPs are adequate. If needed, revise and update SOPs.

	2. EEE-13 is labeled as out-of-service, but it is being used.			
9.1 Issues exist in the glassware washing area.	Issues in the glassware washing area include: 1. There was a big puddle of water on the floor by the water system (Water System #1). 2. The water system is inadequately labeled (masking tape was used to indicate valves). 3. No ID on glassware dryers. 4. The glassware dryers are used for drying critical glassware, however, they are not on a calibration schedule.	No	Lack of an internal audit system.	QA should audit the labs and associated areas to verify: 1. SOPs are adhered to. 2. CGMPs are practiced. 3. Equipment qualifications are completed in a timely manner.
9.2 Issues exist with respect to standard reference materials (SRMs)	Issues include lack of organization of SRMs such as: 1. Test equipment and standard reference Materials are not listed on the master equipment list.	No	Overburdened personnel, and infective GMP training on this subject.	Conduct remedial GMP training and follow-up audits. Hire personnel to keep the metrology lab area organized.

(*Continued*)

Gaps in the System: Laboratory Subelement 3.0 Laboratory Equipment Qualification and Calibration (LE) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
	2. DC-06 (dial thickness gauge) had an incorrect calibration sticker on it. The date was mistakenly written so that the piece appeared to be out-of-calibration. There had been no correction yet made and/or it had not been taken out of service. Personnel were planning on using it if they needed it. GMP retraining needs to be done in reference to this issue.			

Laboratory Control System Subelement:	***4.0 Laboratory Facilities (LF)***
Auditor(s):	J. Felix, A. Lavio, U. Smith, T. Johnson

Description of the QMS Subelement 4.0 Laboratory Facilities (LF)

The Laboratory Facilities subelement has three individual topics as defined in the audit checklist. These are: Laboratory Facilities—General, Safety and Environmental Concerns, and Laboratory Glassware. Each of these topics is addressed separately as part of the subelement discussion in the following sections.

The review of this subelement for all of the following sections involved making copies of the audit checklist and systematically inspecting each one of the separate labs and spaces in the Quality Operations Laboratory area. A final *complete* checklist was then filled out and the individual completed checklists were attached for reference.

Current Practice 4.1 Laboratory Facilities—General

For this section the overall physical layout, outfitting, and construction was evaluated for the Quality Operations Laboratory. This included determining the adequacy of space, the adequacy of utilities and services as well as the availability of SOPs and status of general housekeeping. In several cases, the laboratory was lacking in the areas of HVAC and water systems qualification and maintenance.

Current Practice 4.2 Safety and Environmental Concerns

For this section, the overall status of the safety systems in the Quality Operations Laboratory was reviewed. This included evaluation of the safety and environmental SOPs, the status of hood testing, and hazardous waste handling and disposal. Much of this system could be upgraded to meet current industry standards.

Current Practice 4.3 Laboratory Glassware

This review detailed current practices for manual and mechanical glassware washing the Quality Operations Laboratory. At the time of the self audit, the laboratory was in the process of assisting in development of the new LEVEL II 22,777 *Laboratory Volumetric Glassware Requirements and Glassware and Laboratory Equipment Cleaning*. Therefore, no current Level III document exists and some issues with respect to validation of manual and mechanical glassware cleaning exist.

Site Documents Reviewed

- YLP 011-028
- YLP 01-119
- YLP 02-003
- YLP 02-020

- YLP 02-023
- YLP 02-033
- YLP-09-008 rev8
- LEVEL II 10,101

Gaps in the System versus the Audit Checklist

The following matrix correlates potential gaps uncovered during the self audit and links them to specific line times in the audit checklist. In addition to the gap, the matrix also indicates if the gap represents part of the system, that is in sustainable compliance (e.g. No = a Critical finding which potentially could result in a Form 483 finding, if discovered by FDA), what the potential root cause may be for the gap, and some suggestions for potential corrective action to make the system become compliant. If the auditors did not make suggestions as to the root cause or potential corrective action to become compliant, the statement "None offered" is included in the space.

