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LAL UPDATE®

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Dear LAL User,

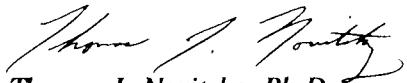
In this UPDATE, I have asked James Remillard and Michael Dawson to share their experiences on software validation. Although this is a timely topic for pharmaceutical use of computers in general, we have a more immediate concern related to those LAL users employing or considering one of the automated tests. When introducing the LAL-5000 to new customers we are often asked about software validation and have given the explanation as outlined in this UPDATE. Recently however, some of our clients have asked "Why isn't your software validated?" This question indicates a basic lack of understanding of validation in general as well as to software in particular. Since the LAL-4000 was the first instrument designed specifically to perform an automated LAL test, and the software was written concurrently, it was easy to follow the concepts of software validation even though these concepts were (and to some extent still are) in a developmental stage. Because the engineering of the LAL-4000/5000 and the writing of the software were under ACC's direct control, the entire development and testing was completely documented. Some microplate manufacturers also have this kind of control. LAL users should be cautious, however, of software programs not provided by the machine manufacturer (including user- or consultant-written programs and software provided by OEM machine suppliers). Such software may lack sufficient documentation to enable validation.

ACC is proud of its development of the LAL-5000. Our computer programmers are also extremely diligent and acutely aware of the regulatory aspects of software in the pharmaceutical industry. Our LAL-5000 Software Verification Package confirms this. As always, ACC is continually working to improve the system. As we approach the sale of our 500th LAL-5000, we are hard at work on a Windows version of the software. On the engineering side, an LAL-6000 machine has reached the prototype stage. More details on the LAL-6000 will be released as development progresses.

Our success with the kinetic turbidimetric LAL test has been affirmed not only by our clients but also by our competitors. At this writing, a total of four LAL manufacturers (US licensed) offer a kinetic turbidimetric LAL! This attests to the low cost and simple elegance of the kinetic turbidimetric assay. For those users who have opted for the chromogenic assay, ACC will introduce PYROCHROME™ chromogenic LAL in the spring of 1993. PYROCHROME is a result of intensive in-house research and our recent collaboration with Seikagaku Corporation of Japan, the group who first commercialized the chromogenic assay (Toxicolor®, Endospecy®). With PYROCHROME, ACC has attempted to produce a high performance alternative to the kinetic turbidimetric assay at a competitive price. This will provide existing chromogenic users with a choice of reagents without having to revalidate the method.

This UPDATE concludes with our regular Calendar feature.

Sincerely,



Thomas J. Novitsky, Ph.D.
Editor

Validation of Computer Software for LAL Applications

by James Remillard and Thomas J. Novitsky

We are sometimes asked "Is the LAL-5000 software validated?" The answer is a qualified "Yes." Associates of Cape Cod, Inc. has made a great effort to ensure that our software performs as intended through a program of rigorous testing. Documentation of testing, together with the source code, is available to users as a Software Verification Package. The title of this documentation, Verification as opposed to Validation, is important and deserves explanation. Many FDA inspectors and experts in validation, including that of computer systems, have made it clear that it is the responsibility of the user to validate a system (Fry, 1988; Kahan, 1977; Tezlaff, 1992c). A vendor cannot do this for you, for software or for anything else. The vendor however, can greatly facilitate validation by providing appropriate documentation and support. In fact, it would be extraordinarily difficult to validate software without the vendor's support. Thus, ACC has validated the software prior to making it available to LAL-5000 users and for our own use. We cannot in good conscience market the software as validated and sell the user on the idea that they are absolved of all responsibility.

In many companies the question of software validation has already been addressed and in-house expertise exists. In other companies, or in quality control labs (most issues concerning validation of software relate to process control), the concept of software validation is completely new. In either case, the first step is to draft a plan or procedure to accomplish the validation. As part of this plan, the "LAL-5000 Automatic Endotoxin Detection System Version 2.0 Software Verification" package should be included. This package contains the Source Code for the LAL-5000 software as well as a series of tests to confirm that data is stored faithfully and that calculations are performed correctly.

When validating computer software it is important to remember that in the pharmaceutical process control or quality assurance sense, the software does not exist or function in isolation. This is especially true of the LAL-5000 Automatic Endotoxin Detection System. Since the LAL-5000 (reader) was developed simultaneously with the software (program), true system integration was achieved. We believe that this represents the ideal situation from a validation standpoint, since validation of the "system" is the ultimate objective. It should be noted that several other "LAL Systems" were developed in this manner, in particular some microplate readers/LAL programs. Users should be aware of the existence of original equipment manufactured (OEM) readers, i.e. readers bearing a private label but which were manufactured for the seller by the original equipment manufacturer. In this case, "system validation" becomes very difficult, since the reader itself has firmware "built-in" which cannot be accessed by independently developed software. Therefore those users obtaining software from a separate source should endeavor to obtain as much information from the instrument manufacturer as possible.

