Technology Update

Validating Computer Systems, Part 1

A GCP Computer System Is a Lifetime Responsibility

Teri Stokes

Users are responsible for the ongoing care and feeding of their systems. Is your GCP system a pampered pet or a dirty dog?

Purchasing a computerized system for use in a GCP-regulated work process is like buying a family pet. Like a well-trained pet, the system is expected to do what we want it to and perform as expected. No mistakes on the carpet, please! Don't crash in the midst of our rush to prepare the final study report, please! Buying a pet is a lifetime responsibility that begins with the initial excitement of first encounters (housebreaking) and continues on for years with daily feedings and walks and health check visits. Buying a GCP system is also a lifetime responsibility, with initial validation (user acceptance) and ongoing change control, repeat testing, maintenance, enhancements, backups, and audits.

Regulatory authorities require life cycle management for GCP systems both during the systems' development (referred to as the software development life cycle, or SDLC) and for the rest of their existence through to retirement and replacement. The initial validation plan prepared by users for user acceptance of a new GCP system must include provisions for the "care and feeding" of a validated system for the rest of its life—after startup through to retirement. The computerized system validation (CSV) package developed at system launch must also establish the ongoing validation environment to keep the system "fit" and performing as expected over the years it is being used. Such long-term planning requires the involvement of management to ensure a supply of user resources to support the system over time.

This first of a series of articles on the subject of system validation discusses the user's role in the process. Later articles describe the roles of the software supplier and of the system installers.

Anatomy of a GCP system

In the 1980s, the computer validation committee of the Pharmaceutical Manufacturers Association produced a diagram to help define terms for validation work.[1] Figure 1 shows an updated view of that classic drawing using an adverse event (AE) system as an example. In this view, a *computer system* is composed of hardware and software, and a *work process* is composed of people, standard operating procedures (SOPs), and often equipment or instrumentation.

When a computer system is used to support a work process, the two together become a *computerized system*—in the example, a serious AE management system. The computerized system performs in an *operating environment* such as pharmacovigilance (in the example) or

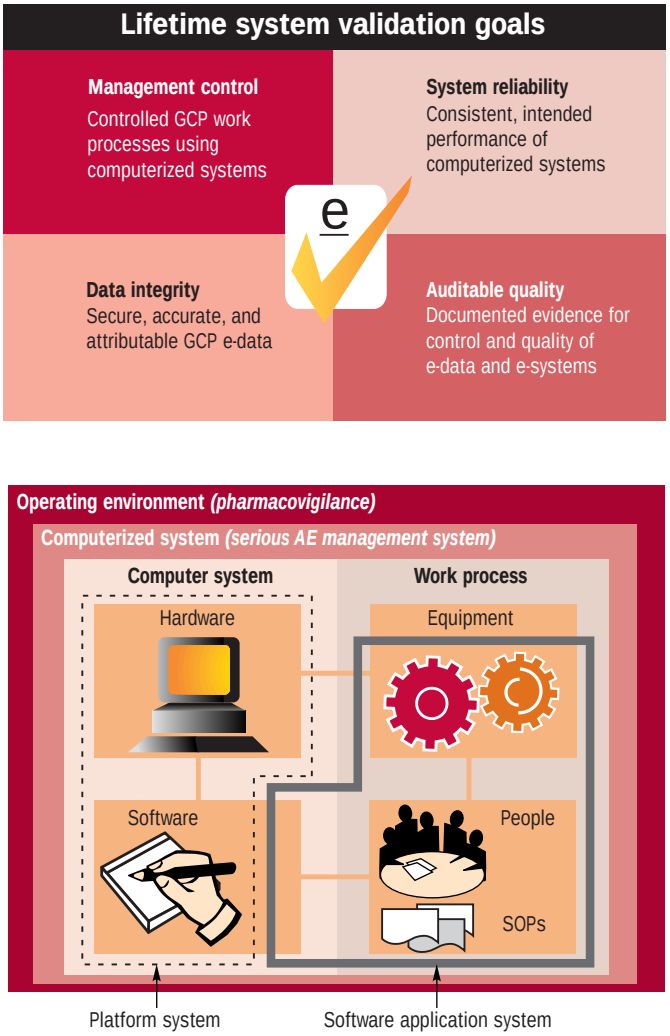

Figure 1. An example of the configuration of a system designed for serious adverse event management.

