LAL Update®

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Letter From the President

Dear LAL User,

As I was celebrating the First Day of this New Year I was reminded of all the "Firsts" that Associates of Cape Cod, Inc. and Seikagaku Corporation have been involved with throughout their history with Limulus (and Tachypleus) amebocyte lysate. When I actually made a list, I realized that since ACC has never been very strong on publicizing its unique accomplishements in the field of endotoxin detection, many of today's LAL users were probably not aware of the significant contributions we have made. My New Year's Resolution therefore is to correct this oversight and to continue our work as innovators in the LAL field. Other "firsts" will continue to be added since our product and service pipeline is full. Later this year the "first" LAL manufacturing facility specifically designed for ACC from the ground up to meet the latest cGMP requirements will come on line. Keep watching this UPDATE for news on this and other ACC/SKK innovations.

Associates of Cape Cod, Inc. and Seikagaku Corporation "Firsts"

1. First to market a gel-clot reagent, "Pregel" (SKK-Japan, 1972 under license to Teikoku Hormone Co.)
2. First manufacturer to offer Control Standard Endotoxin using the same E. coli O113 LPS manufactured by Dr. Rudbach and used (eventually) by the FDA for the RSE's EC-2 to EC-6 (Aug. 1975).
3. First to provide a "Reference LAL" for the FDA to control the manufacture of LAL (Earliest records found for reference lot #4, 1976).
4. First to obtain FDA license (ACC, Sept. 1977).
5. First to introduce 5ml multi-test gel-clot vial (Sept. 1977).
6. First to obtain consistent 0.03 EU/ml gel-clot LAL (Nov. 1977, 0.06 ng/ml with EC-2, 5 EU/ng potency).
7. First to introduce round-bottomed Single Test Vial and Single Positive Control (Sept. 1978).
8. First to offer contract testing for LAL (Oct. 1982).
9. First to produce LAL Reagent Water commercially (Oct. 1984).
10. First to produce LAL reconstitution buffer, Pyrosol (Dec. 1983).
11. First to introduce a chromogenic TAL (SKK-Japan, 1981 via license to Teikoku Hormone Co.) and "Toxicolor" (SKK-Japan 1983).[1]
12. First to market a combination kinetic turbidimetric/gel-clot reagent, Pyrotell-GT (Dec. 1985).
13. First to market a machine designed specifically around the kinetic turbidimetric assay, LAL-4000 (Dec. 1985. Note: the LAL-4000 was also the first application of using LED's to monitor the LAL test)
14. First to introduce the concept of "Time of Onset" and software for analyzing kinetic LAL assays. (Dec. 1985).
15. First to introduce an endotoxin-specific LAL "Endospecy" (SKK-Japan, 1986)
16. First to offer a liquid standard using the highly purified (electrodialyzed) LPS from *Salmonella abortus equi* as a CSE (NP-2 produced by ACC's Pyroquant subsidiary, Oct. 1985)
17. First to introduce a 96-well tube reader system for kinetic assays, LAL-5000 (Aug. 1987).
18. First to market a kinetic turbidimetric-only LAL reagent, Pyrotell-T (Sept. 1987)
19. First to obtain a 5-year (60 month) shelf life for Pyrotell (gel-clot), Pyrotell-GT (gel-clot/turbidimetric), and Pyrotell-T (kinetic turbidimetric) LAL formulations (May 1989)

20. First to introduce an endotoxin-removal device based on a Limulus protein, END-X (June 1990)
21. First to introduce a certified low-endotoxin micro-plate for LAL assays, Pyroplate (Sept. 1992)
22. First US clinical trial for LAL to be used as a diagnostic for endotoxemia, SEPTEST, (Oct. 1992. Note: as a result of this trial the detection of endotoxin in patient plasma was shown not to provide clinical utility, i.e. even though endotoxin could reliably be detected in human blood, no anti-endotoxin therapy existed, and thus LAL is (as yet) not acceptable as a diagnostic test in the US)
23. First to introduce an FDA-approved chromogenic LAL employing diazo-coupling. (July 1993)[1]
24. First to introduce a glucan-specific LAL "Gluspecy" (SKK-Japan, 1993), Glucatell, (ACC, April 2001)
25. First foreign lysate manufacturer to obtain an FDA license (SKK-Japan, 1994)
26. First to introduce a sensitive, non-LAL (latex agglutination-based) assay for bacteria (based on LPS), MicroQuikCheck (Sept. 1995)
27. First kinetic chromogenic test for endotoxin and glucan in human blood approved by Japanese government, "Endospec ES-Test MK" and "Fungitec G-Test MK" respectively (SKK-Japan, 1996)
28. First to introduce a certified low-glucan micro-plate for glucan assay. (Oct. 2000. Note: Although certificates were not provided until 2000, ACC has monitored plates for glucan contamination since April, 1993).
29. First to introduce a reduced-LAL use kinetic test system (8mm tubes, 0.05 ml LAL), PK machine (Nov. 2000) Note: the PK was based on the LAL-6000 which was introduced in Basel, Switzerland at an International PDA meeting (Feb. 1993), but never sold. The LAL-6000 was later copied by a competitor and marketed primarily in Europe under a different name. It should also be noted that the LAL-6000 was a fiber-optic-based machine and also the first tube reader that could read chromogenic, as well as turbidimetric kinetic LAL assays.
30. First to introduce a non-LAL (fluorescence polarization-based) assay for endotoxin, EndoFluor/Polarscan (Jan. 2001)
31. First to introduce an entire line of certified low-endotoxin/low-glucan laboratory accessories, Pyroclear (Jan. 2001)

