APPENDIX I

EXAMPLE AUDIT CHECKLISTS: LABORATORY SUBELEMENTS

The most efficient and effectively executed audits occur when checklists are used as the foundation for inquiry. Checklists should be the core instrument for execution of any audit. An audit should not be undertaken without the creation and use of some type of checklist or similar interview instrument.

Checklists may be used in a several fashions. First, they may be used as guide to help structure interviews and documentation collection and review. After the interviews and document review, checklists can be completed to determine whether all of the appropriate issues have been covered. Second, they may also be used strictly as checklists, in a question-and-answer form, determining whether the laboratory is in compliance with the CGMP components of the subelement. Third, checklists may be handed out to in advance to interviewees for completion with confirmation of the answers by the auditors during follow-up interviews. The audit team leader should review the corresponding checklist with each subelement audit team as part of the training process. Checklists may (and should) be modified as appropriate. This may include adding, removing, or modifying questions as appropriate.

Example checklists corresponding to all seven laboratory control system subelements follow. Considerable effort has been made to insure these checklists reflect current industry thinking with respect to interpretation and

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compliance with the CGMPs as they relate to laboratory operations. Undoubtedly, however, these checklists do not capture every facet of compliance for every laboratory within the pharmaceutical industry, nor in many circumstances be completely applicable to individual laboratory operations. Therefore, the end user is encouraged to use these example checklists as a guide and as a backbone for development of his or her own customized and tailored documents.

LABORATORY MANAGERIAL AND ADMINISTRATIVE SYSTEMS (MS) SUBELEMENT CHECKLIST

Laboratory managerial and administrative systems are those subelements which provide the infrastructure for efficient and compliant operations of an analytical laboratory. It is sometimes difficult to directly relate items within this subelement to CGMPs. However, deficiencies within this subelement that cannot be directly attributed to the CGMPs can lead to compliance failures. For example, 21 CFR Sections 210 and 211 do not specifically require that someone be assigned the duties of training manager. However, failing to have an individual responsible for training and consequently not have an effective training program can degrade the overall quality of data generated by laboratory personnel.

Laboratory managerial and administrative systems subelement includes at least eight individual topics. A laboratory in compliance with CGMPs should address each of these topics (as applicable). These topics include: (1) Organizational structure and roles and responsibilities, (2) Training, (3) Tracking and trending-statistical quality control, (4) Complaints, (5) Laboratory purchasing and requisition, (6) Laboratory administration, (7) Laboratory chemicals, solutions, reagents and supplies, and, (8) Laboratory reference standards and solutions.

These eight topics are outlined in the following lists along with some suggestions on what items should be addressed in each topic. The list of items under each topic is fairly comprehensive but may not be totally include all those components constituting the subelement.

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.1				*Organizational Structure and Roles & Responsibilities*
1.1.1				Are current organization charts available and accurate?
1.1.2				Is there a policy/procedure that defines the responsibility and authority of the quality control unit?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.1.3				Have the responsibilities of each functional group and supervisor been clearly defined, including testing and operational requirements, SOPs, and all other critical functions?
1.1.4				Is an organizational structure in place which is properly staffed to assure that all required testing/monitoring and support activities are performed?
1.1.5				Is the span of control and authority assigned to the quality control adequate to allow proper execution of these activities?
1.1.6				What is the ratio of supervision to analyst? (8:1 recommended)
1.1.7				Are the roles and responsibilities for each position clearly defined?
1.1.8				Are job descriptions available?
1.1.9				Are signature authority, responsibility, and accountabilities appropriate and clearly defined?
1.1.10				Do systems exist to enhance communications, understanding, and working relationships between laboratory and quality assurance personnel?
1.1.11				Does a personnel performance evaluation system exist which tracks laboratory personnel strengths and weaknesses and establishes corrective action procedures to mitigate any weaknesses?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.1.12				Does a master testing schedule or similar document(s) exist to insure smooth workflow and minimize laboratory personnel overcommitment?
1.1.13				Do current CVs and resumes exist for all personnel including consultants?
1.2				*Training*
1.2.1				Have the educational, training and work experience requirements for each laboratory position been clearly defined and do they reflect current standards in the industry?
1.2.2				Are training requirements clearly documented in an SOP or similar guidance document (including managers, supervisors, analysts and temporary staff)?
1.2.3				Has a training curriculum been developed for each position that clearly identifies training requirements for all required SOPs and policies, safety procedures, CGMPs as well as all other internal and external courses or programs? (database or hard copy)?
1.2.4				Is job-specific training identified and executed (e.g., laboratory analyst's qualification system)?
1.2.5				Does each employee have a training file or similar record?
1.2.6				Are the training histories for each individual employee kept current (database or hard copy)?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.2.7				Have all laboratory personnel been properly trained?
1.2.8				Is this training documented and are the documents available for review?
1.2.9				Is SOP training conducted in a fashion other than read-and-understand?
1.2.10				Are metrics used to determine effectiveness of SOP training?
1.2.11				Is there an analyst qualification program in place?
1.2.12				Has an individual been designated as the training coordinator or manager?
1.2.13				Is there evidence of management support for training and training programs?
1.2.14				Does a formal training budget exist?
1.2.15				Do vendor training records exist?
1.2.16				Is there evidence that newly hired employees are evaluated for skill level and competency?
1.2.17				Is there a formal training schedule in place and is it being executed?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.2.18				Is there evidence of employee retraining and requalification?
1.2.19				Is there a positive attitude with respect to training on the part of management and laboratory personnel?
1.3				*Tracking and Trending—Statistical Quality Control*
1.3.1				Is tracking and trending (e.g., control charting) of data performed with the following points to be considered:
1.3.1.1				For finished product testing?
1.3.1.2				For raw material testing?
1.3.1.3				Procedures delineated in an SOP?
1.3.1.4				Appropriate periodic evaluation of control chart data included annual product reviews?
1.3.1.5				Appropriateness of response to evaluations (e.g., excursions or trends are formally addressed as per SOP?)
1.3.1.6				For finished product-stability data (release and retain samples?)
1.4				*Complaints*
1.4.1				Is there a formal product complaint handling system in place, including some system of complaint monitoring and statistical review with the following points to be considered:

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.4.1.1				Procedures delineated in an SOP?
1.4.1.2				Site procedures consistent with standard industry practice?
1.4.1.3				Quality control laboratories are involved and provide testing as appropriate?
1.5				*Laboratory Purchasing and Requisition*
1.5.1				Are levels of approval defined and appropriate for purchasing and requisitions for the laboratory?
1.5.2				Are items purchased from qualified vendors (e.g., raw materials, reagents, standards, instruments, etc.)?
1.5.3				Does the laboratory have a defined yearly budget? Is the budget derived from existing data and projected workloads?
1.5.4				Does the laboratory have a defined capital budgeting process? Is the budget derived from existing data and projected needs?
1.5.5				Does the laboratory have a defined process for requesting and receiving approval to hire new personnel?
1.5.6				Does the laboratory have specific personnel assigned to purchasing and budgeting activities?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.5.7				Do these personnel have the proper skills and training to perform planning, budgeting, and purchasing activities?
1.6				*Laboratory Administration*
1.6.1				Does the laboratory have a general administrator, office manager, or similar administrative support person?
1.6.2				Is someone assigned the responsibility for:
1.6.2.1				Managing work orders for office and laboratory repairs?
1.6.2.2				Budget preparation, oversight, and review?
1.6.2.3				Overseeing stockroom operations?
1.6.2.4				Supervising requisition of administrative and operational supplies?
1.6.2.5				Managing external contractors and contracts?
1.6.2.6				Managing/enhancing communication between the laboratory and internal/external customers?
1.6.2.7				Supervising laboratory safety training and compliance?
1.6.2.8				Monitoring overtime billing?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.6.2.9				Capital equipment purchases?
1.6.2.10				Supervises administrative service personnel such as maintenance and calibration, laboratory computers, documentation section, and training section?
1.6.3				Are there laboratory corrective and preventive action committees or similar groups in place?
1.6.4				Are the laboratory corrective and preventive action committees' meeting minutes published and proposed actions communicated to all appropriate personnel?
1.6.5				Are data reported in all types of reports easily traceable to raw data?
1.7				*Laboratory Chemicals, Solutions, Reagents, and Supplies*
1.7.1				Is there a written procedure for receipt and storage of chemicals and reagents?
1.7.2				Are chemicals and reagents properly labeled with date of receipt, date opened, and expiration and retest dates?
1.7.3				Are laboratory prepared reagents and solutions properly identified? (e.g., chemical name or symbol, concentration, date of preparation, initials of the analyst who prepared it, and expiration date)?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.7.4				Are records available to document preparation and standardization of volumetric solutions?
1.7.5				Is the frequency of standardization of various reagents described? Is it consistent with the current USP?
1.7.6				Are standardized reagents properly stored to assure integrity?
1.7.7				Are there procedures that describe the preparation of laboratory reagents and cultures?
1.7.8				Are there procedures that describe the maintenance of laboratory reagents and cultures?
1.8				*Laboratory Reference Standards and Solutions*
1.8.1				Is there a written procedure for ordering and receipt of compendial reference standards and noncompendial reference standards?
1.8.2				Are the primary standards of the current lot listed in the USP, EP, or JP?
1.8.3				Is the receipt of the standards logged?
1.8.4				Are all standards labeled with name, source, lot number, and expiration date?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Managerial and Administrative Systems Subelement (MS)**
1.8.5				Do written procedures include provisions for prevention of contamination of primary standards?
1.8.6				Are standards stored in a secured area under environmentally controlled and monitored conditions?
1.8.7				Are procedures for assuring standard integrity available?
1.8.8				Are working or house standards checked against primary standards at appropriate intervals?
1.8.9				Are stock solutions appropriately identified and are their expirations based on their true stability?
1.8.10				Do procedures exist for the certification and use of noncommercially available reference standards?
1.8.11				Do certificates of analysis exist for all reference standards and are these certificates stored as controlled documents?
1.8.12				Have provisions been made for handling controlled substance reference standards?
1.8.13				Does the reference standard SOP address (map) proper handling of controlled substance reference standards?
9.0				*Additional Items*

LABORATORY DOCUMENTATION PRACTICES AND STANDARD OPERATING PROCEDURES (OP) SUBELEMENT CHECKLIST

Laboratory documentation practices and standard operating procedures form a critical component of the overall Laboratory Control System. Much of the essence of CGMPs involves the generation, review, approval, revision and control of procedures and data. In compliance parlance, "If it isn't written down, it didn't happen."

