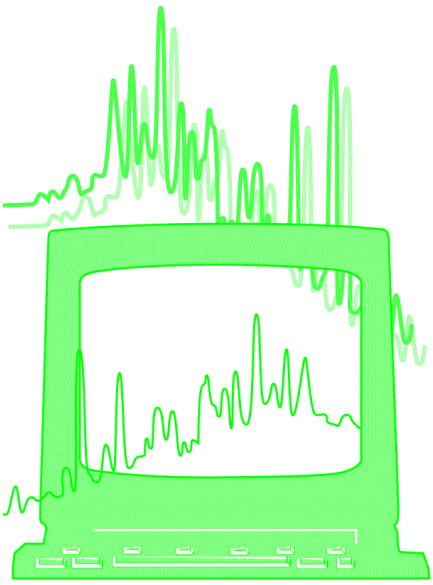

Chromatography Data Systems III: Prospective Validation of a CDS

R.D. McDowall, McDowall Consulting, Bromley, Kent, UK.

Is your chromatography data system fit for purpose?

The first two parts of this series on chromatography data systems (CDS) covered the fundamentals of a system (1) and the specification, evaluation and selection of a system (2).

In this part, I want to discuss the prospective validation of a CDS. By prospective validation, I mean undertaking the validation work in parallel with progress through the life cycle of the project. Unfortunately, this is not always the situation; usually just before the system goes live, someone thinks perhaps we should validate the system. This approach will add between 25 and 50% to the validation costs of the project. The reason is mainly because documentation that should have been written at key stages of the project were missed or, if written, may not have been of sufficient quality for laboratories working under regulations (Good Manufacturing Practice or Good Laboratory Practice) or voluntary guidelines (ISO Guide 25, soon to be ISO 17025). Retrospective validation of a CDS involves documentation and testing after the system has gone live, a subject covered in a recent article by Wikenstedt et al (3).

Why Bother to Validate?

There are a number of reasons for validating your CDS:

Investment protection: The investment in computerized systems, including CDS, has risen dramatically over the past decade, but what is the success rate? Validation is a way of building quality into a CDS and increases the odds that the system will meet expectations. Therefore, the investment that an organization makes is protected from purchase on a whim.

Consistent product quality: Product quality can be used in the widest scope. The product of a laboratory is information and, as such, with research and development laboratories validation is used to ensure that the results generated to support product development are correct. Chromatography data systems can be heavily involved with manufacturing and, therefore, it is important to know that data used to release a product are correct, thus ensuring consistency in the quality of the final product.

Compliance with regulations: Both the Food and Drug Administration (FDA) and the European Union (EU) (3, 4) expect manual and computerized systems to show equal quality. Good validation practices will ease or expedite regulatory inspections and audits, and reduce the risk of non-compliance. Also, confidence in computerized data establishes a good foundation for management control especially throughout a multinational company where it can result in better communication across teams and also with regulators.

Validation Definitions and Issues

Before beginning, we need to define a few terms.

What is a computerized system? A computerized system comprises several components (Figure 1). It is important to realize early in your project that if you are validating a computerized system, you don't just concentrate on the computer hardware and software. Validation is more encompassing as I'll discuss now.

The elements comprising a computerized system are as follows:

- Hardware: The elements that comprise this are the computer platform that the CDS runs on (PC or server plus clients etc.), and the network components such as hubs, routers, cables, switches and bridges. The CDS system may run on a specific segment of a network or over a general segment of it. Peripheral devices such as printers, plotters and the analogue-to-digital (A/D) units and connecting cables are also included in this category.
- Software: Again this comprises several elements including the operating systems of the clients and server, and the network operating system. Also included is the application itself (CDS) and any utility software, such as a database or reporting language.
  Together the hardware and software comprise a computer system.
- Equipment and instruments are linked to the computerized system. In the instance of a CDS these will be the chromatographs for high performance liquid chromatography, gas chromatography and capillary zone electrophoresis. The linkage can vary from just the analogue detector output to the A/D unit, an additional wire to transfer the vial number from the autosampler to the data system or full instrument control cable, usually based on IEEE 488 protocol. Ideally the equipment connected to the data system should be qualified before the validation of the CDS is undertaken, otherwise how do you know that you are generating quality results?
- The equipment and the data system must be operated by trained staff who follow written procedures both from standard operating procedures as well as the manuals.
  The equipment and the trained users comprise the controlled function.
- A computerized system is made up of a computer system, together with a controlled function.