[1] Note: Although our parent company Seikagaku Corporation of Tokyo was the first company to commercialize the chromogenic LAL assay (using the Asian horseshoe crab, Tachypleus), this assay was not submitted for approval to the USFDA until others had already obtained approval. Thus, I concede one "first", i.e. the licensing of a chromogenic LAL in the US to one of our competitor's.

This UPDATE concludes with an article from ACC's Pyros Development Team which includes substantial input from Jim Remillard, ACC's Head of Information Systems. Jim has been with ACC for 18 years and has been involved in every one of our computer applications and software development. As you can see from the article, he is also an expert on Part 11 compliance. Although it would be nice to be the "first" company to market a Part 11 compliant software for LAL, ACC's primary goal is to provide the "first" Part 11 compliant "system", i.e. software, machine, and technical support that meets ALL our users' needs. To that end, we are well on the way to complete testing of our new software and anticipate market introduction mid-2002.

Happy New Year.

21 CFR Part 11 and Quality Assurance - What to Expect From Vendors

Pyros Development Team

Executive Summary: Compliance with FDA's 21 CFR Part 11 means more than simply implementing software with the Part 11 required features and functions. Part 11's must critical requirement is the "validation of systems". To meet this requirement means that the system must be developed according to a Quality Assurance Plan for System Development and installed according to a Quality Assurance Plan for System Operation. Absent either a QA plan for system development, or a QA plan for system operation, it will not be possible to validate the system and thus achieve compliance with Part 11 regardless of the software's functionality. ACC's Pyros Development Team expects to release Pyrosoft-11, a fully Part 11 compliant version of Pyrosoft, by the middle of this year.

Introduction

Since August of 1997, computerized systems and software used in GMP environments are required to be compliant with FDA's 21 CFR Part 11- Electronic Records/Electronic Signatures (ER/ES). The objective of Part 11, and its predicate rulings, is to protect the integrity, veracity, and reliability of the data. Part 11's specific purpose, as defined in the preamble section of the Final Rule, is to define the "… criteria under which FDA will consider electronic records to be equivalent to paper records, and electronic signatures equivalent to traditional hand written signatures."

Part 11 is not a guideline. It is substantive law and legacy systems are not exempt. FDA recognized that industry needed time to upgrade or replace critical computer systems. This year, however, Part 11 will be five years old. Plans and timetables are expected to be in-place for upgrading or replacing non-compliant systems. As evidenced by the increasing number of 483 citations, introducing non-compliant computerized systems into a GMP environment is indicative of a lack of understanding of the purpose, scope, and scale of Part 11.

Lab managers need to exercise caution and discrimination when evaluating vendor claims to Part 11 systems and software. No independent agency or association exists that certifies computerized systems and software as compliant. Adherence to the regulation is the sole responsibility of the end user. Companies should have committees in-place to perform gap analyses on existing systems as well as evaluate new systems for compliance.

Part 11 Software

Managers evaluating vendor commitments to Part 11 may tend to focus on the system's software. Evaluating that the software meets the requirements for Part 11 is critical. Software has to be designed with specific functionality such as the ability to generate accurate and complete copies of records (11.10b), limit system access (11.10d), generate audit trails (11.10e), and implement operational system, authority, and device checks (11.10f, g, h). The software must also facilitate the signing of electronic records with name, date, and meaning (11.50a). Records must be in readable form (11.50b), and signings must be linked to records so that they cannot be excised, copied, or transferred (11.70a). User name and password management features of the software are also required. The software should ensure the uniqueness of passwords and prevent their reuse or reassignment (11.100a). Software systems that were not designed specifically with these functions cannot be compliant with Part 11.