Laboratory documentation practices and standard operating procedures subelement includes at least nine individual topics. A laboratory, which is in compliance with CGMPs, should address each of these topics (as applicable). These topics include: (1) SOPs—General, (2) SOPs—specific topics, (3) Laboratory test procedures, (4) Laboratory data and results, (5) Security of data, (6) Distribution of results, (7) Chromatography, (8) In-process testing, and (9) Assignment of retest/expiry dates.

The following text lists nine topics along with some suggestions on what items should be addressed in each topic. The list of items under each topic is fairly comprehensive but may not be totally inclusive of all those components constituting the subelement.

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.1				*SOPs—General*
2.1.1				Is there a comprehensive and current laboratory document control system in place?
2.1.2				Is there a list of all approved SOPs?
2.1.3				Are the SOPs current, clearly written, and accessible to all appropriate personnel?
2.1.4				Is there a system for periodic review of all SOPs to insure that they are consistent with current company and industry practices?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.1.5				Is there an SOP governing the SOP or document control system (e.g., an SOP on SOPs)?
2.1.6				Is there a system for controlling the issuance and revision of all SOPs?
2.1.7				Do policies and manuals exist which supplement the SOPs? (e.g., Level I and Level II guidance documents)
2.1.8				Are the guidance documents readily accessible to all laboratory personnel?
2.1.9				Are all SOPs reviewed and updated at least every year?
2.2				*SOPs—Specific Procedures*
				Are there specific standard operating procedures covering:
2.2.1				Change control?
2.2.2				Record review and approval requirements?
2.2.3				Description of the requirements for performing data review?
2.2.4				Laboratory records (e.g., data recorded in bound notebooks or controlled worksheets)?
2.2.5				Dissolution testing?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.2.6				Sample receipt, documentation, handling, storage, and control?
2.2.7				Laboratory investigations, deviations and handling of OOS results?
2.2.8				Policy for identification and reporting of new impurities and/or higher levels of previously known impurities?
2.2.9				Validation and transfer of analytical methods?
2.2.10				Laboratory computer validation?
2.2.11				Preparation, labeling, identification, expiration-dating, and storage of chemicals, reagents, and solutions?
2.2.12				Equipment/Instrument use, PM, calibration and qualification?
2.2.13				Appropriate labeling of out of use lab equipment?
2.2.14				Glassware washing (mechanical and manual)?
2.2.15				Practices regarding housekeeping, safety glasses, eating in labs, smoking, etc.?
2.2.16				Hazardous waste disposal?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.2.17				Handling and disposing laboratory samples?
2.2.18				Is there an SOP for defining appropriate sampling plans for all quality control laboratory testing?
2.2.19				Are samples randomly chosen and are they representative of all portions of the lot(s)?
2.2.20				Is there an SOP for the receipt, documentation, handling, storage and distribution of laboratory samples?
2.2.21				Is a sample logbook maintained?
2.2.22				Are samples tracked? Is sample disposition included in tracking?
2.2.23				Are storage areas maintained for sample disposition (e.g., retention and destruction)?
2.2.24				Is there a master signature list, including persons' names, initials, and responsibilities?
2.2.25				Are samples labeled appropriately to include: sample description, source, quantity, date sampled, date sample received for testing?
2.2.26				Are sample storage areas properly identified and maintained?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.2.27				Is there a backlog with respect to sample analysis, and if so is the backlog great enough to have an impact on testing results and product release?
2.3				*Laboratory Test Procedures*
2.3.1				Is there an index listing the testing documents and specifications?
2.3.2				Is this list updated and properly controlled?
2.3.3				Do the test procedures include sufficient instructions on how to conduct the testing and operate the specific lab instruments?
2.3.4				Is there a system for controlling the issuance and revision of all testing related records?
2.3.5				Are laboratory test procedures and specifications approved by the quality assurance unit?
2.3.6				Is there a written change control procedure that describes how analytical method changes are made?
2.3.7				Do specifications for compendial products meet compendial requirements?
2.3.8				Is there a procedure for determining in-house or tighter release specifications?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.3.9				Are raw materials released by using validated analytical methods?
2.4				*Laboratory Data and Results*
2.4.1				Is data documented in bound prenumbered logbooks, notebooks, or other data storage and acquisition systems?
2.4.2				Is the use of scrap paper, Post-its, or similar uncontrollable paper specifically prohibited in the laboratory?
2.4.3				Are corrections to data entry errors covered in an SOP?
2.4.4				Are all handwritten documents/data recorded in permanent ink?
2.4.5				If bound notebooks are used, is there a system for control, issuance, use, and return?
2.4.6				Is each notebook page dated and signed by the analyst and second-reviewing authorized individual and performed in a timely manner?
2.4.7				Are all entries checked and approved for completeness of sample identity, proper use of reagents, standards, and execution of experimental procedures?