In addition to the findings correlated directly to the audit checklist, additional gaps are included in the matrix. In some circumstances the description serves as the gap and therefore the gap block may state "Same as description."

Gaps in the System: Laboratory Subelement 4.0 Laboratory Facilities (LF)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
4.1.1 Are the physical construction of the laboratory areas adequate for testing and all routine activities with respect to:	The ceiling and walls of room 222 are not the same quality of the manufacturing areas they serve. Also the floor paint is peeling causing housekeeping concerns.	No	Area relocated and not upgraded. Physical facilities are not adequate for testing and other routine activities (room too small).	Replace or upgrade ceiling and walls to meet requirements of the draft LEVEL II. Clean and paint floor. Explore possible relocation.
4.1.1.1 Size 4.1.1.2 Layout and design 4.1.1.3 Sample receipt 4.1.1.4 Appropriate tables for balances/instruments, etc. 4.1.1.7 Data entry, recording, writing areas 4.1.1.8 Sample storage and retention 4.1.1.9 Refrigeration	In room 327 access to electrical panel is blocked by a storage cabinet. Overall, room 327 is very full thus restricting access to equipment. In extended release lab room 319, a balance is located on a table top. In stability room 319, a balance is located under an air supply register. Electrical device panels and receptacles are inconsistently identified in all QO laboratory and manufacturing areas.		SOP YLP 011-122 was not followed. No system in place in the engineering area for the identification of electrical devices.	Generate a workorder to move balances (scales) from current location to an adequate one. Make purchase order for a marble balance table. Follow SOP YLP 011-122. Generate a control system (SOP). See YLP 09-008 a related SOP for major electrical equipment.

(*Continued*)

Gaps in the System: Laboratory Subelement 4.0 Laboratory Facilities (LF) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
4.1.2 Are proper systems in place to minimize cross-contamination during sample preparation and laboratory testing?	In room 222, samples from more than one product are stored together in one small storage area. Stacking of samples in containers is required.		Lack of sufficient storage facilities and space.	Design space and storage facilities to eliminate common storage.
4.1.3 Are all controlled temperature/humidity storage areas, incubators, etc., monitored to assure that proper conditions are maintained?	There are no chart recorders installed in the QO incoming and in-process laboratory facilities to assure that proper conditions are maintained in each individual room.	No	See 4.1.7	See 4.1.7
4.1.4 Have temperature monitoring systems and equipment been properly validated?	Computer system for building management has not been validated.	No	See 4.1.7	See 4.1.7

Laboratory Control System Subelement:	***5.0 Methods Validation and Technology Transfer (MV)***
Auditor(s):	J. Foosball, W. Link, E. Vazquez, D. Blistex

Description of the QMS Subelement 5.0 Methods Validation and Technology Transfer (MV)

The Laboratory Methods Validation and Technology Transfer subelement has three individual topics as defined in the audit checklist. These are: Validation of Analytical Methods—General, Cleaning Methods Validation, and Procedures for Methods Transfer. These three topics are addressed separately as part of the subelement discussion in the following sections.

CURRENT PRACTICE 5.1 VALIDATION OF ANALYTICAL METHODS-GENERAL

This review was limited in scope due to the fact that the majority of the methods validations are initiated and performed primarily by the Research and Development Group in Tahiti. However, technology transfer is an important part of the Quality Operations Laboratory involvement with respect to methods validation. It should be noted however, that the QO Laboratory at SITE does perform some limited methods validations on older products in an effort to upgrade the quality of the methods in order to comply with CGMPs. In order to perform a complete assessment, one older product and one newer product were selected for review. Specifically, Vanilla and Egg Salad documents related to methods validation and technology transfer (including the NDA CMC sections) were reviewed using the audit checklists and additional checklists created specifically for this portion of the audit. These additional checklists that were generated using existing Level II and Level III documents for methods validation and cleaning validation. The overall results of these assessments concluded that SITE has not yet been involved in an analytical methods validation/technology transfer exercise that fully uses the guidance spelled out in the Level II and Level III documents. Therefore, it is difficult to state what the true current state of compliance with industry standards. Because of this, the Tahiti R &D Group should be consulted to determine when the next methods transfer will occur and a future audit should be scheduled for some time following its transfer.