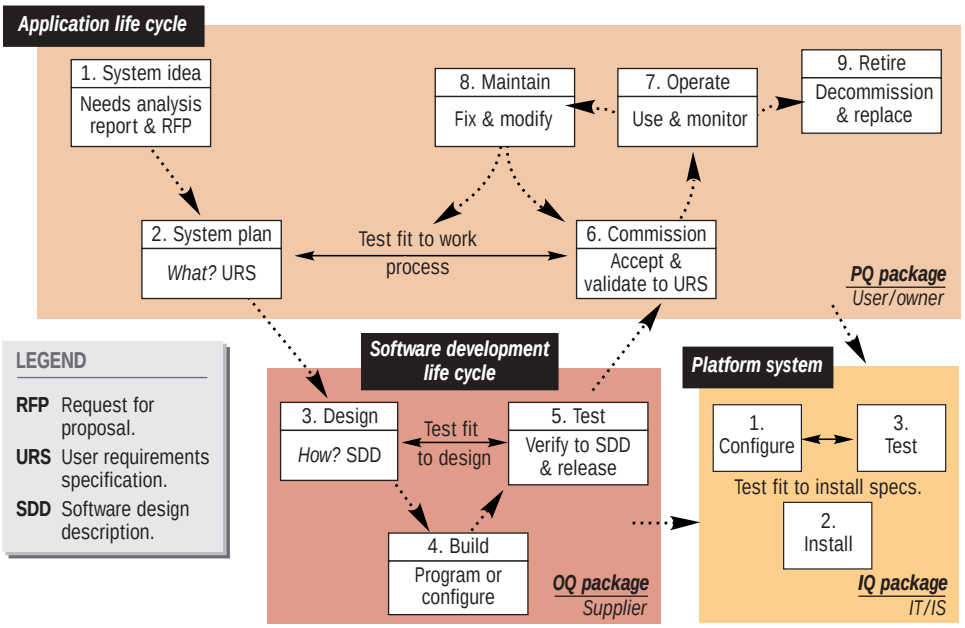

Figure 2. The life cycle of a GCP-compliant system, illustrating the PQ, IQ, and 0Q packages in relation to one another.

Testing Components

performance qualification (PQ) User testing to answer the question, "Does the application system perform as expected to meet user requirements specification (URS) in a simulated work process environment?"

installation qualification (IQ) Platform testing to answer the questions, "Is the software application properly installed, are all its physical and logical requirements (per manufacturer's specifications) met, and is its platform adequately configured for user access in the work process?"

operational qualification (OQ) Supplier testing to answer the question, "Does the application software work as intended just above, just below, and at the operational limits set in its design specification?"

product safety. To make user acceptance validation work practical, however, it is necessary to add to the basic diagram two new concepts. The software that performs in the work process and that users see and "touch" with a keyboard, mouse, or bar code wand is the *software application system*. Everything else that is required for the software application to perform as expected is part of the *platform system*. The platform system includes the hardware, operating systems, databases, query and other software tools, and network communications for server and desktop configurations that supply the infrastructure support to the regulated application.

The software application cannot function without its platform system support and users cannot reach the software application without desktop or handheld systems and network communications. One platform system can, however, support more than one software application system if it is large enough and the infrastructure requirements are the same for both applications.

Creation of validation packages

Figure 2 shows the full life cycle of a regulated software application and its platform system. As shown in the figure, there are three separate CSV packages to be prepared at the startup of a new computerized GCP system: the performance qualification (PQ) package, the installation qualification (IQ) package, and the operational qualification (OQ) package.