Although recommendations for software validation are constantly being refined, ACC is ready to provide all the assistance necessary to help our clients validate their LAL-5000 systems. Dr. Michael Dawson gives an example of an LAL-5000 software validation on the next page.

Calendar

BioEast 93, January 24-27, 1993
Omni Shoreham Hotel, Washington, DC Booth #606
National Association of Nephrology Technologists
Technical Seminar
Marriott Hotel, LaGuardia Airport, February 11, 1993
"Control of Endotoxins in Purified Water Systems"
by Marilyn J. Gould, Ph.D.
PDA International Congress
Validation for Pharmaceuticals and Biopharmaceuticals
February 22-24, 1993 Basel, Switzerland
PDA Spring Meeting, March 10-12, 1993
Wyndham Franklin Plaza Hotel, Philadelphia, PA Booth #228
Boston Area Chapter of ISPE, March 16, 1993
Howard Johnson's Hotel (Sage), Cambridge, MA
2nd LAL Users Group Meeting
Sutton Coldfield, England March 17, 1993
"The Kinetic LAL Alternatives- Turbidimetric vs. Chromogenic"
by Thomas J. Novitsky, Ph.D.
Center for Professional Advancement Course
"LAL Testing: Drugs, Medical Devices, and Biotechology-
Endotoxin Detection in QA/QC and Product Development"
Amsterdam February 17-19, 1993
East Brunswick, NJ March 29-31, 1993
Course Director - Michael E. Dawson, Ph.D.
Ultrapure Water Expo '93 May 3-5, 1993
Wyndham Franklin Plaza Hotel , Philadelphia, PA
"Evaluation of Microbial/Endotoxin Contamination
Using the LAL Test" by Marilyn J. Gould, Ph.D.

Validation of the LAL-5000 System

An Example

by Michael E. Dawson, Ph.D.

1. Set up a test on the LAL-5000. The test could include two negative controls and six standard endotoxin concentrations, with 5 replicates of each concentration. Other test configurations could serve equally well but a series of standards is recommended.

2. Ensure that the printer is turned on, on line and has plenty of paper. Immediately prior to adding the Pyrotell-T to the first reaction tube, press the F4 function key on the computer. This will print out the LAL-5000 output as received by the computer.

3. Turn off the printer (F4) when the optical densities of the samples have all reached at least 40 milliabsorbance units on the display.

4. Terminate the test. If the option to display/print numerical data in data analysis has not been selected, activate that option (ref.: LAL-5000 manual, section 3.3.2, item 28, page 24). Analyze the data file and print out the numerical data as well as the test results, onset times, regression parameters and endotoxin concentrations.

5. Verify that the OD values given in the numerical data have been correctly calculated from the A/D values and that the appropriate values have been stored. Do this for one tube location (ref.: LAL-5000 Software Verification Package (SVP), Section 4.1 and 4.2, pp.9-25).

6. Verify baseline correction and calculated onset time for a single tube (ref.:SVP, Section 4.3 and 4.4, pp.26-34). Compare the calculated onset time with that given by the system computer.

7. Verify the standard curve parameters by performing regression/correlation analysis (on a calculator) of the $\log_{10}$ corrected onset times of the standards (from the LAL-5000 Data Analysis printout) on $\log_{10}$ concentrations of the standards (ref.: SVP, Section 4.5, pp.35-36). Compare the calculated slope, y intercept and correlation coefficient with that given by the system computer.

8. Using a calculator, determine the endotoxin concentrations for standards and any unknowns from their onset times. Compare these values with those given by the system computer (ref.: SVP, Section 4.6, pp. 37-38).

Carefully record the results of all tests. The calculated values should agree with those given by the LAL-5000 system and so confirm the work performed by Associates of Cape Cod, Inc. The above tests should give sufficient confidence in the verification package to enable the software to be accepted as validated. Most companies that have validated their software decided that it is not necessary to set up the data tap (as described in the SVP) and repeat the independent collection of data, though a few companies have done this as well. The above tests and calculations can be performed in a few hours and will give an increased understanding of the workings of the software as well as the assurance that the system does what it is supposed to do---the essence of validation.

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For previous listings see LAL UPDATE, Vol. 7, No.2.