Environmental Analysis

FDA 21 CFR PART 11 COMPLIANCE AND VALIDATION OF A TITRATOR SOFTWARE

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In food and drug labs analytical devices typically work together with software and computers. In most cases the software is part of the instruments. The software produces so called "electronic records". This item "electronic records" is defined by the FDA (Food and Drug Administration in the USA) as:

Electronic record means any combination of text, graphics, data, audio, pictorial or other information representation in digital form, that is created, modified, maintained, archived, retrieved or distributed by a computer system [1].

Following this definition at least all information as e.g. analysis results and methods, stored on a computer are electronic records. As a consequence software in a FDA compliant lab has to be 21 CFR part 11 compliant.

An important condition is the validation of the software beside the special part 11 requirements:

Subpart B -- Electronic Records

Sec. 11.10 Controls for closed systems.

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

In the following text both requirements are discussed, part 11 requirements as well as the software validation. As an example a software for titration control is used, TitriSoft 2.60 P [2]. Practical information about validation is described in [6]; this is quoted in this paper.

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SOFTWARE VALIDATION

Validation is a necessary part of CFR part 11. This has some serious reasons. The FDA's analysis of 3140 medical device recalls conducted between 1992 and 1998 reveals that 242 of them (7.7%) are attributable to software failures. Of those software related recalls, 192 (or 79%) were caused by software defects that were introduced when changes were made to the software after its initial production and distribution [6].

Software validation is a requirement of the Quality System regulation, which was published e.g. in 21 (CFR) Part 820 [3].

A requirement can be any need or expectation for a system or for its software. Requirements reflect the stated or implied needs of the customer, and may be market-based, contractual, or statutory, as well as an organisation's internal requirements.

There can be many different kinds of requirements (e.g., design, functional, implementation, interface, performance, or physical requirements). Software requirements are typically derived from the system requirements for those aspects of system functionality that have been allocated to software [6].

Typically software is developed following a life circle model (*Figure 1*). This describes the steps from the quality planning over customer requirements, the installation of the ready software and at the end of the life circle the retirement.

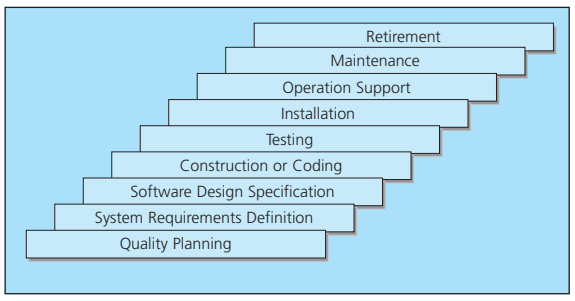


Figure 1: Life circle of a software

The requirements of the software are translated into a software design specification. A specification is defined as "a document that states requirements." (See 21 CFR 820.3(y), [3]) It may refer to or include drawings, patterns, or other relevant documents and usually indicates the means and the criteria whereby conformity with the requirement can be checked.

The decision to implement system functionality using software is one that is typically made during system design. Software requirements are typically derived from the overall system requirements and design for those aspects in the system that are to be implemented using software.

There are user needs and intended uses for a finished device, but users typically do not specify whether those requirements are to be met by hardware, software, or some combination of both. Therefore, software validation must be considered within the context of the overall design validation for the system.

A documented requirements specification represents the user's needs and intended uses from which the product is developed. A primary goal of software validation is to then demonstrate that all completed software products comply with all documented software and system requirements.

One important part of the software design is the software risk analysis, where all functions are examined for an acceptable risk *(Figure 2*). All risks between acceptable and unacceptable need special e.g. hints in the documentation.

Figure 2: Software risk analysis

The following table shows the analysis for a wrong calculated equivalence point in titration software:

Table 1: Description of a certain risk point

Requirement	Reliable calculated EQ	
Function design	EQ is calculated as the maximum of the first derivativ	
Risk descriptions	No EQ calculated ❶	Wrong EQ calculated ❷
Occurrence of probability	**2**	**2**
Description	■ An EQ can not be calculated, if the titration curves too early ■ The graph of the curve shows no EQ ■ The electrode may be defect	■ The electrode may be defect ■ The curve is very noisy
Extent of loss	**1**	**6**
Description	■ No result, no consequences, sample has to be recalculated or repeated ■ Every result is reviewed and additionally approved from competent lab managers, with special training and knowledge ■ It may be no more sample available	■ Every result is reviewed and additionally approved from competent lab managers, with special training and knowledge ■ It may be no more sample available ■ Everybody trust the calculated result ■ The curve shows clear the plausibility of the EQ
To Do	■ Acceptable	■ Acceptable ■ Hint in documentation

A common way of the realisation of a software project is the "V-Model". *Figure 3* shows a simplified V-Model. In this model need the steps requirements -> specification -> coding -> system test -> integration -> operation verifications and the comparison requirements -> operation and specification -> integration are validations.