Software application: The PQ package. Preparation of the performance qualification pack-age for the software application system is the responsibility of the user acceptance team. This process focuses on how the application performs in its operating environment. It consists of a package of documented evidence that "paper trains" your system to behave itself in the work process. Regulatory authorities hold users responsible for GCP validation of both the application and its platform. Because a user team is seldom equipped to address platform issues, the users normally depend on subcontracting development of the platform CSV package to the information technology/information systems (IT/IS) department. An internal or external service level agreement (SLA) is then used to define roles and responsibilities for the startup validation support and the ongoing service and success of the system over time.

Platform system: The IQ package. The installation qualification package for the platform system includes startup testing, backup, recovery, contingency planning, SOPs, change control, maintenance, configuration management, and ongoing services. This platform CSV package process is like preparing the yard so your pet dog can play in safety and comfort (invisible fencing, dog house, water dish); it is the subject of Part 2 in this series.

This formal division of validation labor allows the respective teams to focus on what they know best. An IT/IS team cannot know the work process as well as the user team and thus cannot conduct performance testing that fully exercises the application in the same way users can. It is also important that real users have the chance to work with the system to prepare their working materials (SOPs, work instructions, guidelines) and fine-tune their work process to the idiosyncrasies of the system and vice versa before the application goes live. Software problems arising during user acceptance testing can then be resolved without interrupting GCP operations, which can lead to a troublefree launch of the system.

Figure 3 illustrates the division of labor between the user acceptance team and the platform package team.

Software supplier testing: The OQ package. Yet a third team involved in the startup of a new software application system is that of the software supplier and/or configuration provider, who perform the operational qualification of the system. Regulatory authorities also hold the users responsible for the quality of work and testing performed by this third team, whether the team is internal or external to the user's organization. Thus, the "pedigree" of your GCP system must be as well documented as the kennel registration of your purebred pet, including what kind of "shots" (testing) it has had to ensure good health and immunity to known diseases.

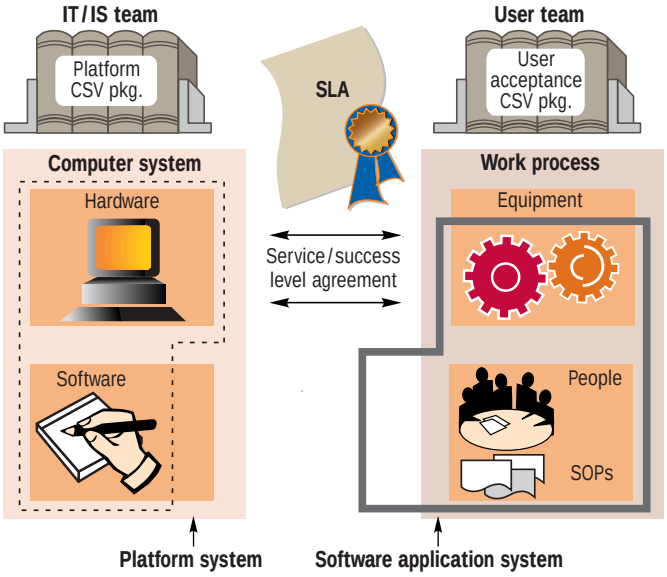

Figure 3. Two packages, two teams.

The operational limits programmed into an application are tested by the module and system integration level testing is performed by the software supplier. This testing is performed before the release of the application for shipping to a customer. Usually the user team exercises its check of the supplier/provider's work by conducting an audit or walk-through review of the software development life cycle and writing a formal audit report of their findings. The supplier's CSV package is the focus of Part 3 of this series.

Management's role in lifetime system validation

Buying a purebred pet requires taking on daily responsibility for the animal during its lifetime, and purchasing a strategic GCP system requires a similar level of care and attention. For management to be in control of a computerized work process, the organization must be set up to support lifetime validation for a regulated system. Figure 4 shows how a sponsor or CRO can be organized to support lifetime validation for strategic GCP systems.