To repeat, you must realize that validation is not just a matter of testing software,

calibrating or testing the A/D converter units; there is a greater range of items to consider under the scope of validation.

We'll look at the various elements that comprise the validation package for a CDS. The linking element in all items is documentation: if you didn't write it down you didn't perform the action and you cannot demonstrate what you've done to an inspector, auditor or assessor. In short, if it's not written, it's a rumour. Therefore, you'll need something that is tangible, and a document is both the medium and the message where validation is concerned. As a corollary, document control is also important, as we'll see later.

What is validation? Validation is probably best defined as:

"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes" (4).

The key concepts in the definition above are

- documented evidence
- a high degree of assurance
- predetermined specification.

Note that in this definition there is no mention of computerized systems: it is applicable to all processes.

There are other regulatory or quality guidelines from the EU (5), the Organization for Economic Cooperation and Development (6), Japan (7) and the International Standards Organization (8). They may have slightly different demands but all come down to the same series of requirements: in general, validation is concerned with generating the evidence to demonstrate that the CDS is fit for the purpose you use it for and continues to be so when it is operational, and that there is sufficient evidence of management control. This usually means that an action must be documented. Another feature of validation is to produce an auditable system, having the appropriate documentation to aid any audit or inspection.

The problem is how to respond to the requirement for validation. Any response should

- be scientifically sound
- be structured
- provide adequate compliance
- reflect the way you use the application.

This last point is most important because there is no reason to validate a function of a CDS that is not used.

Computer validation must provide confidence in the CDS, first and foremost, to laboratory management and users, second to an internal quality audit and third to an external inspector. Inspectors only audit the laboratory on a periodic basis. All others work in the laboratory and use its computerized systems daily. The users must have the confidence in a system above all others, otherwise the investment will be wasted.

Problems with validation: These include

- Self regulation: Regulatory agencies take the view that the end-users of a CDS are responsible for its validation. The agencies will audit the system and will inform you if there are any problems with the work you have done. This is not very satisfactory as the end-users can rarely perform more than black-box testing unless they have detailed knowledge of the design specification of the system and the aid of skilled computer scientists.
- What am I to do? This leads to the problem of how to interpret the guidelines in a cost-effective approach to validation. Often many iterations of trial and error can be involved, where validation is either over-engineered or not sufficiently rigorous.
- Complete testing of a system is a myth: Unless there is a very simple system, it cannot be tested completely. This was

