

Validation for Compliance to 21 CFR part 11

Results and Conclusion

- 1) Both the TPW II and Prelude products were ultimately determined to be compliant with the requirements of 21CFR part 11.
- 2) The generic validation plan approach appears to greatly improve the efficiency of validation for subsequent products
- 3) By including the generic test requirements in product design specifications compliance is assured through the design process.
- 4) Customer input helps to evolve a consistent approach toward verifying compliance.
- 5) The applicability of the generic approach will need to be tested with new products that have different software architectures.

Acknowledgments

Without the input and advice of our customers this project would not have been as successful in meeting the overall pharmaceutical industry needs.

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Abstract

Purpose. To present a chronology of the process of validating a previously developed and commercially available instrument for compliance to 21 CFR 11. **Method.** Became familiar with the standard, developed protocols, industry expert review, pharmaceutical user review, protocol execution, exception reports, and any necessary product revisions. **Results.** A generic template applicable to a wide variety of instruments was developed which could be easily modified to validate specific products. The product was found to have one minor noncompliance issues. **Conclusions.** There are several areas in the standard which are unclear and subject to interpretation. An effective approach was developed to assure compliance to 21 CFR 11 in the development process.

Purpose

- 1) To present a chronology of validating a previously developed laboratory instrument for compliance to 21 CFR part 11.
- 2) To review the process used to gather general information about the standard and develop an interpretation of the standard.
- 3) To demonstrate the feasibility of developing a generic test case applicable to other products.
- 4) To provide increased value to pharmaceutical customers required to be compliant to 21 CFR part 11.

Methods

Understanding the Regulation

Aside from the regulation itself various articles, papers, guidelines, consultants and customers were used as informational resources. Customer's automation validation groups proved the helpful since they have formed their interpretation of the standard. Some areas where interpretation was necessary were:

- 1) The appropriate level of security. Security had to be reasonable to prevent a person from acting alone to break into the system.
- 2) Unattended terminals. The FDA Guidance on Computerized Systems Used in Clinical Trials states that a reasonable period of time should be specified to prevent an unattended terminal from being used. Rather than establishing this time period CaliperLS determined that all functions should require authorization each time used.
- 3) System configuration. Among others, there are interpretations that state if a system can be configured to be non-compliant then the system is non-compliant. System compliance has to be considered along with operational controls and policy. Those controls and policies dictate configurations set by the system administrator.



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Methods (continued)

Developing the Validation Plan

Developing the plan was a two step process.

- 1) The first step created a generic validation plan that listed generic test cases that could be used for any product. The generic validation plan, became the template that could be used for step two.
- 2) Step two details a specific validation plan unique to each product. Each of these steps is described in more detail below.

Generic Validation Plan

When creating the generic validation plan it was necessary to define the scope of the plan.

- 1) By overall project objective it was determined that the generic plan should cover all CaliperLS products intended for the regulated pharmaceutical industry.
- 2) It was also necessary to determine if the scope should include electronic signatures in addition to electronic records. Electronic signatures were determined equally applicable because it was necessary to document the analysts using the system.
- 3) The standard clearly defines open and closed systems. All CaliperLS systems are closed because system access is controlled by those responsible for the data.

Prior to defining specific test scripts, it was necessary to create a requirements traceability matrix. A requirements traceability matrix is a table where the first column lists all of the requirements aligned with one or more generic test cases for each requirement. Using this matrix, one can be sure they provide at least one test for each and every requirement. (see Example 1)

Example 1. 21 CFR Part 11 Requirements Traceability Matrix (excerpt)

11.10 Controls for Closed Systems	Test Case Description	Test #
(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.	A Validation Plan to confirm that the functional requirements were met was created and executed.	3.1
(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency.	Accurate and complete copies of records can be printed to a computer file. This data is confirmed to be accurate and complete by comparing the information against the actual data within the secure database. Accurate and complete copies of records can be printed on paper. This data is confirmed to be accurate and complete by comparing the information against the actual data within the secure database.	3.13 3.14
(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.	New data records do not overwrite old data records. Unauthorized users cannot modify or remove data records.	3.9 3.10
(d) Limiting system access to authorized individuals.	Passwords are required and are stored in encrypted form and cannot be viewed by anyone including security administrators. Users can change their password at any time. Non-administrators can not create or modify user name and security level. Different levels of security exists to allow only authorized user to perform specific operations that can create, modify, or delete electronic records.	3.3 3.6 3.7 3.8
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail information shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.	New audit trail records do not overwrite old audit trail records. Unauthorized users cannot modify or remove audit trail records. A time-stamped audit trail of any changes to the electronic records is created automatically by the system. Records include time, date, operator, old value, new value, and transaction type. Previous versions of a changed record can be reviewed.	3.9 3.10 3.11 3.12

Specific Validation Plan

The first product to test was the Tablet Processing Workstation II (TPW). The TPW was selected because it was an existing or "legacy" product, developed before the existence of the regulation, whose primary focus is for use in pharmaceutical QC labs. Coincidentally, it had been given a recent software upgrade that incorporated a brand new security module. Customers have requested certification for compliance for this instrument.

To properly document and test a product, it is important to understand its functionality and data architecture. The primary applications of the TPW are sample preparation for assay, content uniformity, related substances, and stability testing. The Unit performs basic functions such as tablet dispersing, dilution, and filtration of samples. It can then feed the sample into a detection device such as an HPLC or UV, or it can store the sample using a sample collection product called EasyFill.

Figure 1 shows the TPW Robotic Unit. The hardware includes test tube racks, robotic arm, filter dispenser, disperser station which contains a 3-place balance, and a dispense station which contains a 4-place balance.



Figure 1. TPW Robotic Unit

Figure 2. TPW Data Architecture

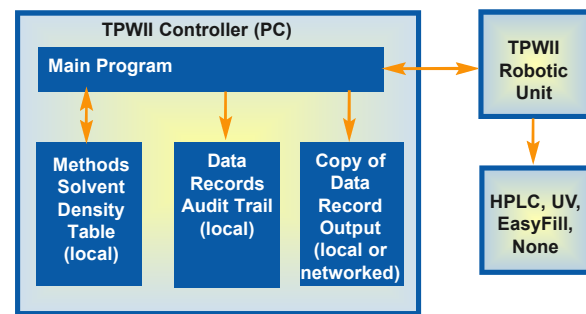


Figure 2, is the data architecture diagram for TPWII. There are 3 boxes: The PC, the Robotic Unit, and the output device. The blocks within the PC show data. Methods and Solvent density are saved in individual files.

Data Records are produced and stored locally in a SQL Server Database and in an Excel spreadsheet. Copies of the data can also be sent to another database or spreadsheet using the Advanced Data Channel option. Audit Trail information is stored locally in the SQL Server Database.

With general product knowledge, the specific test cases can then developed. During this process additional questions arose.

- 1) Can the plan just reference design level testing performed during product development? It was determined that auditing the test would be difficult and gaps would be found with the original testing as it relates to 21 CFR part 11.
- 2) Does this test plan need to cover every type of operation that the system can perform? It was decided that the testing would include a typical set of operations since product functionality was not being tested.
- 3) What are the instrument boundaries? i.e. Where does the testing stop when considering external devices?

Instrument Boundaries

- 1) Advanced Data Channels option for the system. It allows the user to store data outside of the TPW's secure database in a user provided platform. The position developed was that this is a copy of the secure record and therefore is not within the instrument boundary.
- 2) External detection devices such as an HPLC or UV. The data from these devices is not part of the system since it is not returned to the TPW.

The generic test cases were then specifically adapted to the TPW. This was a short process relative to the rest of the process. An example of a test adapted to the TPW follows. (See Examples 2 and 3)

Example 2. 3.2 Unique Combination of User Name and Password

Test Objective: A unique combination of username and password for each individual is required to operate the system.
Test Procedure: Our systems require a unique username. Verify that a new user with the same name of an existing user cannot be created.
Test Case Setup: None.

Unique User Name Test

Step	Action	Expected Result	Observed Result
1	Login as NT System Administrator. Open the NT User Manager. Confirm the existence of a user named 'TPWRun.'	User 'TPWRun' exists	
2	Select User -> New User. Enter 'TPWRun' for Username, Password, and Confirm Password. Press OK. When Error box shows, Press OK. Press Cancel to exit 'New User' menu.	Error occurs when save is attempted.	
3	Confirm that only one user with the name 'TPWRun' exists.	One user 'TPWRun' exists.	

Pass [] Fail []

Completed By: _____ Date: _____

Example 3. 1.1. Previous Versions of Records

Test Objective: Previous versions of a changed record can be reviewed.

Test Procedure: TPWII provides no ability to modify or delete output records, only the ability to create output records. Therefore, all output records have only one version. Previous versions of Methods are archived. Verify that archived methods are created and can be accessed. Changes to the Solvent List are recorded in the audit trail. Verify that the audit trail stores this information.

Test Case Setup: None.

Verify Method Archiving Test

Step	Action	Expected Result	Observed
1	Login to NT Workstation as 'Administrator.' Edit method '21CFR11Test' and change step 1 addition volume from 100ml to 50ml.	Method appears with new name made up of the original name and the time and date stamp of the last change.	
2	Save the method.	Method Step1 addition volume is 100ml.	
3	Note the time and date the method was saved. Press Edit and navigate to Method Archive directory.	Method appears with new name and the time and date stamp of the last change.	
4	Select the archived file from step 1 and open it. Open method '21CFR11Test' and change step 1 addition volume from 50ml to 100ml. Save the method. Note the time and date the method was saved.	Method Step1 addition volume is 50ml.	

Verify Solvent Density Records Test

Step	Action	Expected Result	Observed Result
1	Add a new Solvent: Test2, 0.9999, Aqueous. Save and Exit Solvent Menu.	New Solvent is created. Edits are accepted.	
2	Edit the new Solvent. Change Density to 1.0000 Select View -> Data menu Select: Date Range Enter today's date in the Starting Date and Ending Date fields. Press New Query button Observe Event Data log	Event Data includes entry for Test2, 0.9999, Aqueous, new solvent; and Test2, 1.0000, Aqueous, Change made to solvent.	

Pass [] Fail []

Completed By: _____ Date: _____

Expert and Customer Review

Once a draft of the validation plan was developed it was reviewed by an outside expert. A well-known pharmaceutical industry consulting group was used. The following advice was provided.

- 1) Keep in mind the purpose of the regulation. The purpose can be summarized as follows:

(a) make sure that electronic records and signatures are as credible as paper records and signatures.

(b) make sure the FDA can access this information.

2) Provide an overview of the product. This should include what the instrument does and how data is stored and manipulated.

3) The test cases should be organized in a more logical manner. Originally the test cases were ordered to match that of the sections from the requirement. The order was changed to represent how the user would approach the machine.

CaliperLS's customers were very happy to give feedback on the test plan. Their advice was a direct reflection on what they felt the FDA would like to see based on direct experience.

1) Do not assume that the system would work a certain way - even if it were a function of the PC's operating system. Make sure the test was only against defined requirements.

2) Record the test results using screen captures.

3) Test scripts should be very detailed.

Execution & Results

One non-compliance issue was discovered involving the documentation of failed login attempts. CaliperLS used this information to create and release a software patch that made the product fully 21 CFR Part 11 compliant.

The testing also exposed some suggested improvements not required by the regulation. This included good feedback on usability.

Applying the Generic Validation Plan to Another Product

After validating TPW II Compliance to 21 CFR 11 our objective was to test the applicability of the generic validation plan to the development of a specific plan for a new product. The new product is CaliperLS's Prelude Workstation.

Prelude functionality and data architecture were reviewed. The primary applications of the Prelude include a wide range of dilutions, standard preparation, drug substance analysis, potency assays, and solubility testing. It can feed samples into a measuring device such as an HPLC or UV, or it can store the sample using a sample collection product call the EasyFill.

The Prelude hardware includes test tube racks, robotic arm, filter dispenser, a dispense station which includes a 4-place or 5-place balance, and a barcode reader. Options that will become available soon include a sonication station. The software architecture was identical to the TPWII.

Figure 3. Prelude Robotic Unit



The Prelude was determined to be 100% compliant without modification. By having a test standard in place for 21 CFR Part 11 compliance, this product was designed to meet the regulation. The specific validation test plan and its execution were completed in less than one week.