The business decision group. Senior management—such as the director of clinical research and the directors for clinical data management, biostatistics, pharmacovigilance, and clinical quality assurance—has ultimate regulatory responsibility for GCP data in the clinical trial work process. This group of managers forms the logical composition for a business decision group (BDG) to plan and provide resources for compliance efforts for strategic GCP systems.

The BDG addresses broad issues, such as: Can we add another country of users to the system? Should we add another application to the same server or get a new server? How many users can we send to the supplier's user training this quarter? Which work process gets the next upgrade to its computerized system? When do we retire this system, and do we upgrade with the current supplier or move to a new vendor or new technology at retirement? How much do we redesign our work process to fit the system? Who is responsible for keeping the system in a validated state?

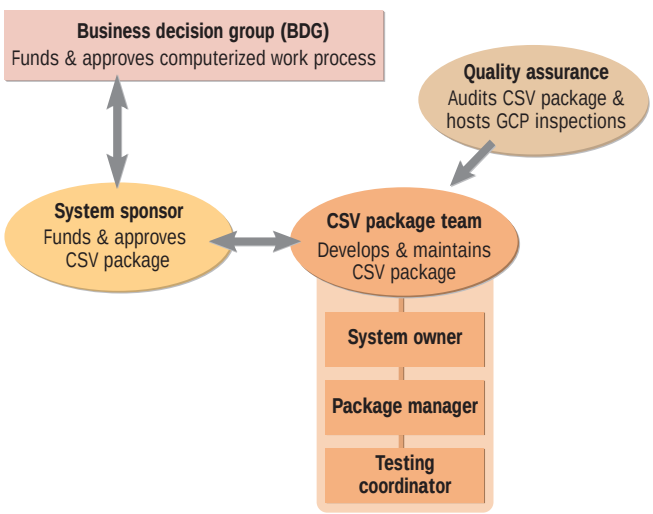

Figure 4. Lifetime validation requires a lifetime package team: system owner, package manager, and testing coordinator.

The system sponsor is the senior manager responsible for a particular computerized work process such as clinical data manage-ment or pharmacovigilance. The system sponsor carries the local responsibility for funding and approving the validation effort of computerized systems in that work process.

The system sponsor addresses such issues as: Who will I appoint as system owner to lead a CSV package team? How can I locate others to help the three key package team members with regular tasks so that they have time to develop the startup CSV package on time? How do I budget and gauge their ongoing duties for training new users, troubleshooting, and keeping the system validated after the system goes live and they return to their full-time jobs?

The system owner is usually the key user in the operating environment who is held responsible for having the system available for users in the computerized work process. This person assigns a package manager who drives the documentation process and a test coordinator who manages the testing activities. The system owner leads this core team in developing and maintaining the CSV package. Other users are included in an ad hoc capacity as testers and witnesses, and specialty resources may be added as necessary to provide specific expertise.

The quality assurance role stays outside of the package development process to be able to audit the CSV package. QA audits of the CSV package midway and at the end of development give the team and the BDG an independent view of the ability of the package to pass compliance inspections.

The user acceptance CSV package

Once the need for a new GCP system has been established, the needs analysis document itself starts the application life cycle and becomes the first document in a users' CSV package. The request for proposal (RFP) becomes the second document in the package. When a system is chosen, it is time to identify the package team and write a validation plan. The Institute for Electrical and Electronics Engineers, Inc. (IEEE) gives a document outline and explanation of expected content for a validation plan in its standard 1012-1986.2

The user acceptance package for computerized system validation is designed by the validation plan to provide documented evidence for

- management control of the system, its users, and its regulated data.
- reliability of the system to perform as intended every time.
- protection of data integrity

CSV Package Items

The validation plan developed by a user acceptance team includes more than just testing. The boxes on the left side of Figure 5 focus on control of the physical and logical environment for the application and the two boxes on the right address control of user interaction and the human interface to the system. Each of these items is discussed briefly below in order of appearance in the figure.