Current Practice 5.2 Cleaning Methods Validation

This review looked at the cleaning validation documents associated with Zoofoot. A checklist which was developed using LEVEL II 22,169 *Cleaning Validation for Drug Products and Active Pharmaceutical Ingredients* in addition to the audit checklists. The cleaning validation package for Zoofoot was then reviewed against it. Cleaning validation studies are initiated by protocol at SITE and involve determining recoveries from various surfaces. Although a Level II document does exist there is no corresponding

Level III procedure. Cleaning validation summary reports are generated as the finished product for these studies.

Current Practice 5.3 Procedures for Methods Transfer

As stated in 5.1, the SITE has not yet been involved in an analytical methods validation/technology transfer exercise, which fully uses the guidance spelled out in the new Level II and Level III documents. Therefore, it is difficult to state what the true current state of compliance with industry standards is. However, methods transferred to this point have been executed via issuance of a protocol and completed by publication of technology transfer summary reports in alignment with current industry practice.

Site Documents Reviewed

- YLP-01-019
- *Zoofoot Tablets 10 mg Analytical Technology Transfer Protocol Addendum,* Nov 32, 2007
- *Zoofoot Tablets 10 mg Analytical Technology Transfer Protocol for Drug Products Methods,* MV 01-103 Nov 2. 2011
- *Zoofoot Tablets 10 mg Analytical Technology Transfer Report for Drug Products Methods,* MV 01-103 Dec 18, 2011
- *Training Program for the Analytical Laboratory Testing of Zoofoot Tablets, 10 mg,* Nov 2, 2001.
- YLP-02-019
- Master list, process validation activities for 2009
- NDA CMC Section for Egg Salad
- NDA CMC Section for Vanilla
- Protocol*: Validation of Analytical Methodology, Rinse and Swab Sampling Technique for Zoofoot API on Product Contact Surfaces for Cleaning Validation Studies*
- STP 689
- STP 690
- Summary Report*: Validation of Analytical Methodology, Rinse and Swab Sampling Technique for Zoofoot on Product Contact Surfaces for Cleaning Validation Studies* MV-00-0009
- LEVEL II 23,102
- LEVEL II 22,305
- LEVEL II 23,706

Gaps in the System versus the Audit Checklist

The following matrix correlates potential gaps uncovered during the self audit and links them to specific line times in the audit checklist. In addition to the gap, the matrix also indicates if the gap represents part of the system that is in sustainable compliance (e.g., No = a Critical finding which potentially could result in a Form 483 finding, if discovered

by FDA), what the potential root cause may be for the gap, and some suggestions for potential corrective action to make the system become compliant. If the auditor did not make suggestions as to the root cause or potential corrective action to become compliant, the statement "None offered" in included in the space.

In addition to the findings correlated directly to the audit checklist, additional gaps are included in the matrix. In some circumstances the description serves as the gap and therefore the gap block may state "Same as description."

Gaps in the System: Laboratory Subelement 5.0 Methods Validation and Technology Transfer (MV)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
5.1.1 Is there a general SOP for methods validation?	SITE is performing methods validation but does not have an active Level III SOP.	No	The SITE QC Laboratory does not have the primary responsibility for developing and validating analytical methods. However, due to the flexible nature of work they are some times called upon to perform limited methods validations/revalidations but do not have a Level III SOP to support this effort.	Create a Level III SOP based on existing Level II standard.
5.2.2 Is cleaning validation conducted according to a master plan or schedule?	SITE is not performing cleaning validation according to a master plan or schedule.		A lack of detailed scheduling and planning with Nation Wide and Local Technical Services often causes work to be performed in a rushed manner and increases excessive	Communication with Nation Wide Technical Services and Local Technical Services needs to be improved. The QO Laboratory needs to approach improving communications from a process diagram format.