(*Continued*)

Checklist (*Continued*)

Step	Yes	No	Na	Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)
2.4.8				Are all outputs, such as chromatograms, spectra, etc., appropriately identified, stored, referenced to notebooks, and readily retrievable?
2.4.9				Are all data, calculations, and results verified by second qualified individual for accuracy, completeness, and compliance with specifications?
2.4.10				Are the qualifications of persons conducting data review documented and acceptable?
2.4.11				Is data review documented by full signature and date?
2.4.12				Are data review and approval activities captured in LIMS?
2.4.13				Are data reviewed by the laboratory and approved by quality assurance before distribution? Is this process defined by an SOP?
2.4.14				Is there a system in place to assure that the method being used in the laboratory is the current approved-version method for testing?
2.4.15				Is the method used for analysis recorded onto the laboratory testing results sheet or recorded into LIMS?
2.4.16				Is there a written SOP for handling of reintegration of HPLC/GC data?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.4.17				If a computer software package is used to calculate results, is there an example calculation included with the reported results verifying proper algorithm execution?
2.4.18				Are all correction factors used in calculations expressed with the proper units?
2.4.19				Are raw data defined in an SOP?
2.5				*Security of Data*
2.5.1				Is access to stored data limited?
2.5.2				Are data protected from fire, water, and other environmental hazards?
2.5.3				Are data readily retrievable?
2.5.4				Is the length of time that documents need to be retained defined in writing and does this time frame meet current industry practice?
2.5.5				Are backup copies of data stored at an offsite location?
2.5.6				Is there a disaster recovery plan and has it been rehearsed?

(*Continued*)

Checklist (*Continued*)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.6				*Distribution of Results*
2.6.1				Are results entered into a LIMS or other electronic management system?
2.6.2				Is LIMS used to compare testing results to the specifications for determining pass/fail decisions?
2.6.3				Is LIMS used to provide data for use in annual product reviews?
2.6.4				If data are transcribed from notebooks and reports, is transcription accuracy being verified?
2.7				*Chromatography*
2.7.1				Is system suitability performed routinely? (e.g., HPLC methods, GC methods, etc.)
2.7.2				Are the system suitability parameters determined from validation data?
2.7.3				Must system suitability parameters be calculated and met prior to executing a quality control sample analysis?
2.7.4				Is there an SOP that delineates a standard sample queue (i.e., interspersing of standards and samples during the course of the chromatographic run)?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.8				*In-Process Testing*
2.8.1				Are validated methods used for in-process testing?
2.8.2				Do formal sampling plans exist for all in-process testing?
2.8.3				Are there established acceptance criteria/ranges/ specifications for in-process tests?
2.8.4				Is sample integrity preserved during handling and storage of in-process samples?
2.8.5				Are all the necessary industry standard in-process tests conducted (i.e., blend uniformity, weight variation, hardness, thickness, etc.)?
2.9				*Assignment of Retest/Expiry Dates*
2.9.1				Are expiration/retest dates based on available in-house storage (stability) data or otherwise justified?
2.9.2				Does an SOP exist which differentiates between retest and expiry dating?
2.9.3				Is there a limit for extending the retest life of the substance evaluated?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Documentation Practices and Standard Operating Procedures Subelement (OP)**
2.9.4				Are there procedures for handling/storage of reference standards and reference cultures?
9.0				*Additional Items*

LABORATORY EQUIPMENT QUALIFICATION AND CALIBRATION (LE) SUBELEMENT CHECKLIST

Since the vast majority of data in a modern analytical laboratory are acquired via instrumentation, it is essential that these instruments have been properly installed, qualified, and are kept in proper working order. The laboratory equipment qualification and calibration subelement addresses these issues.

Laboratory equipment qualification and calibration include at least three individual topics. A laboratory, which is in compliance with CGMPs, should address each of these topics (as applicable). These topics include: (1) Laboratory equipment procedures—General, (2) Laboratory equipment procedures—Specific, and (3) Laboratory equipment procedures—Computer controlled.

The following text lists these three topics along with some suggestions on what items should be addressed in each topic. The list of items under each topic is fairly comprehensive but may not be totally inclusive of all those components constituting the subelement.

Step	Yes	No	Na	**Laboratory Equipment Qualification and Calibration Subelement (LE)**
3.1				*Laboratory Equipment Procedures—General*
3.1.1				Are the laboratories equipped with all of the necessary instruments for the analytical testing to be performed?
3.1.2				Is there a written qualification, calibration, and preventive maintenance program in place described in an SOP?
3.1.3				Is there a master equipment list available and is it properly maintained?
3.1.4				Is there a master equipment maintenance and calibration schedule?
3.1.5				Are specific personnel assigned to maintain the master equipment list and equipment maintenance and calibration schedule?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Equipment Qualification and Calibration Subelement (LE)**
3.1.6				Are calibration/service vendors qualified and are their training records available?
3.1.7				Is there a validation master plan indicating timing and responsibility for equipment qualification and requalification?
3.1.8				Are there triggers (e.g., specific criteria and/or circumstances) for requalification and are they integrated into the master plan?
3.1.9				Does each piece of equipment have a logbook or file documenting instrument maintenance, calibration, and repair histories?
3.1.10				Does each piece of equipment have a usage log?
3.1.11				Do labels on the instruments identify the person who performed the calibration, date of calibration, and due date of next calibration?
3.1.12				Are IQ, OQ, and PQ requirements, which clearly define performance testing acceptance criteria for each piece of equipment, clearly defined in an approved protocol?
3.1.13				Have IQ/OQ/PQ been performed and properly documented for all equipment?
3.1.14				Are IQ, OQ, and PQ performed during initial system installation?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Equipment Qualification and Calibration Subelement (LE)**
3.1.15				Is calibration and preventive maintenance (PM), including tolerances, based on the manufacturer's recommendations?
3.1.16				Are cleaning procedures included in the SOPs for instrument qualification or calibration?
3.1.17				Is there an SOP that requires that instruments failing calibration are removed from service?
3.1.18				Does the SOP provide directions for investigations when instrumentation is found to be out-of-calibration, yet still is being used to generate CGMP data?
3.1.19				Are the qualification specifications for equipment based on sound scientific principals?
3.1.20				Are calibration/metrology records secure (locked up)?
3.2				*Laboratory Equipment Procedures—Specific*
3.2.1				Are balances checked for corner loading?
3.2.2				Are pH meters standardized and calibrated?
3.2.3				Are balances calibrated at both upper and lower weighing capability using NIST-traceable standards?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Equipment Qualification and Calibration Subelement (LE)**
3.2.4				Are calibration correction factors attached to thermometers (if appropriate)?
3.2.5				Are pH meters calibrated at two points, not differing by more than 4 pH units?
3.2.6				Are UV spectrophotometers calibrated for wavelength and photometric accuracy?
3.2.7				Is there a written procedure for set-up, calibration, and operation of dissolution baths?
3.2.8				Are there written procedures for calibration and maintenance of HPLCs, including pumps, auto sampler reproducibility, and wavelength accuracy?
3.2.9				Do HPLC PMs include seal and valve changes?
3.3				*Laboratory Equipment Procedures—Computer Controlled*
3.3.1				Is there a written policy or procedures for validation of computer-interfaced instrumentation?
3.3.2				Have the computer systems/software, which control instruments, been validated?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Equipment Qualification and Calibration Subelement (LE)**
3.3.3				Is there a system in place to install new software versions and to decide what scope of revalidation must be done during software upgrades?
3.3.4				Is computer software validation a part of the OQ process?
3.3.5				Is computer software validation documented?
3.3.6				Are there systems in place to prevent installation of unauthorized software?
3.3.7				Are integrators validated using a validated signal generator?
3.4				*Additional Items*