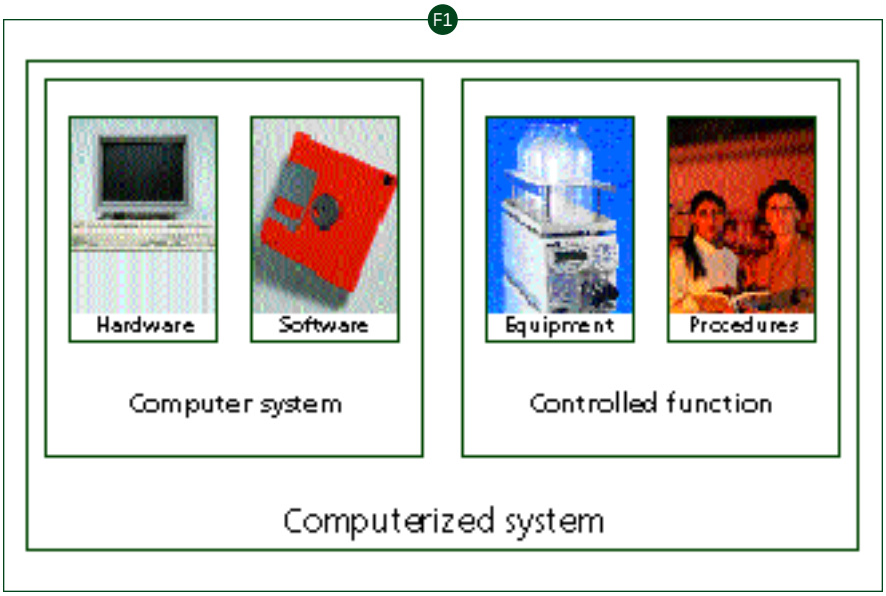

Figure 1: Elements of a computerized system.

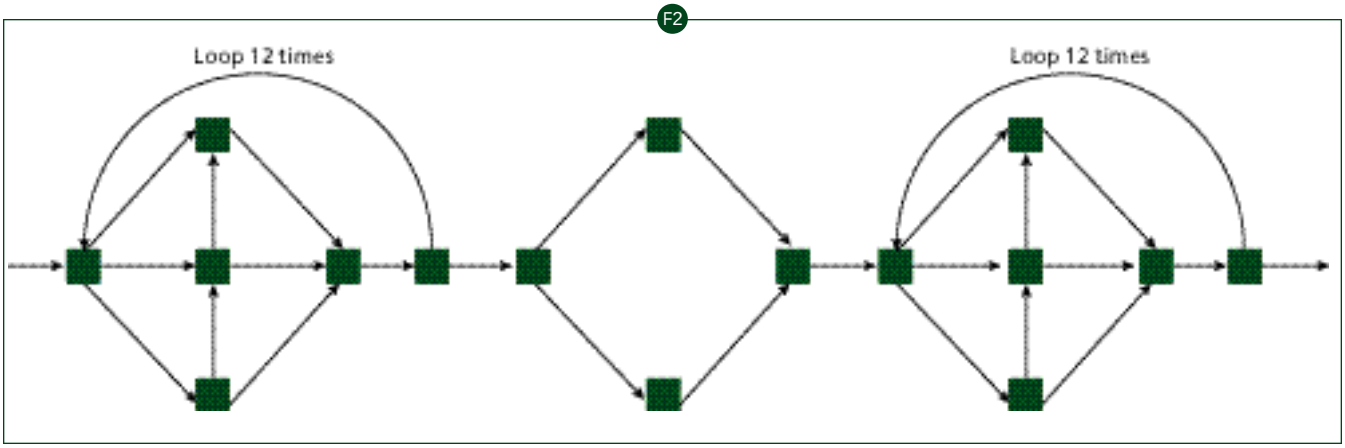

Figure 2: Complete testing of software is impossible (Boehm 1970).

demonstrated by the work of Boehm (9) who described the simple program flow segment shown in Figure 2. The number of conditional pathways and hence possible tests of the software in this segment was calculated to be 10^{21}. If the absurd assumption is made that one test can be conceived, designed, executed and documented per second, then it will take more than three times the geological age of the earth to validate this program segment. Unfortunately most CDS are far more complex. Therefore, procedures to record and fix errors are very important, and we'll discuss them in part IV of this series.

- Consistency of audit: The human element, in the form of what will pass without comment with one inspector or auditor but not another, will never completely disappear. The computer literacy of inspectors is increasing and with this will come increased scrutiny of computerized systems, including CDS. However, consistency of regulatory approach and inspection is highly desirable.

FDA Form 483 and warning letters: To gain a greater understanding of regulatory requirements, either a quick Internet trip to http://www.fda.gov or reading of selected issues of the "Gold Sheet" (10) is highly recommended. In the electronic reading room is a list of warning letters issued between 1996–97. Here you can see a health authority in action. The citations associated with computer validation can be grouped into six categories (11):

- evidence of management responsibility
- evidence of system design and control of the design
- evidence of testing
- evidence of training
- evidence of audit and review
- evidence of document control.