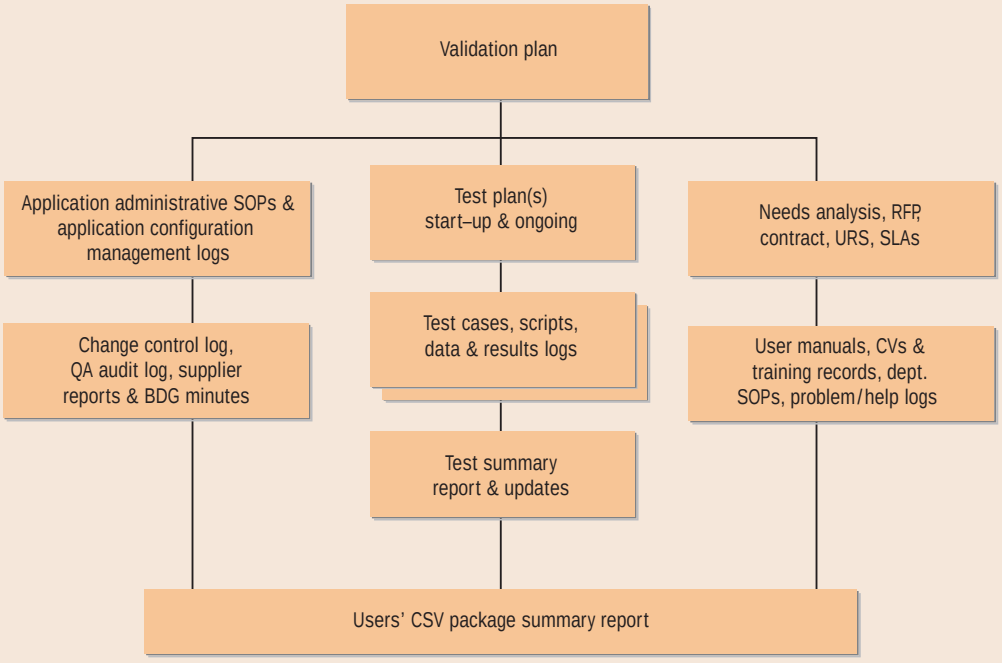

Figure 5. A standard user acceptance CSV package, prepared and maintained by a user department's team.

Control of physical/logical environment

Application administration SOPs. Descriptions of user types and their privileges on the system, procedures for system administration, backup and restore activities.

Application configuration management logs. A logbook binder used on an ongoing basis to keep a current description of the application, its backup log, maintenance records, support actions, change control decisions and actions taken, ongoing testing, problem tracking, release notes, supplier correspondence, the service level agreement (see below) with the platform supplier and/or with the application provider, record of user training events, and list of authorized users.

Change control log. A change control SOP for the system and monthly change control reports for system changes made by user, platform, and/or supplier actions. Report should include the extent of repeat testing performed and/or updates made to relevant CSV package items.

QA audit log. A record of any QA audits performed on the CSV package itself or on behalf of the CSV package, such as QA audits of suppliers.

Supplier reports. This log includes any walkthrough reports developed by the users when reviewing the platform CSV package or other supplier activities. It also includes follow-up reports on supplier milestone performance under service level agreements.

BDG minutes. The business decision group, consisting of line managers responsible for the operating environment and its computerized work processes, documents its financial, operational, and resource decisions about the regulated system in meeting minutes that are a part of the system's CSV package.

Control of user interaction

Needs analysis. The initial document examining the work process and describing the type of computerization it might benefit from.

Request for proposal (RFP). A formal document sent to prospective suppliers describing the work process needs and requesting a response from vendors showing how they could meet those needs with their products and/or services.

Contract. A legal document describing the roles, responsibilities, and financial elements in the business relationship (purchase, lease, rental) between system users and external suppliers of systems or services.

User requirements specification (URS). A formal, approved document describing the users' needs for a computerized system from a work process perspective, such as the types of data to be handled, the flow of data across the work process, data inputs and outputs to the work process, size and location of user groups, types of user roles, and access privileges needed.