LABORATORY FACILITIES (LF) SUBELEMENT CHECKLIST

As with a manufacturing area, it is essential that the laboratory be properly designed and equipped. This insures that the data generated accurately reflect the true composition of the sample from which they came. In addition, it insures a safe working environment for laboratory personnel.

The laboratory facilities subelement includes three individual topics. A laboratory, which is in compliance with CGMPs, should at least address each of these topics (as applicable). These topics include: (1) Laboratory facilities—General, (2) Safety and environmental concerns, and (3) Laboratory glassware.

The following text lists these three topics along with some suggestions on what items should be addressed in each topic. The list of items under each topic is fairly comprehensive but may not be totally inclusive of all those components constituting the subelement.

Step	Yes	No	Na	**Laboratory Facilities Subelement (LF)**
4.1				*Laboratory Facilities—General*
4.1.1				Is the physical construction of the laboratory areas adequate for testing and all routine activities with respect to:
4.1.1.1				Size?
4.1.1.2				Layout and design for optimum workflow and efficiency?
4.1.1.3				Sample receipt?
4.1.1.4				Appropriate tables for balances/instruments, etc.?
4.1.1.5				Location of SOPs, location of methods, specification sheets, and safety data sheets?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Facilities Subelement (LF)**
4.1.1.6				Location of reagents, standards, solutions, solvents?
4.1.1.7				Data entry, recording, writing areas?
4.1.1.8				Sample storage and retention?
4.1.1.9				Refrigeration?
4.1.2				Are proper systems in place to minimize cross-contamination during sample preparation and laboratory testing?
4.1.3				Are all controlled temperature/humidity storage areas, incubators, etc. monitored to assure that proper conditions are maintained?
4.1.4				Have temperature monitoring systems and equipment been properly validated?
4.1.5				Have humidity monitoring systems and equipment been properly validated?
4.1.6				Are controlled substances properly segregated and controlled according to DEA requirements?
4.1.7				Is the environment/temperature control correct for the areas for different types of equipment?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Facilities Subelement (LF)**
4.1.8				Are radioisotopes (if used) in proper storage areas?
4.1.9				Are uninterruptible power supply units (UPS) used to minimize the impact of power surges and outages?
4.1.10				If a UPS exists, has it been qualified and has an SOP describing its use been written?
4.1.11				Are piping systems specified at the correct pressure and have they been cleaned, flushed, leak-tested passivated (sanitary use), and certified?
4.1.12				Have appropriate hood air filters been installed and smoke tests performed?
4.1.13				Have facility monitoring systems been validated?
4.1.14				Have purified water systems been validated?
4.1.15				Is there an SOP for lab or engineering maintenance of the air system?
4.1.16				Are there appropriate controls available/specifications for handling particulate matter and microbes?
4.1.17				Is there control of HVAC in instrument rooms, balance area, etc.?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Facilities Subelement (LF)**
4.1.18				Does the hood exhaust into an appropriate location (e.g., a sufficient distance from the air intake system as to not interfere with lab operations)?
4.1.19				Is the HVAC for stability/retention samples adequately monitored?
4.1.20				Has the laboratory water system been properly qualified?
4.1.21				Is there routine monitoring to assure adequate quality of the water?
4.1.22				Are the types of water required for the lab identified and are specifications properly set?
4.1.23				Is lab water part of the site water monitoring program and is testing frequency established and appropriate?
4.1.24				Are there action plans for following water related out of specification results or deviations?
4.1.25				Is there a schedule for servicing the laboratory water system?
4.2				*Safety and Environmental Concerns*
4.2.1				Is there a safety and environmental SOP?
4.2.2				Is there testing of hoods?