Validation must address all of these issues, not only during the development of a system, but also during its operational life.

Validation roles and responsibilities: There are three key roles in validating a CDS from a laboratory perspective; these are the users, quality assurance and information technology (IT). Each will be described below together with an outline of their responsibilities.

- Users: responsible for the overall validation of the CDS. This is achieved by defining the system's functions, selecting the system, verifying its installation and defining and executing the validation plan. Users will need to have standard operating procedures (SOPs) written for operating and supporting the application, the user base must be trained and users must ensure that the complete documentation of the system is available for audit and inspection. Although the end-user is responsible for these areas, they need help, advice and support in this. Active support by management is essential for making the resources available for the validation effort and to take the responsibility for authorizing the use of the system in the regulated environment. Furthermore, management must encourage the participation of the quality assurance (QA) department in this process.
- Quality assurance: responsible for assistance in the interpretation of regulatory guidelines for computerized systems and how they apply to the CDS. The QA personnel will review the key documentation produced during the validation effort. Monitoring of the testing and validation effort and offering assistance in developing SOPs are additional roles and responsibilities for QA. If there are any vendor audits to be undertaken, then QA should be involved in the planning and execution of this activity. However, some QA personnel may not be very computer literate, but this must change as many regulations involving computerized systems require the active involvement of this department.
- Information technology: responsible for help in purchase, installation and operation of the CDS for systems running on a network. If a group is not available or the users take on this role, then the responsibilities outlined here will be transferred to the users. Responsibilities will include running the hardware and software, back-ups, resolving problems etc. However, in offering support for a regulated CDS, the IT group become bound by the regulations or guidelines that the laboratory works under. What is not often realized both by the users and the IT group is that any unauthorized change to the operating system or network will make a validated CDS non-compliant. We'll come back to this area in the next article in this series.

External roles may include the following:

- System vendor: The CDS vendor should be able to help with advice on the sizing of the system, hardware needed for good performance, assistance with vendor audits and help with qualification of the system (installation qualification (IQ) and operational qualification (OQ) only).
- Consultants: for advice on the overall validation process or specific portions of it.

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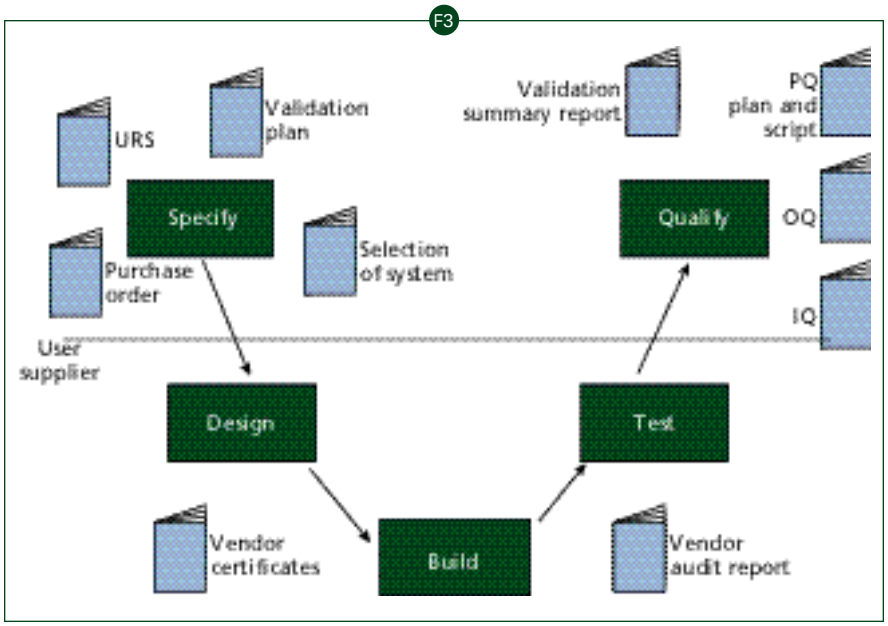

Figure 3: Key documents to support validation and their place in the life cycle. URS = user requirements specification, IQ = installation qualification, OQ = operational qualification, PQ = performance qualification.