Service/success level agreements (SLAs). Formal, approved documents between system user BDGs and internal or external suppliers to describe roles and responsibilities on both sides for keeping the regulated system in successful operation and continually validated.

User manuals. Printed materials from system suppliers instructing users how to work with the regulated system.

CVs and training records. Curriculum vitae showing the users' educational backgrounds and work experience that indicate competence to perform in the work process, and training records showing formal and on-the-job training given to ensure that a user is qualified to use a regulated system in the work process.

Department SOPs. Department standard operating procedures, guidelines, and/or work instructions that are specific for using the computerized system in the GCP work process.

Problem/help logs. Logbook binder to record user problems as they arise and their resolution as they are settled. A standard incident report form might be used to facilitate this recording. Department should have work instructions for how to report problems and where to go to get help with the system. Records describing problems and resolution should be reviewed monthly for trends and training issues.

Test Plan Outline—for Startup or Ongoing Testing

- ☐ **Test plan ID number.** Coded to relate the test plan to the associated validation plan.
- ☐ **Introduction.** Briefly describes system to be tested and references the related URS.
- ☐ **Test items.** List of software application and system versions to be tested.
- ☐ **Features to be tested.** System features traced to requirements from URS.
- ☐ **Features not to be tested and why.** Installed feature not used by work process.
- ☐ **Approach.** Describes overall strategy, techniques, and limits for testing.
- ☐ **Pass/fail criteria.** If just one test script fails, does the whole system fail?
- ☐ **Testing suspension criteria and resumption requirements.**
- ☐ **Test deliverables.** Documents required: test plan, test cases, test logs, test summary report.
- ☐ **Testing tasks.** Tasks necessary to prepare for, perform, and report testing.
- ☐ **Environmental needs.** Physical, logical, and security requirements for testing.
- ☐ **Responsibilities.** Identified for test developer, tester, and witness.
- ☐ **Staff training needs.** Specifies skill level for test writer, tester, and witness.
- ☐ **Schedule.** Estimated time to do each task and definition of milestones.
- ☐ **Risks and contingencies.** Identify high-risk assumptions of test plan and specify how plan addresses each risk.
- ☐ **Approvals.** Specify names and titles of all who must approve this plan with space for signatures and dates.

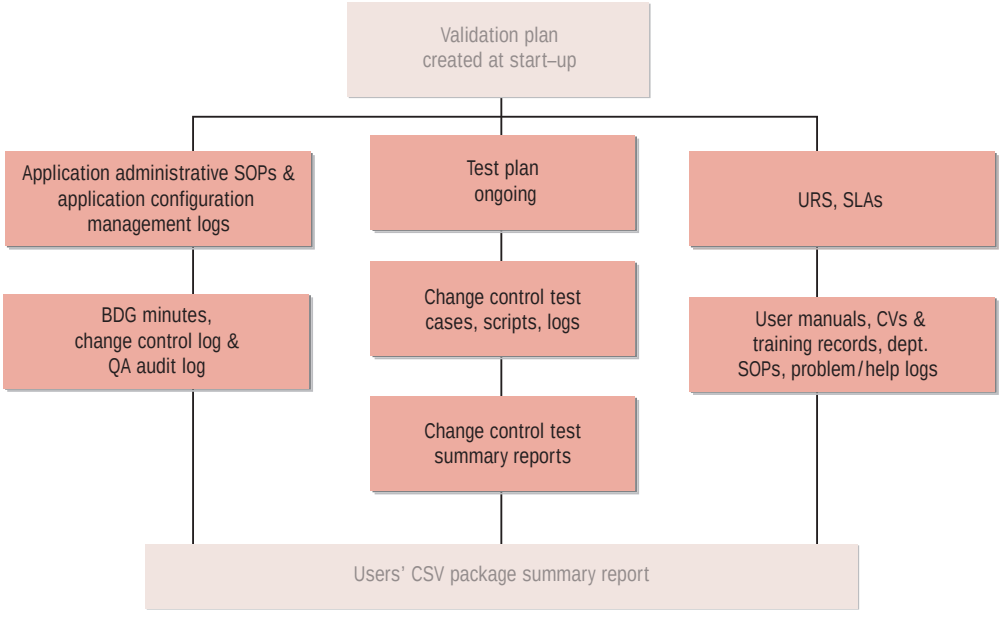

Figure 6. The ongoing test plan illustrates management control through to retirement.

during handling by the system.
- auditable quality of the system, its data, and user activities with the system over time.