(*Continued*)

Checklist (*Continued*)

Step	Yes	No	Na	**Laboratory Facilities Subelement (LF)**
4.2.3				Are hazardous materials identified and segregated?
4.2.4				Are safety data sheets available and are they kept current?
4.2.5				Is there a program that describes handling and disposal of biohazardous waste?
4.2.6				Are toxic/dangerous chemicals handled and disposed of according to local, state, and federal regulations?
4.2.7				Are employees trained to handle toxic/dangerous materials?
4.3				*Laboratory Glassware*
4.3.1				Has glassware washing/cleaning been validated to include demonstrating the removal of chemical residue?
4.3.2				Is there a PM program for mechanical glassware washers?
4.3.3				Is there a program in place to check for defective and worn glassware?
9.0				*Additional Items*

METHODS VALIDATION AND TECHNOLOGY TRANSFER SUBELEMENT (MV)

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. The methods validation process for analytical procedures begins with the planned and systematic collection validation data to support analytical procedures. In addition, the methods validation process is considered to be complete once the methods have been successfully transferred from the originating to the receiving or end user laboratory.

The methods validation and technology transfer subelement includes at least three individual topics. A laboratory, which is in compliance with CGMPs, should at least address each of these topics. These topics include: (1) Validation of analytical methods—General, (2) Cleaning methods validation, and (3) Procedures for methods transfer.

The following text lists these three topics along with some suggestions on what items should be addressed in each topic. The list of items under each topic is fairly comprehensive but may not be totally inclusive of all those components constituting the subelement.

Step	Yes	No	Na	**Methods Validation and Technology Transfer Subelement (MV)**
5.1				*Validation of Analytical Methods—General*
5.1.1				Is there a general SOP for methods validation?
5.1.2				Are the requirements in the SOP consistent with FDA/ICH/USP guidelines?
5.1.3				Are methods validation protocols used for each validation?
5.1.4				Are all of the appropriate elements of validation included in the methods validation protocol such as:
5.1.4.1				Accuracy?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Methods Validation and Technology Transfer Subelement (MV)**
5.1.4.2				Precision (repeatability and intermediate precision)?
5.1.4.3				Selectivity/Specificity?
5.1.4.4				Robustness?
5.1.4.5				Linearity?
5.1.4.6				Range?
5.1.4.7				Limit of detection?
5.1.4.8				Limit of quantitation?
5.1.4.9				System suitability?
5.1.4.10				Sample solution stability?
5.1.4.11				Completeness of extraction (from dosage forms)?
5.1.4.12				Filter retention studies?
5.1.4.13				Forced degradation studies?

Checklist (***Continued***)

Step	Yes	No	Na	**Methods Validation and Technology Transfer Subelement (MV)**
5.1.5				Is there an SOP or section within an SOP that discusses the requirements for the verification of compendial methods?
5.1.6				Have compendial methods been shown to work under the actual conditions of use?
5.1.7				Have impurity methods been properly validated? Are they stability indicating and selective or specific?
5.1.8				Are method validation reports published following validation of an analytical method?
5.1.9				Can results presented in method validation reports be tracked back to raw data?
5.2				*Cleaning Methods Validation*
5.2.1				Is there an ongoing cleaning validation program in place?
5.2.2				Is cleaning validation conducted according to a master plan and schedule?
5.2.3				Are there validated sampling procedures developed to support cleaning validation studies?
5.2.4				Are there written acceptance criteria?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Methods Validation and Technology Transfer Subelement (MV)**
5.2.5				Were recovery studies conducted?
5.2.6				Are there validated analytical methods developed to support cleaning validation studies?
5.2.7				Does the cleaning validation testing include analysis of area swap samples?
5.3				*Procedures for Methods Transfer*
5.3.1				Are there site policies and procedures governing transfer of methods, and do these documents include defining acceptance criteria?
5.3.2				Are the responsibilities for who is in charge clearly defined (e.g. receiving laboratory or originating laboratory)?
5.3.3				Is there a requirement to form an analytical technology transfer team or similar organization to transfer methods?
5.3.4				Is a formal receiving laboratory readiness assessment performed to include evaluation of equipment, facilities, and personnel?
5.3.5				Is the receiving laboratory given the opportunity to review the analytical methodology prior to the transfer process?

Checklist (***Continued***)

Step	Yes	No	Na	**Methods Validation and Technology Transfer Subelement (MV)**
5.3.6				Is an analytical technology transfer qualification strategy document generated and used to guide the transfer of methods?
5.3.7				Are personnel in the receiving laboratory given the opportunity to use the method under the supervision of the originating personnel subject-matter experts prior to formal transfer?
5.3.8				Is an analytical technology transfer protocol, with predetermined acceptance criteria, used to formally transfer the methodology?
5.3.9				Is a reviewed and approved technology transfer report generated upon successful execution of the transfer protocol?
5.3.10				Can results presented in the cleaning methods validation reports be tracked back to raw data?
9.0				*Additional Items*

LABORATORY COMPUTER SYSTEMS (LC) SUBELEMENT

In a modern analytical laboratory, nearly every instrument is either controlled by or has data residing and processed by a computer. Subsequently, it is critical that reliability of these systems and their associated software be evaluated.