It is incorrect, however, to assume that a computer system will be in a state of compliance with Part 11 simply because the software's Part 11-required functions have been implemented and verified. Part 11 requires the "Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records" (Part B, 11.10a). In computerized laboratory data acquisition systems the software is only one part of "the system." Computers, processors, instrumentation, durable storage devices, sensors, and computer networks may all be part of, or associated with, the system.

Because computer systems validation encompasses such a wide range of developmental, procedural, and operational activities, the requirement for validation is the most significant and comprehensive of the Part 11 requirements. In fact, FDA's recently released Draft Guidance for Industry 21 CFR Part 11- Validation (August 2001) focuses almost exclusively on the validation of computer systems for Part 11 compliance with little or no mention of the required software functionality.

Computer System Validation

Computer system validation has been written about extensively in the GMP and regulatory literature. It is perhaps best defined in PDA Technical Report #18 which defines computer validation as, "Establishing documented evidence which provides a high degree of assurance that a specific computer-

related system will consistently operate in accordance with pre-determined specifications." Thus, computer systems validation requires a broad based approach that encompasses the complete system life cycle, from the earliest stages of development when the "pre-determined specifications" (i.e. requirements) are defined, to the operation of the system where it must function "consistently" and with "a high degree of assurance". Lab managers should thus frame their evaluations of Part 11 products, not only on the system's software functions, but more importantly on the quality assurance plan used to develop the system and the quality assurance plan that will be used to qualify the operation of the system.

Absent the vendor's commitment to quality assurance during system development, or a commitment to assist the end user in qualifying the operation of the system, attempting to validate computerized systems to Part 11 is futile regardless of the software's inherent Part 11 functionality.

Quality Assurance Plan for System Development

Compliance with Part 11 is not possible if the software for a computerized system was not specified, designed, written, tested, and managed in accordance with a quality assurance plan for software development. Developers should have standard operating procedures for software development that require rigorous adherence to generally recognized standards of coding and follow the software development life cycle.

Software development should closely abide by the regulations in the Quality System Regulation (21 CFR Part 820) specifically subpart B (Quality System Requirements) and subpart C (Design Controls). There should be design and development planning which includes activities such as design input (requirements), design output (verifying requirements) and design review (formal documented reviews and approvals of development). The requirements specification is especially critical for validating the software to Part 11 compliance. Developers should have documentation that traces each Part 11 required software function to an element in the requirements specification.

Before the purchase of a system, end users should have a requirements specification documenting the tasks and functions that the system is expected to perform. The Draft Guidance for Industry states, "End users should document their requirements specifications relative to Part 11 requirements…" and "If possible, the end user should obtain a copy of the developer's requirements specification for comparison."

The guideline further states, "Without first establishing end user needs and intended uses, we believe it is virtually impossible to confirm that the system can consistently meet them." Developers should provide end users with the software's requirements specification and a traceability analysis to demonstrate that all of the requirements have been implemented.

Testing of the software by the developer is also critical in the validation of the system to Part 11 compliance. It is well known that all software has bugs and that software quality can never be "tested-in". To minimize the occurrence of bugs, especially in code that performs critical functions, testing and verification of code must be designed in from the earliest stages of development. The Draft Guidance for Industry states, "While dynamic testing is an important part of validation, we believe that by using dynamic testing alone it would be virtually impossible to fully demonstrate complete and correct system performance. A conclusion that a system is validated is also supported by numerous verification steps undertaken throughout system development." Developers should provide end-users with access to the software development test plans and results that document testing throughout the development process.

Managers evaluating Part 11 systems and software do not have to be software programmers or engineers to evaluate the developer/vendor's quality assurance system for software development. The draft guideline states, "Once you have established end user needs and intended uses, you should obtain evidence that the computer system implements those needs correctly and that they are traceable to system design requirements and specifications." The "evidence" that vendors should provide includes, at the very least, software quality development SOPs, a design history file, and a requirements specification. Test plans and software verification packages should also be readily available for review, inspection, and purchase. The recently released General Priciples of Software Validation; Final Guidance for Industry and FDA Staff (January 11, 2002) states that vendor documentation should include defined "user requirements; validation protocols used; acceptance criteria; test cases and results; and a validation summary." Without this foundational documentation it will not be possible for the developer to claim that the software was developed according to a quality assurance plan. For the end user, there is no recovery from badly designed and documented software regardless of the extent of dynamic testing. Without a quality assurance plan for software development the validation of the software, and hence compliance with Part 11, will be severely jeopardized.

Quality Assurance Plan for System Operation

Compliance with Part 11 is not possible if the system is not operated in a controlled environment as part of a quality assurance plan. A quality assurance plan for system operation can be partitioned into three basic tasks: qualifying the computing/network environment, qualifying the users, and qualifying the Part 11 system equipment.