		peak workloads. Work is often a surprise to the analysts. In addition, no single individual within the QC Laboratory communicates and coordinates these efforts.	By showing how these other departments impact upon the QO Lab workflow, a better understanding and appreciation of what the lab has to accomplish may be imparted.
9.1 Analysts at the bench level are not involved in constructing the technology transfer protocols, thus degrading the executability of the protocols, which can lead to errors.	Same as description	None offered.	Have bench-level personnel review technology transfer protocols prior to their approval.
9.2 A lack of detailed scheduling and planning with Nation Wide and Local Technical Services often causes work to be performed in a rushed manner and creates excessive peak workloads.	Same as description.	Lack of planning and lack of project management.	Communication with Nation Wide Technical Services and Local Technical Services needs to be improved. The QO Laboratory needs to approach improving

(*Continued*)

Gaps in the System: Laboratory Subelement 5.0 Methods Validation and Technology Transfer (MV) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
Work is often a surprise to the analysts. In addition, no single individual within the QC Laboratory communicates and coordinates these efforts.				communications from a process diagram format. By showing how these other departments impact upon the QO Laboratory workflow, a better understanding and appreciation of what the lab has to accomplish may be imparted. Personnel for all departments need to receive some basic project management training.

Laboratory Control System Subelement:	***6.0 Laboratory Computer Systems (LC)***
Auditor(s):	M. Gummy, W. Link, E. Vazquez, R. Gillen

Description of the QMS Subelement 6.0 Laboratory Computer Systems (LC)

The Laboratory Computer Systems subelement has seven individual topics as defined in the audit checklist. These are: Laboratory Computer Systems—General, Centralized and Network-Attached Data Systems, Stand-Alone Data Systems, SOPs and Records, Laboratory Information Management Systems (LIMS), Spreadsheets, and Other Systems. Each of these topics is addressed separately as part of the subelement discussion in the following sections. Audit of this subelement involved interviews with laboratory representatives who are working with the site computer personnel to address computer related issues identified during previous corporate QA audits. In addition, a rewritten version of the audit checklist was developed and used to evaluate the laboratories current status.

Current Practice 6.1 Laboratory Computer Systems-General

In general, the Quality Operations Laboratory has several issues with respect to validation of computer systems and documentation, in general. As examples, there are currently no procedures in place, that govern data naming conventions for projects, analyses, products, and so on. Moreover, there currently is no disaster recovery plan in place for laboratory computer systems. These types of laboratory computer infrastructure issues impose substantial risk to the short-term and long-term security and integrity of laboratory data.

Current Practice 6.2 Centralized and Network-Attached Data Systems

The Quality Operations Laboratory is currently in the process of establishing a more formal relationship with the corporate IT group, which is located in Tahiti. As part of that relationship, SOPs are being created which address data management, incident management, performance monitoring, and so on, for server based laboratory applications. Until these SOPs are completed, no formal policy or procedure exists to address network-attached data systems.

Current Practice 6.3 Stand-Alone Data Systems

Issues related to stand-alone data systems are currently the responsibility of the individual group leaders within the Quality Operations Laboratory. These responsibilities relate to data back-up procedures and schedules, storage of back-up media, and restoration of data when necessary. None of these procedures is currently defined in a formal SOP.

Current Practice 6.4 SOPs and Records

SOPs for addressing laboratory computer systems have until recently been part of the laboratories responsibility and thus no formal SOPs exist. These responsibilities are being transferred to the corporate IT group who will generate formal, reviewed and approved SOPs. The laboratory needs to be involved in those processes.

Current Practice 6.5 Laboratory Information Management Systems (LIMS)

LIMS is currently not in use in the SITE Quality Operations Laboratory.

Current Practice 6.6 Spreadsheets

No evidence was discovered during the audit, which showed the use of unvalidated spreadsheets to generate CMGP data. Spreadsheets are currently used in the read-only mode and are unalterable. No SOP exists defining their generation and use, however.

Current Practice 6.7 Other Systems

The only system falling under this category is the electronic training record software, XTrain. This is a centrally supported application and it has been validated by the corporate IT department.