Laboratory computer systems includes at least seven individual topics. A laboratory, which is in compliance with CGMPs, should address each of these topics (as applicable). These topics include: (1) Laboratory computer systems—General, (2) Centralized and network-attached data systems, (3) Stand-alone data systems, (4) SOPs and records, (5) Laboratory information management systems (LIMS), (6) Spreadsheets, and (7) Other systems.

The following text lists these seven topics along with some suggestions on what items should be addressed in each topic. The list of items under each topic is fairly comprehensive but may not be totally inclusive of all those components constituting the subelement.

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.1				*Laboratory Computer Systems—General*
6.1.1				Is there an inventory of laboratory data systems (both centralized and benchtop systems) including any associated servers?
6.1.2				Is a disaster recovery plan in place addressing laboratory data systems?
6.1.2.1				Has it been tested?
6.1.2.2				Is documentation for both the plan and any tests available for review?
6.1.3				Have all GMP laboratory data systems and associated file servers etc., been validated in accordance with applicable standards and procedures?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.1.4				Have all GMP laboratory data systems and associated file servers, etc. been reviewed for compliance with 21CFR Part 11?
6.1.4.1				Is there a remediation/replacement plan for those which were found to be deficient?
6.1.5				Are GMP workstations clearly labeled as such?
6.1.6				Is access to laboratory workstations provided through operating systems, having individual user accounts?
6.1.6.1				Are passwords properly controlled and protected by end users?
6.1.6.2				Are passwords properly managed with assignment of permissions and privileges?
6.1.7				Are workstations configured with password-controlled screensavers or other automatic locking mechanism?
6.1.8				Are data structures for laboratory systems documented?
6.1.8.1				Does this include defining folders/directories on local hard drives and file servers where data are stored?
6.1.8.2				Do system SOPs specify these folders/directories for data storage as appropriate?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.1.9				Are procedures in place to govern data naming conventions for projects, analyses, products, etc.?
6.1.10				Is data archiving performed on one or more laboratory data systems?
6.1.10.1				Is the distinction between archiving and backing up data understood by laboratory staff?
6.1.10.2				Is archived data subject to formalized retention standards?
6.1.10.3				Has the dearchival process ever been tested?
6.2				*Centralized and Network-Attached Data Systems*
6.2.1				Are back-ups of data files made regularly?
6.2.1.1				Is it governed by SOP?
6.2.1.2				Is there an individual who is assigned this responsibility?
6.2.1.3				Is the back-up media securely stored, with inventory data that is current and accurate?
6.2.2				Are there documented service-level agreements with the central support organization defining mutual expectations and responsibilities?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.2.3				If back-ups are performed by an automatic procedure provided by a central support organization is clear documentation in place to define expected data structures and problem alerting/resolution procedures?
6.2.4				Are data restores governed by an SOP?
6.2.5				Are the restores documented as required by SOP?
6.2.6				Does the central support organization have server/application SOPs, which address data management, incident management, performance monitoring, etc., specific to the laboratory?
6.3				*Stand-Alone Data Systems*
6.3.1				Are back-ups performed either automatically (scheduled through a system procedure) or manually as defined by SOPs?
6.3.2				Is there a procedure in place to determine whether back-up media have been modified?
6.3.3				Are back-up media identified and securely stored?
6.3.4				Are the restores documented as required by SOP?
6.4				*SOPs and Records*
6.4.1				Do SOPs exist for validation of laboratory data systems?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.4.2				Has appropriate laboratory staff been trained on the laboratory data system SOPs?
6.4.3				Are training records for personnel trained on the SOPs available for review?
6.4.4				Do SOPs exist for operation of CGMP laboratory data systems?
6.4.5				Has appropriate laboratory staff been trained on the CGMP laboratory data system operation SOPs?
6.4.6				Are training records for personnel trained on the SOPs available for review?
6.5				*Laboratory Information Management System (LIMS)*
6.5.1				If a LIMS System is used for data management (either custom or commercial system) has it been validated?
6.5.2				Has the validation been properly documented and the data available for review?
6.5.3				Is the system operated and maintained by laboratory staff or a systems support organization?
6.5.4				Is the system maintained under change control delineated in an SOP?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.5.5				Have lab personnel been trained on LIMS data entry and are training records available for review?
6.5.6				Are there automated data entry and extraction points in the LIMS? Have the links been validated for:
6.5.6.1				Bar code readers?
6.5.6.2				GC data stations
6.5.6.3				HPLC data stations?
6.5.6.4				Balances?
6.5.6.5				Spreadsheets
6.5.6.6				Other components?
6.5.7				Is there a definition of what is considered raw data?
6.5.8				Can data entries be made by only authorized, password-protected individuals?
6.5.9				Are electronic signatures used in the LIMS system and are they in compliance with 21CFR Part 11?

(*Continued*)

Checklist (*Continued*)

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.6				*Spreadsheets*
6.6.1				How are spreadsheets used in the laboratory and if so, do they reside on the following:
6.6.1.1				Networks?
6.6.1.2				Workstation hard drives?
6.6.2				Are procedures in place governing the development/ modification of spreadsheets for GMP use?
6.6.3				Are the spreadsheets in use unalterable and:
6.6.3.1				Qualified/validated?
6.6.3.2				Are procedures in place to ensure that correct versions of spreadsheets are being used?
6.6.4				Are there procedures in place for archiving and retrieving retired versions of spreadsheets?
6.7				*Other Systems*
6.7.1				Is an electronic document management system used and if so, is it validated?
6.7.2				Is an electronic training-record database used and if so is it validated?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Computer Systems Subelement (LC)**
6.7.3				Are laboratory periodic maintenance and calibration activities scheduled and recorded by a maintenance management system and if so is it validated?
9.0				*Additional Items*

LABORATORY INVESTIGATIONS (LI) SUBELEMENT

CGMPs exist to not only prevent problems from occurring, but to mitigate and address deficiencies when they do occur. The laboratory investigations subelement is designed to systematically identify the root cause of failures, determine how to correct the problems, and to prevent them from reoccurring in the future.

Laboratory investigations includes at least three individual topics. A laboratory, which is in compliance with CGMPs, should address each of these topics (as applicable). These topics should include: (1) Laboratory investigations—General, (2) Laboratory investigations—Execution, and (3) Laboratory investigations—Documentation.

The following text lists these three topics along with some suggestions on what items should be addressed in each topic. The list of items under each topic is fairly comprehensive but may not be totally inclusive of all those components constituting the subelement.

Step	Yes	No	Na	**Laboratory Investigations Subelement (LI)**
7.1				*Laboratory Investigations—General*
7.1.1				Is there an SOP that defines in detail when and how laboratory investigations are conducted?
7.1.2				Does the SOP distinguish between out of specification (OOS), deviations, or atypical events?
7.1.3				Does the SOP have a flowchart and/or decision tree to assist in performing laboratory investigations?
7.1.4				Does the SOP have a checklist to assist in determining the root cause of the deviation or failure?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Investigations Subelement (LI)**
7.1.5				Does the checklist include review of specifics such as:
7.1.5.1				Use of proper test methods and proper execution of the test method?
7.1.5.2				Performance of proper calculations without mathematical error?
7.1.5.3				Use of proper reagents, standards, and glassware?
7.1.5.4				Execution of proper sample preparation?
7.1.5.5				Execution of proper standard preparation?
7.1.5.6				Analysis of proper samples?
7.1.5.7				Execution of proper analytical technique such as mixing, shaking, centrifuging, filtering weighing, and dilution?
7.1.5.8				Use of proper equipment?
7.1.5.9				Use of properly qualified and calibrated equipment?
7.1.5.10				Special considerations for proper execution of HPLC methods?

(*Continued*)

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Investigations Subelement (LI)**
7.1.5.11				Special considerations for proper execution of GC methods?
7.1.5.12				Special considerations for proper execution of dissolution testing?
7.1.5.13				Special considerations for proper execution of IR analysis?
7.1.5.14				Special considerations for proper execution of UV/Vis spectroscopy analysis?
7.1.5.15				Special considerations for proper execution of titrations including Karl Fischer?
7.1.6				Are OOS investigations handled in a manner consistent with the Barr decision and FDA guidance documents?
7.1.7				Does the SOP prevent release of product by continuous testing, retesting, or resampling (e.g., testing into compliance)?
7.1.8				Does the SOP clearly define situations when reanalysis or retesting are appropriate and provide guidelines on how it will be executed?
7.1.9				Does the SOP address special circumstances such as unidentified chromatographic peaks or shifting retention times of known peaks?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Investigations Subelement (LI)**
7.1.10				Are roles and responsibilities for executing laboratory investigations clearly defined in the SOP?
7.1.11				Are all laboratory personnel trained in the proper execution of laboratory investigations?
7.2				*Laboratory Investigations—Execution*
7.2.1				Is supervisor immediately notified of an OOS, deviation, or atypical event?
7.2.2				Are test material (glassware, test solutions, standard solutions, etc.) retained?
7.2.3				Are equipment and instrumentation left in the same conditions as when the event which caused the investigation to occur?
7.2.4				Are investigations performed in a timely manner?
7.2.5				Are the individuals responsible for generating the OOS, deviation, or atypical event involved in the investigation?
7.2.6				Is a concerted effort made to find a root or assignable cause of all laboratory investigations?
7.2.7				Are investigations closed in a timely manner?

(*Continued*)

Checklist (*Continued*)

Step	Yes	No	Na	**Laboratory Investigations Subelement (LI)**
7.2.8				If the OOS is discovered after product release, is there a system in place to evaluate impact of product which is in the market?
7.2.9				Is the quality assurance unit integrated into the laboratory investigations process?
7.2.10				If laboratory investigations cannot be completed in their allotted time frame, is there a formal mechanism in place to extend their due date?
7.3				*Laboratory Investigations—Documentation*
7.3.1				Is software (e.g., tracking, trending, and reporting) used to complete laboratory investigations?
7.3.2				Has the software been validated?
7.3.3				Is there a standard report or forms, which are used for documenting laboratory investigations?
7.3.4				Are investigations supported with sufficient data to include chromatograms, spectra, raw data, etc.?
7.3.5				Is there a process for implementing corrective and preventive actions upon closure of laboratory investigations?
7.3.6				Are laboratory investigations tracked and trended?

Checklist (***Continued***)

Step	Yes	No	Na	**Laboratory Investigations Subelement (LI)**
7.3.7				Are the trending reports used during annual product reviews?
7.3.8				If the root cause of the investigation is not determined, is a conscious and rational decision on the impact of continued testing made?
7.3.9				Can final investigation reports be understood from someone outside the organization and stand on their own with limited verbal explanation?
9.0				*Additional Items*