Life-Cycle Approach to Validation

If you remember the first article in the series you will recall that we looked at a version of the system development life cycle in the shape of a 'V'. We can take that model and map onto it the documentation that could be produced in the life cycle and show its relationship to the life cycle (Figure 3). This shows each document's relative position in the life cycle and the areas that it covers.

The documents that could be produced are listed below and the key ones are

discussed in more detail in the next section. Table 1 provides an outline description of the function of each document.

Taken together this documentation will provide the validation package to support the contention that the CDS is fit for purpose. Please note that this is a suggested minimum list; you may write fewer or more documents than outlined here. The extent that you differ will depend on the amount of regulatory risk that the organization or laboratory management wishes to carry.

Validation plan: The name for this document varies so much from laboratory to laboratory: validation plan, master validation plan, validation master plan or even quality plan. Regardless of what you call it in your organization it should cover the steps you are going to take to demonstrate the quality of the CDS in your laboratory. Ideally it should be written as early in the process as possible to define the overall steps that are required and the documents to be produced from each.

T1

Table 1: Validation Package Documentation.

Document Name	Outline Function in Validation
Validation plan	• Documents the intent of the validation effort throughout the whole life cycle • Defines documentation for validation package • Defines roles and responsibilities of parties involved
Project plan	• Outlines all tasks in the project • Allocates responsibilities for tasks to individuals or functional units • Several versions as progress is updated
User requirements specification (URS)	• Defines the functions that the CDS will undertake • Defines the scope, boundary and interfaces of the system • Defines the scope of tests for system evaluation and qualification
System selection report	• Outlines the systems evaluated either on paper or in-house • Summarizes experience of evaluation testing • Outlines criteria for selecting chosen system
Vendor audit report and vendor quality certificates	• Defines the quality of the software from vendor's perspective (certificates) • Confirms that quality procedures match practice (audit report) • Confirms overall quality of the system before purchase
Purchase order	• From vendor quotation selects software and peripherals to be ordered • Delivery note used to confirm actual delivery against purchase order • Defines the initial configuration items of the CDS
Installation qualification (IQ)	• Installation of the components of the system by the vendor • Testing of individual components • Documentation of the work performed
Operational qualification (OQ)	• Testing of the installed system • Use of a vendor's protocol or test scripts • Documentation of the work performed
Performance qualification (PQ) test plan	• Defines user testing on the system against the URS functions • Highlights features to test and those not to test • Outlines the assumptions, exclusions and limitations of approach
PQ test scripts	• Test script written to cover key functions defined in test plan • Scripts used to collect evidence and observations as testing is performed
Written procedures	• Procedures defined for users and system administrators • Procedures written for IT related functions • Practice must match the procedure
User training material	• Initial material used to train super users and all users available • Refresher or advanced training documented • Training records updated accordingly
Validation summary report	• Summarizes the whole life cycle of the CDS • Discusses any deviations from validation plan and quality issues found • Management authorization to use the system

Content of a validation plan: The content of a validation plan is listed in Table 2. This is taken from the IEEE standard for validation and verification plans (12). The purpose of the validation plan is to define the validation documentation to be produced during the initial stages of the life cycle, together with the roles and responsibilities involved and to provide a plan of intent for the life cycle.

Design — The URS: Remember from the definition of validation presented in the early part of this article the phrase "predefined specifications" was included? The document that provides the laboratory with the predefined specifications is the user requirements specification (URS). Without the URS or equivalent you cannot validate your CDS. The content of the specification for a system is discussed in a separate article (13).

Ideally, an independent group of users (not involved in writing the document) should evaluate the URS and challenge the specifications and any interfacing requirements between analytical instruments or any other computer applications. If any missing requirements or inconsistencies can be found at this stage they are easy to correct. Therefore, the extra work in ensuring that the user requirements specification is correct is time and resources well spent. Problems that should have been rectified at this stage are far more expensive to solve further into the life cycle. When

T2

Table 2: Validation Plan Outline Format (based on IEEE Std 1012–1986).