Site Documents Reviewed

- Computer server system validation protocols
- YLP 01-102
- Milan OQ/PQ software validation protocols
- LEVEL II 22,110 to LEVEL II 2,116 DRAFT

Gaps in the System versus the Audit Checklist

The following matrix correlates potential gaps uncovered during the self audit and links them to specific line times in the audit checklist. In addition to the gap, the matrix also indicates if the gap represents part of the system, that is in sustainable compliance (e.g., No = a Critical finding which potentially could result in a Form 483 finding, if discovered by FDA), what the potential root cause may be for the gap, and some suggestions for potential corrective action to make the system become compliant. If the auditors did not make suggestions as to the root cause or potential corrective action to become compliant, the statement “None offered” in included in the space.

In addition to the findings correlated directly to the audit checklist, additional gaps are included in the matrix. In some circumstances the description serves as the gap and therefore the gap block may state “Same as description.”

Gaps in the System: Laboratory Subelement 6.0 Laboratory Computer Systems (LC)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
6.1.2 Is a disaster recovery plan in place addressing laboratory data systems?	There is no IT disaster recovery plan for the site. It is being developed with cooperation of user organizations and is in draft stage at this time.	No	Lack of awareness of importance of a disaster recovery plan.	Complete development of the plan which is now in progress ensuring participation by laboratory staff.
6.1.3 And 6.1.4 Have all GMP laboratory data systems and associated file servers been validated in accordance with applicable standards, and reviewed for compliance with 21 CFR Part 11?	Laboratory data systems have not been validated in accordance with applicable standards and procedures.	No	Incomplete OQ/PQ protocols were generated during initial validation. Outdated or incomplete validations are presently in place. In addition, an inaccurate Part 11 assessment was conducted.	Investigate system status as assessed and documented by SITE, corporate (Tahiti) staff. Assess implications for SITE laboratory and recommend a course of action.
6.1.5 Are GMP workstations clearly labeled as such?	GXP workstation is not labeled.		Lack of training on GXP labeling.	Label correctly and retrain responsible personnel.
6.16 Is access to laboratory workstations through operating systems that provide individual	1. IT has no formal procedure which documents the	No	Lack of understanding of need for proper documentation.	Develop formal documentation of configuration and

(*Continued*)

Gaps in the System: Laboratory Subelement 6.0 Laboratory Computer Systems (LC) (*Continued*)

Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
user accounts? How are they controlled?	configuration of workstations and the requirements for users who access them. 2. Windows 95 is still in use for some workstations.		Old (legacy) system	requirements for users. Provide training for all site personnel who have workstation access. Replace software application with compliant version.
6.1.7 Are workstations configured with password-controlled screensavers or other automatic locking mechanism?	One computer in immediate release area had screensaver and password turned off.		Miss configuration and/ or user modified setting.	Review all computer workstations for compliance with IT standard.
6.1.9 Are procedures in place to govern data naming conventions for projects, analyses, products, etc.?	There are currently no procedures in place, which govern data naming conventions in general.		None offered.	Implement Level II and III documents.
6.2.2 Are there documented service-level agreements with the central support organization defining mutual expectations and responsibilities?	IT has no documented, routinely updated service agreement with the lab to identify needs and expectations from systems they support.		Lack of knowledge.	Schedule a meeting to establish needs. SOP can then be written to cover the agreements.
6.2.6 Does the central support organization have server/ application SOPs which address	1. IT has an incomplete set of SOP's for basic operational functions		Lack of resources in the IT Department.	Assign priorities in order to properly develop and implement procedures.