Figure 5 shows the contents of a standard user acceptance CSV package. Although the testing functions in the central column are the usual perception of activities under a validation plan, the other two columns are of even greater importance for ensuring the smooth, ongoing operation of the system in a validated state. See the CSV Package Items box for brief descriptions of these other activities.

Formal testing practices in CSV packages. All testing performed in support of releasing a computerized system for GCP use is to be performed in a formal manner. That means it is to be fully thought through, documented, approved, and reported upon under the guidance of a signed validation plan and a signed test plan.

A startup test plan is used at the installation of a new system. The Institute for Electrical and Electronics Engineers, Inc. (IEEE) provides a good standard outline to be used for any system (see Test Plan Outline box).[2]

The test plan points to other formal testing documentation to be developed under its directives. These documents include the following.

Traceability matrix. A three-column table that identifies the key user requirements in the work process down the first column, the system features/functions supporting each key requirement down the second column, and the test cases checking and challenging the respective system functions down the third column.

Test case description. A document that describes a logical grouping of test activities associated with the system and its place in the work process. Test Case 1 should be designed to check for workplace preparedness by reviewing system manuals, work instructions, SOPs, and training records. Test Case 2 should check system administrative functions for setting up users, database structure, and so on. Test Case 3 should be designed to check and challenge the system with examples of the work process activities in a simulation mode.

Test script. A document that manages the individual testing experience and records the pass/fail conclusion. There can be one or more test scripts per test case.

Step procedure. A document specifying the detailed steps to be performed during testing, the expected results, and identified spaces for recording system response, problems occurring, and resolution to problems. There can be one or more step procedure documents per test script.

Result log. Identified space in a step procedure for recording system response to the testing activity.

Change control and the ongoing test plan. For repeat testing after the system has gone live and fixes and updates occur, a separate ongoing test plan is created, as shown in Figure 6. The ongoing test plan is written and approved as one of the final validation plan tasks to be completed before writing the CSV package summary report. Figure 6 also shows the other CSV package items that may require updates or adjustments depending on the size and scope of the fixes, updates, or enhancements made to the system.

Keeping a GCP system vali-

Change Control Test Summary Report

- ☐ **Test summary report identifier.** Unique ID traceable to associated ongoing test plan.
- ☐ **Summary.** Describes change(s) being tested. Describes items tested (application version), test environment (platform system), and test approach (test cases used).
- ☐ **Variances.** States any deviations from test case or test scripts and reasons for deviations.
- ☐ **Comprehensive assessment.** Discusses assumptions and limits to scope of testing. Were scope of testing and results obtained sufficient to assess system reliability for change(s) made? Discuss reasons for limits chosen.
- ☐ **Summary of results.** Gives table of testing results per test case. Table of anomalies and their resolutions. List of outstanding issues and risks (unresolved anomalies).
- ☐ **Evaluation.** Pass/fail conclusion based on test results and criteria in the ongoing test plan.
- ☐ **Summary of activities.** Describes tester/witness staffing, testing location(s), and test documentation preparation and approval process.
- ☐ **Approvals.** Names, titles, signatures, dates with meaning of signatures.
- ☐ **Appendix.** Table of contents list for test documentation produced.