- Purpose
- Reference documents
- Definitions
- Validation overview
  - organization
  - master schedule
  - resources summary
  - responsibilities
  - tools, techniques and methodologies
- Life cycle validation
  - management of validation for concept phase
  - requirements phase
  - design phase
  - implementation phase
  - test phase
  - installation and checkout phase
  - operation and maintenance phase
- Software validation reporting
- Validation administration procedures
  - anomaly reporting and resolution
  - task iteration policy
  - deviation policy
  - control procedures
  - standards, practices and conventions

the URS is complete, the outline selection tests can be generated.

Vendor certificates and vendor audits: Many CDS vendors will be certified to ISO 9000 of some description and will offer you a certificate that the system conforms to their quality processes. This is fine but please remember that there is no requirement for product quality in any ISO 9000 schedule and if you look at the warranty of any software product there is no guarantee that the CDS is either fit for purpose or error free. The certificates are fine but if the system is critical to your operation my advice is to consider a vendor audit.

The vendor audit should take place once the product has been selected and the purpose is simply to see whether the ISO 9000 quality system is operated effectively. The evaluation and audit process is a very important part of the life cycle as it ensures the design, build and testing stages (which are under the control of the vendor) have been checked to ensure compliance with the regulations. The audit should be planned and cover items such as the design and programming phases, product testing and release, documentation and support. A report of the audit should be produced after the visit. A previous "Questions of Quality" column and two articles in Scientific Data Management have covered vendor audits in more detail (14–16).

Installation qualification: Put simply this is the installation of the components of the order into the system with a check that it works correctly. The best people to undertake this work will be the vendors as they know their products best; however, there could be several groups working on the installation:

- server installation by the server supplier or maker
- workstation and peripheral installation by either the IT department or contractors working on their behalf
- installation of network infrastructure by specialist contractors
- installation of the CDS software by the vendor
- installation of A/D units and any associated equipment by the CDS vendor.

Many of the organizations will not be familiar with the regulations or guidelines that you are operating under. You'll need to be proactive to ensure that documentation of these activities is collected, and planning and discussion is essential here otherwise you'll end up with little from this phase of work with the exception of the CDS vendor.

Operational qualification: The OQ is an extension of the IQ and is intended to demonstrate that the whole system works the way the vendor says it will. Most vendors will supply OQ scripts. These of necessity will only cover a subset of functions and will not be a substitute for the user acceptance tests or performance qualification (PQ) tests.

Performance qualification: The PQ is the user acceptance testing, undertaken by the users and based upon the way that the system is used in a particular laboratory. Therefore, your CDS cannot be considered validated simply because another laboratory has validated the same software; the operations of two laboratories may differ markedly even within the same organization.

How can we approach the testing from a user perspective? This needs a discussion of white-box and black-box testing.

White-Box and Black-Box Testing

There are two approaches to testing: conventionally known as white-box and black-box testing.

White-box testing: This type of testing requires the full knowledge of what the program unit or module does (Figure 4(a)). This will include the complete specification of the inputs, outputs and processing algorithms within each module of the CDS application. The design specification is used to devise tests to prove that the functions described work as designed as can be seen from the V model in Figure 3. In essence, you need to have a programming background to execute white-box testing. Users will not be able to undertake technical testing because either they do not have the full technical specification of the system, or they do not possess the technical skills to undertake this type of testing or, as is usually the situation, both.

Black-box testing: In contrast, in black-box testing (Figure 4(b)) the tester only knows the overall function of the module with input limits. No programming knowledge is required, only training in how to use the application. Therefore, users will undertake black-box testing, where known inputs will be entered and the outputs compared with those expected (anticipated results).

Performance Qualification Test Plan and Test Scripts

A PQ test plan outlines the features to test and those that will not be tested. Associated with this are the written notes of the assumptions, exclusions and limitations to the testing undertaken.