data management, incident management, performance monitoring, etc. specific to the laboratory?	such as configuration management, performance management, backup and restore, plus others. 2. The lab has SOP YLP 02-102 dealing with SuperSmart administration and operation, which should be transferred to IT.		By the time of implementation responsibilities were not clearly defined.	A change authorization needs to be generated to transfer procedure to IT area.
6.3.1 Are back-ups performed either automatically (scheduled through a system procedure) or manually as defined by SOP?	No formal SOP exists that define how data back-ups are to be performed.	No	None offered.	Create and implement an SOP.
6.4.1 Do SOPs exist for the validation of laboratory data systems?	Existing SOPs for system validation do not meet current standards.	No	The new Level II document on computer validation and system life-cycle needs and the supporting Level III SOPs at the site have not been completed or implemented.	Continue existing efforts on computer management.
6.6.2 Are procedures in place governing the development/ modification of spreadsheets for GMP use?	No SOP exists defining the generation and use of spreadsheets in the laboratory.		None offered.	Create and implement an SOP.

Laboratory Control System Subelement:	***7.0 Laboratory Investigations (LI)***
Auditor(s):	R. Minky, B. McMillan

Description of the QMS Subelement 7.0 Laboratory Investigations (LI)

The Laboratory Investigations subelement has three individual topics as defined in the audit checklist. These are: Laboratory Investigations—General, Laboratory Investigations—Execution, and Laboratory Investigations—Documentation. Each of these topics is addressed separately as part of the subelement discussion in the following sections. Audit of the subelement involved interviews with laboratory personnel who are performing investigations. In addition, a random selection of completed laboratory investigation reports (LIRs) was reviewed and assessed for their completeness and accuracy as well as the training records of all laboratory personnel associated with these investigations. Fourteen LIRs were chosen in all. The Laboratory Investigations were reviewed for:

- Description of the event
- Root cause determination
- The investigation thought process
- Conclusion
- Corrective action–preventive action recommendations
- Assessment of impact event cause investigation

Current Practice 7.1 Laboratory Investigations—General

The Quality Operations Laboratory has successfully created and implemented a Level III SOP within the last year. This SOP is based on corporate guidance documents and the Level II SOP as well. The Level III SOP is very thorough and provides sufficient detail to be used as a daily working document. All personnel engaged in performing laboratory investigations have been trained on this procedure. The SOP includes flowcharts, checklists, and forms, which structure the investigation and guide the investigator through the investigation process. Detail is included within the checklist to insure that special considerations, which may be specific for certain analytical techniques are addressed during the investigation.

Current Practice 7.2 Laboratory Investigations—Execution

Laboratory investigations are conducted by specialists who were specifically hired and trained to conduct deviation and out of specification investigations for the Quality Operations Laboratory. Currently there are two full-time investigators on staff. These investigators work closely with the analysts who generated the aberrant results, the front line supervisors, mid level management and QA to complete the investigations within the specified time frame required by SOP. The Level III SOP and associated forms are used in every case.

Current Practice 7.3 Laboratory Investigations—Documentation

The laboratory investigation process is supported by the use of a validated, in-house software program is used to insure the timely and accurate completion of the investigations. Supporting documentation is collected, compiled and filed appropriately in a paper filing system. However, all supporting paperwork is scanned and made available electronically through secure document format (pdf files). All investigations are tracked and trended as appropriate and the data are used to support annual product reviews. Whenever possible, the root causes of the events are determined and reported.

Randomly Sampled Competed Investigations—Findings

Of the 14 randomly sampled laboratory investigation reports, the overall findings were generally adequate in:

- Describing the event
- Determining the root cause
- Performing the investigation
- Supporting the conclusion with data
- Recommending a course of action or product disposition
- Providing a corrective action and instituting a preventive action
- Correctly assessing impact

Site Documents Reviewed

- Corporate Level I Guidance Document *Frame Work for Conducting Investigations*
- SITE Level II Guidance Document *Conduct Manufacturing and Laboratory Investigations*
- SOP YLP 02-007 *How to Conduct Laboratory Investigations*
- LIR 02-SUX-044
- LIR 02- SUX -069
- LIR 02- SUX -085
- LIR 02- SUX -087
- LIR 02- SUX -132
- LIR 02- SUX -144
- LIR 02- SUX -057
- LIR 02- SUX -011
- LIR 02- SUX -014
- LIR 02- SUX -017
- LIR 02- SUX -033
- LIR 02- SUX -047
- LIR 02- SUX -055
- LIR 02- SUX -066