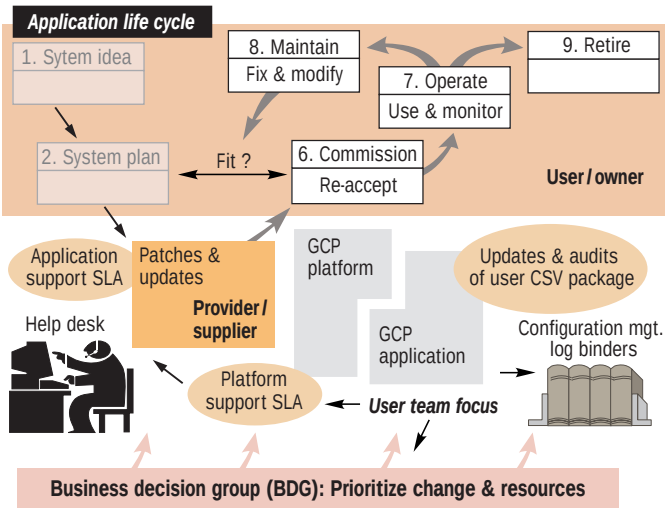

Figure 7. User team focus and business decision group responsibilities through to system retirement.

dated requires keeping all of its relevant documentation up-to-date as the system is tuned to a changing work process or a problem is resolved, or when a supplier provides a new feature. User training and user instructions in manuals and SOPs may have to be adjusted to ensure proper use of the system. Management needs to be kept informed of trends in changes and the scope of changes over time.

System change requires repeat testing to some extent determined by the ongoing test plan, and all formal testing documentation must be kept for audit purposes. The reuse of startup test scripts provides a degree of "regression testing" that checks for consistent results with prior findings. Some startup test scripts can also be used for training new users on the system. Such training test experience can also be used for periodic checks of the system, and so should be kept and recorded for "double credit" whenever possible.

Test summary report. When any formal testing is performed, a test summary report must be prepared to give management a review and analysis of the experience and assessment of the testing's impact on the validation status of the system tested. A pile of test result logs remains just a pile of paper until a responsible person who understands what the testing means has analyzed it and reported the conclusions. A good test summary report includes the points outlined in the Change Control Test box (adapted from the IEEE Standard for Software Test Documentation).3

As Figure 7 shows, many changes can occur with a GCP system after startup. The longest part of a successful system's lifetime is during its operational phase in the work process.

The user team continues to focus on the GCP software application system by training new users, resolving issues and problems with the system, and keeping the configuration management logbook binder up-to-date with system activities. The user team also manages the SLA process with platform and application suppliers, performs formal testing of changes to the system, and keeps the BDG informed with quarterly updates on system status. When the GCP system user community becomes multisite, multinational, and multidivisional, the user team roles become full-time positions.

A successful relationship

We have all seen uncontrolled, poorly disciplined pets become a nuisance to everyone around them—sometimes their behavior is a danger to themselves and others. The same situation can easily arise with computerized systems left unmanaged. The purchase of software for clinical research is serious business and the failure of software to function as intended must be considered for its impact on the safety, efficacy, and quality of study data and the medical decisions made on the basis of computerized systems in the GCP work process.

The operational phase of a GCP software application system is the longest phase of its life, and management must exert ongoing control of the system to ensure its continued compliance to validation standards. The user team's startup CSV package should also establish the documented procedures for ongoing control of the GCP system, and management should provide the strategic focus and ongoing resources needed to achieve the goal of expected performance with lifetime system validation for its essential GCP systems.

References

1. Pharmaceutical Manufacturers Association Computer Systems Validation Committee, "Validation Concepts for Computer Systems Used in the Manufacture of Drug Products," Pharmaceutical Technology 10 (5), 24–34 (1986).
2. Institute for Electrical and Electronics Engineers, Inc., IEEE Standard for Software Verification and Validation Plans, Standard 1012-1986 (IEEE, Piscataway, NJ, 1992), pp. 12–19.
3. Institute for Electrical and Electronics Engineers, Inc., IEEE Standard for Software Test Documentation, Standard 829-1983 (IEEE, Piscataway, NJ, 1993), pp. 10–12, 15–16.

Teri Stokes, *PhD, is senior consultant and director of GXP International, 131 Sudbury Road, Concord, MA 01742, (978) 287-4393, fax (978) 369-5620, gxpintl@ma.ultranet.com.*