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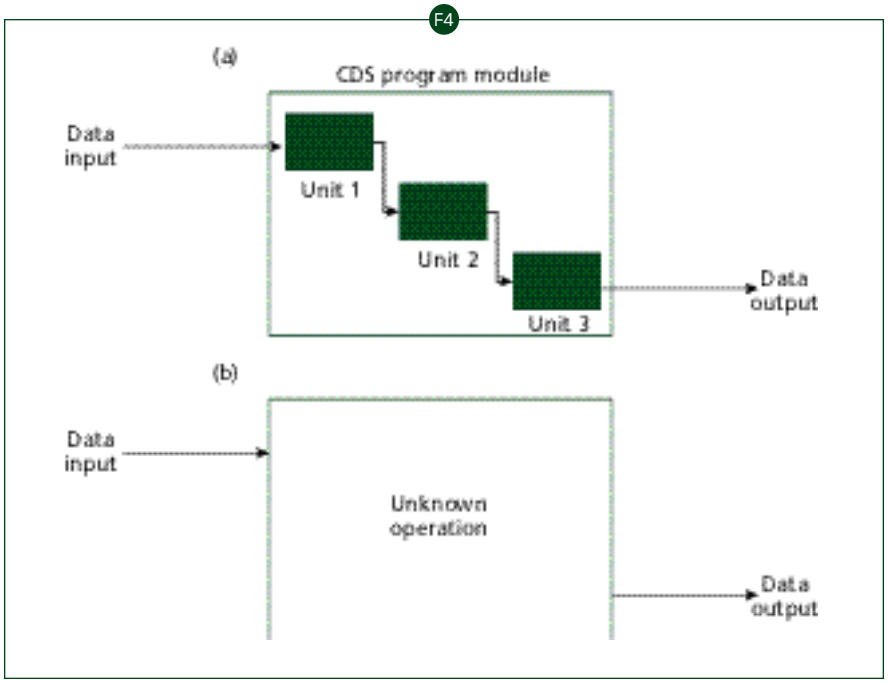

Figure 4: White box and black box testing. a) = white box testing: All code, specifications of units and algorithms known to the tester; (b) = black box testing: Overall function known only.

T3

Table 3: Validation Summary Report based on IEEE Std 1012–1986 (12).

Summary of all validation tasks and results
Summary of anomalies and their resolution
Summary of deviations from the validation plan and rationale for such deviations
Statement from management of the system's validation status
Operational release of the system signed by management

The test scripts are the heart of any validation attempt and will take some time and effort to get correct. The concept is that the test script will form the testing log. The archive for the actual testing and all experimental data and output will be recorded here. Some of the types of test that could be performed are

- boundary test: the entry of valid data within the known range of a field, for example, a pH value would only have acceptable values within 0–14
- stress test: entering data outside of designed limits, for example, a pH value of 15
- predicted output: knowing the function of the module to be tested; a known input should have a predicted output
- consistent operation: important tests of major functions should have repetition built into them to demonstrate that the operation of the system is reproducible
- common problems: both the operational and support aspects of the computer system should be part of any validation plan. The predictability of the system under these tests should generate confidence in its operation.

The format of the document and more details of PQ testing are found in an earlier article (3).

Validation summary report: The validation summary report brings together all of the documentation collected throughout the whole of the life cycle and presents a recommendation for management approval when the system is validated. One outline of a summary report, based on the IEEE methodology is presented in Table 3. The emphasis is on using a summary report as a rapid and efficient means of presenting results, as the detail is contained in the other documentation in the validation package.

Now you've completed the easy part: Congratulations! Your CDS is now validated and released for operational use. You have completed the first and easiest part of validation of your CDS. The difficult part is to maintain the validation status of the system throughout its whole operational life. This is more difficult as there are a number of changes that will happen: bug fixes, software upgrades, hardware upgrades, back-up, recovery, revalidation and periodic review. We'll look at these topics and more in the next part of this series.

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