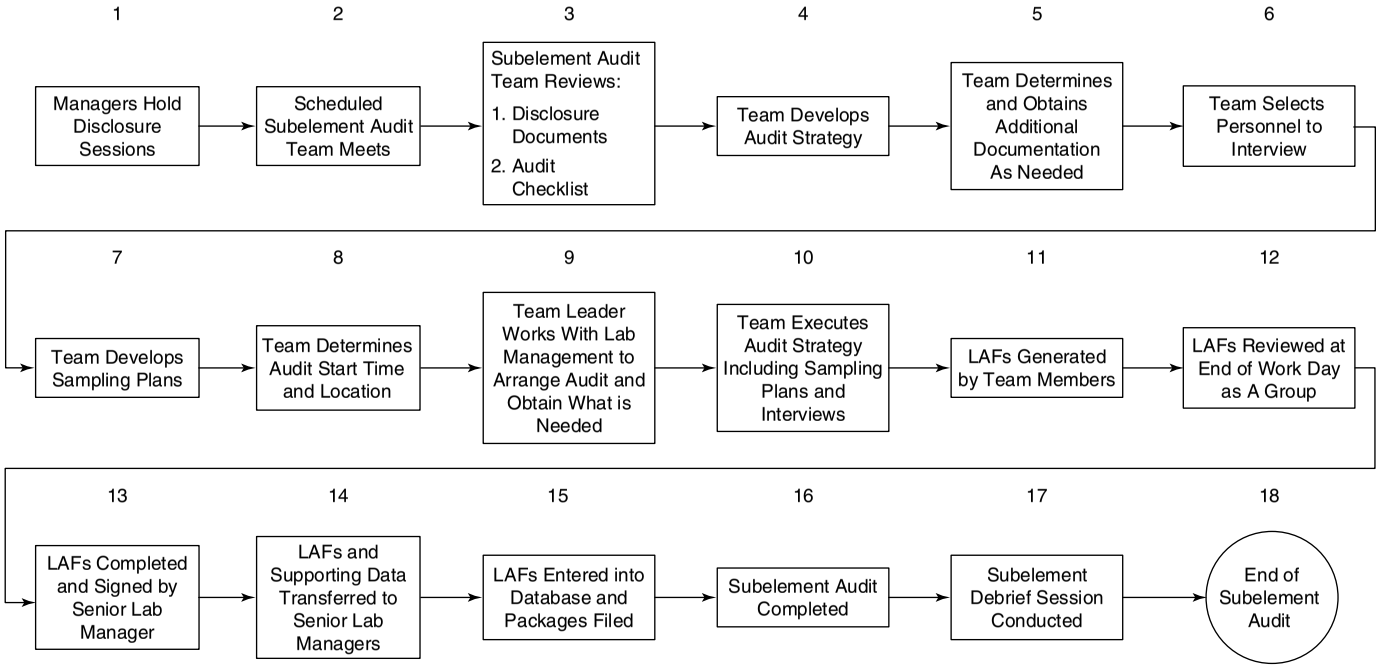
Gaps in the System

The following matrix summarizes the gaps and indicates if the gap is considered critical (e.g., potentially could result in a Form 483 finding, if discovered by FDA), what the potential root cause may be for the gap, and some suggestions for potential corrective action to become compliant are in this case shown in the preceding narrative. Since the Quality Operations Laboratory has, within the last year, undergone a wholesale revision of their laboratory investigation system, few gaps exist for this particular Laboratory Control System subelement.