Qualifying the computing/networking environment requires that computers, networks, and any associated computerized systems be documented, controlled, and secured prior to the introduction of a Part 11 compliant system. A computer system quality assurance plan should exist which addresses standard operating procedures for computer and network access, security and password management, virus protection, backup and recovery, maintenance, change control, and user training, etc. Part 11 systems connected to networks require a more scaled approach. Huber and Budihandojo (2001) state, "To comply with Part 11, your networked systems require the same validation and qualification steps as those for a single computer."

Qualifying the users who will be operating a Part 11 system requires company procedures and policies to verify users and document training. Part 11 specifically requires that the persons who maintain and use electronic records and electronic signatures have the education, training, and experience to perform assigned tasks (11.10i). Also, a written policy should be established that holds individuals accountable and responsible for actions under their electronic signatures (11.10j). Companies must also verify the identity of individuals (11.100b) and certify to FDA their intention to use electronic signatures (11.100c).

Qualifying the Part 11 equipment and software is accomplished by following a documented validation plan. FDA's Draft Guidance for Industry states, "We consider thorough documentation to be extremely important to the success of your validation efforts. Validation documentation should include a validation plan, validation procedures, and a validation report and should identify who in management is responsible for approval of the plan, the procedures and the report." Validation procedures should include installation qualification, operational qualification, and performance qualification. Stress testing of the system should be included as well as maintenance and change control procedures.

Managers evaluating Part 11 systems should audit how the vendor has implemented the Part 11 system in their own facilities. Examine, if possible, the SOPs used by the vendor to qualify the computer/network environment. Determine the policies and procedures the vendor uses to train the users of the system. Vendors should also provide training to end-users. For equipment qualification, the vendor should be able to help the end user create a requirements specification that coincides with the system's design requirement specification. Vendors should also have equipment qualification templates (IQ, OQ, PQ, Stress Testing, Maintenance, Change Control) and procedures available to assist in the qualification process at the end user's facility.

Summary

21 CFR Part 11 systems are commonly advertised and evaluated as a set of software functions and features. Software functions are relatively easy to incorporate into new software by the developer and relatively easy to verify by the end user. But simply purchasing and installing software with the requisite software functions does not make the system compliant with Part 11. Although verifying the software functionality is critical to achieving compliance, it is the requirement that systems be validated that necessitates a far greater commitment to quality plans and systems by both the developer and end user.

The ability to meet the validation requirement for a computer system is dependent on the vendor having developed the software to a quality assurance plan compatible with the Quality System Regulation. Vendors who will not, or cannot, provide the developmental documentation (design history files, validation plans, requirements specifications, test plans and results, etc.) counteract the end user's ability to meet Part 11's "validation of systems" requirement.

Validation and Part 11 compliance is also dependent on the operation of the system within a quality assurance environment of company procedures, policies, and training. Installing Part 11 compliant software in an uncontrolled environment in which the users are not trained adequately or the computer system is not properly installed, maintained, or secured jeopardizes the integrity of the system and data and thus invalidates the system's Part 11 compliance. Vendors should therefore provide training and equipment qualification templates and procedures (IQ, OQ, PQ, etc.) to help end users qualify the system in their facilities.

Managers considering purchasing or upgrading computerized systems need to be diligent when considering vendor claims to Part 11 compliance. It is not possible to achieve compliance without a strong vendor commitment to developing and supporting Part 11 systems. Managers should determine, based

on the system's intended use and the critical nature of the data, the effort level that will be required to meet Part 11's "validation of systems" requirement. Vendors should only be considered if they have the quality development systems in place and can support the end-user in meeting the "validation of systems" requirement and thus compliance with Part 11.

References:

1. Huber and Budihandojo. Qualification of Network Components and Validation of Networked Systems, BioPharm, October, 2001.
2. Quality System Regulation; Final Rule, 21 CFR 820, 61 Federal Register: 52602 (October 7, 1996).
3. US FDA - Draft Guidance for Industry: 21 CFR Part 11; Electronic Records; Electronic Signatures - Validation (August 2001).
4. US FDA - General Principles of Software Validation; Final Guidance for Industry and FDA Staff (January 11, 2002)
5. US FDA - Code of Federal Regulations, Title 21, Food and Drugs, Part 11, "Electronic Records; Electronic Signatures; Final Rule." Federal Register 62(54), 13429-13466 (March 20, 1997).
6. Validation of Computer-Related Systems. Technical Report No. 18. PDA Journal of Pharmaceutical Science and Technology 1995, Vol.49, No.1

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