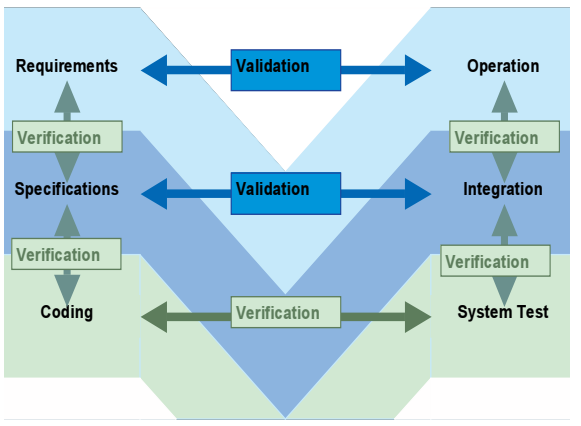


Figure 3: V-Model

Software verification provides objective evidence that the design outputs of a particular phase of the software development life cycle meet all of the specified requirements for that phase.

Software verification looks for consistency, completeness, and correctness of the software and its supporting documentation, as it is being developed, and provides support for a subsequent conclusion that software is validated. Software testing is one of many verification activities intended to confirm that software development output meets its input requirements [6].

FDA considers software validation to be "confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

The validation is at least a comparison of the functions described in the specifications with the functionality of the finished software. Every point of this list has to be proven by tests or any other objective evidence.

The validation process from the specification to the finished software (integration) is typically done by the manufacturer of the analytic device, in this case by the titrator company. The second validation procedure is typically in the responsibility of both, manufacturer and user.

While the manufacturer accumulates the requirements of a lot of users, the individual user may have particular requirements, which have to be validated. In practice the manufacturer delivers his part of the validation documents and the user can add and validate his special requirements.

This can e.g. be done in the range of an operational qualification, which includes the confirmation that the need of the customer is fulfilled.

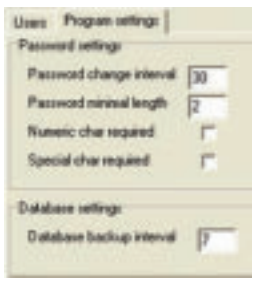


Figure 4: Some requirements for passwords

The controls for open or closed systems require restrictions for the user and in practice it is not so easy to fulfil the FDA requirements on one side and allow effective work. In the example titration software five user levels allow a differentiated access in the user level as well in the administrator level. Several requirements for the password guarantee that any electronic record can traced back to the correct user (*Figure 4*). Of course the same password can not be used twice!

Every change in any electronic record must be saved (when necessary with a comment) in an audit trail. This is data base table, which includes any kind of addition, deleting or change in the data base (*Figure 5*). Of course it must be possible to review all changes in the audit trail. A comfortable function can save a lot of time in such a case.

Any kind of method or analysis result of a sample can be signed with an electronic record. This electronic record is like a manual written signature on a printed paper. Beside date, time and name also the function is important. In the titrations software any kind of electronic record can reviewed and approved. At least three different persons are necessary until an electronic record is approved: One person generates e.g. the result of an analysis, a second experienced person reviews the result and a third person approves it. User friendly software guarantees that the minimum of separate logins are necessary by internal checks of these requirements. *Figure 6* shows an example of an approved sample.

This example of titration software shows that FDA requirements can accompany with user friendly solutions.

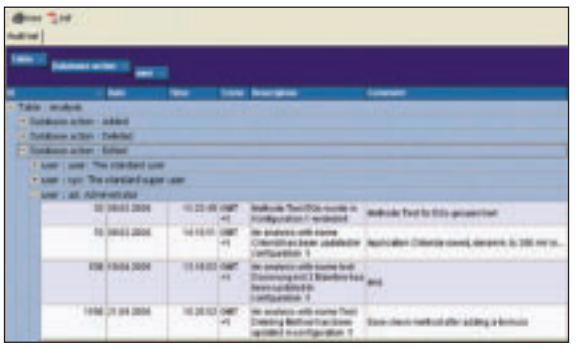


Figure 5: Example audit trail.

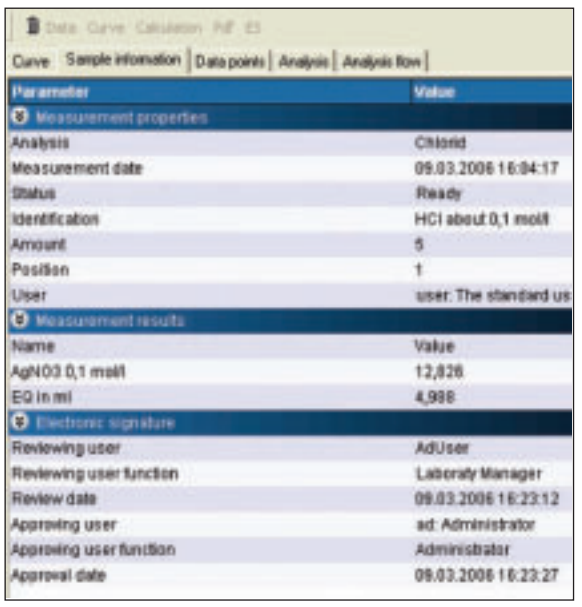


Figure 6: Electronic signature of a titration result

21 CFR PART 11 REQUIREMENTS

In pharmaceutical labs the 21 CFR Part 11 requirements play an important rule. The 21 CFR part 11 includes the following parts:

Subpart A- General Provisions Sec.

11.1 Scope.

11.2 Implementation.

11.3 Definitions.

Subpart B - Electronic Records

11.10 Controls for closed systems.

11.30 Controls for open systems.

11.50 Signature manifestations.

11.70 Signature/record linking.

Subpart C - Electronic Signatures

11.100 General requirements.

11.200 Electronic signature components and controls.

11.300 Controls for identification codes/passwords.

The electronic records (ER) are typically stored in a data base. It should not be possible to view ER or change data without using the application; this means no changes with other data base software.

The data base should have a reminder for a continuous backup. On the other side it can be guaranteed that in the far future the software still runs on available hardware.

Pdf files are an excepted readable format of electronic information also in future.

[1] TITLE 21--FOOD AND DRUGS; SUBCHAPTER A – GENERAL; PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES, [Revised as of April 1, 2004]

[2] TitriSoft 2.60 P (Pharma), 21 CFR Part 11 compliant titration software of Schott Instruments GmbH

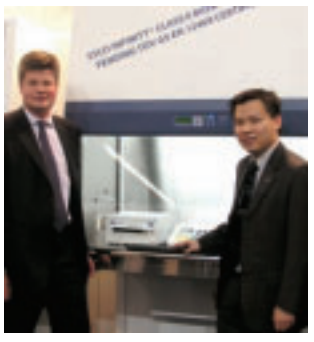
[3] TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN SERVICES PART 820 QUALITY SYSTEM REGULATION, [Revised as of April 1, 2005]

[4] Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application; August 2003 Pharmaceutical CGMPs; U.S. Department of Health and Human Services Food and Drug Administration

[5] GAMP/SIG/21 CFR Part 11; Final Draft Sep. 2000, GAMP 21 CFR Part 11 Special Interest Group

[6] General Principles of Software Validation; Final Guidance for Industry and FDA Staff; Document issued on: January 11, 2002; U.S. Department Of Health and Human Services Food and Drug Administration

Exclusive Marketing Agreement Announced to Promote Safer Biodecontamination Technology



Esco Micro finalised an exclusive marketing agreement to promote Bioquell's patented hydrogen peroxide vapour (HPV) biodecontamination technology. The HPV biodecontamination technology is a safer alternative to the carcinogenic formaldehyde decontamination method traditionally employed for biosafety cabinets to bio-deactivate micro-organisms such as bacteria, viruses and fungi.

HPV is non-carcinogenic and the decontamination process is residue-free, which guarantees complete safety for laboratory personnel. The process of hydrogen peroxide vapour generation is routinely used for research and manufacturing facilities including fermentation/ purification suites.

Along with the marketing of this new technology, Esco debuted its HPV-compliant and decontaminatable biosafety cabinet, the Infinity® Class II Type A2, at the ACHEMA 2006 tradeshow in Frankfurt, Germany. Based on Esco's internationally-certified Labculture® Class II Type A2 biosafety cabinet, this new model offers numerous functions and unique features in addition to the standard Esco features such as the superior ULPA filters, antimicrobial Isocide™ coating, ergonomic sloped front and Accuflow™ microprocessor-based motor-speed controller. Inherent double-fan system guarantees safety even in the event of failure of 1 fan. The Infinity® biosafety cabinet is pending GS certification to EN12469. Shown here are Mark Bodeker (Chief Operating Officer, Bioquell PLC) and Lin XiangQian (Vice President, Esco Micro Pte Ltd) at Esco's booth during ACHEMA 2006

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