Gaps in the System: Laboratory Subelement 7.0 Laboratory Investigations (LI)

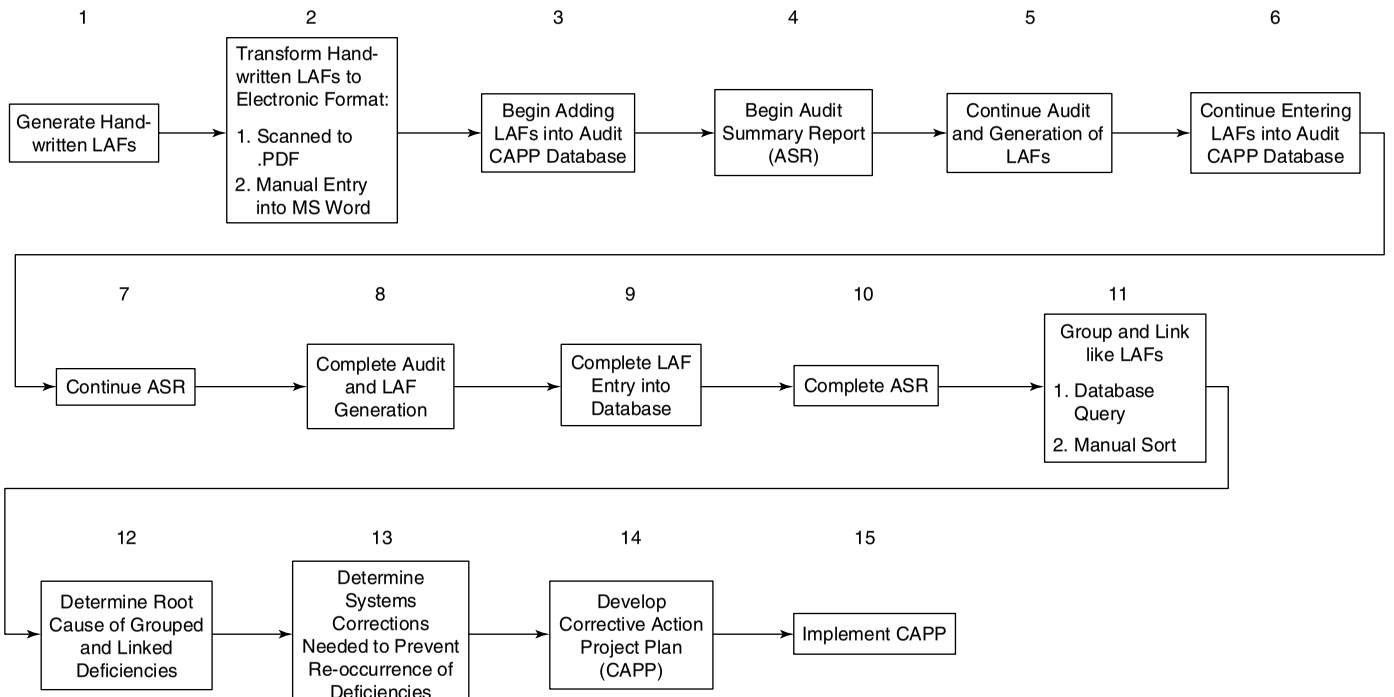
Checklist Item Number and Description	Gap	In Substantial Compliance?	Potential Root Cause	Potential Corrective Action
7.1.11 Are all laboratory personnel trained in the proper execution of laboratory investigations?	Some of the laboratory personnel responsible for creating aberrant results are not properly trained on the laboratory investigations SOP.		Since the Quality Operations Laboratory has two specialists who were specifically hired and trained to conduct deviation and out-of-specification (OOS) investigations some bench chemists have lapsed in their knowledge of the investigations process.	Insure that periodic retraining occurs on the investigations SOP for everyone in the laboratory.
9.1 A scientifically valid root cause was not determined for investigation LIR 02-SUX-033	Same as description.		The investigation specialist was not substantially familiar with the analytical technique used, which resulted in the aberrant result. Subsequently, management did not catch the lack of adequate root cause assignment.	Train the specialist on the analytical technique. Train managers to be aware that just because they have a specialist conducting investigations, they must remain actively involved in the investigation review process. The specialist must be trained to resist the urge to rubber stamp a completed investigation.

APPENDIX A SELF-AUDIT WORKFLOW



NOTES:

APPENDIX B LAF-TO-CORRECTIVE ACTION PLAN WORKFLOW



NOTES: