# A Case Study Approach: 21 CFR Part 11 and Common Sense: Do they Co-Exist?

*by* ***Len Grunbaum***

## Introduction

In response to a question posed by the publisher, I said that, from my experience, the biggest problem with respect to 21 CFR Part 11[1] is the lack of a very basic ingredient when it comes to compliance … the application of common sense. The publisher, in turn, said that this response surprised him, that it was an "interesting" perspective. Thus was born the idea for this article.

The relationship of common sense to the effort to comply with 21 CFR Part 11 – and there indeed is such a relationship, or should be – is the subject of this article. The structure of the article is as follows:

The relationship of common sense to the effort to comply with 21 CFR Part 11 – and there indeed is such a relationship, or should be – is the subject of this article.

- Compliance – A business issue discusses the premise that compliance is first and foremost a business issue, requiring good common business sense
- A Common Sense Quiz presents brief case studies in the form of a "pop quiz" to allow you to test your "common sense" abilities
- Common Sense – Quiz results will examine how common sense was applied – or not as the case may be (yes, you can't make this stuff up) – in the situations described in the case studies
- Conclusions will present a very practical suggestion for bringing common sense to the compliance effort.

## Compliance – A Business Issue

We are in the business of prolonging and enhancing the quality of human life. At the end of the day, business success is defined in terms of being able to obtain approvals for drugs with minimal problems or delays, at the least possible expense, and with maximum profitability. Characteristics of successful companies include, but are certainly not limited to, the following: strong leadership and vision, solid patents, sound decision-making, knowledge of the regulatory environment, and an infrastructure that allows for growth. In today's economy, this, in turn, is dependent on being able to use technology effectively.

Effective use of technology enables us to be bigger, better, and faster. It allows us to maximize infrastructure elements, such as processing efficiencies, knowledge-sharing capabilities, file storage capacity, and processing speed. This can translate into outcomes, such as reducing time to market approval, making information available more effectively and efficiently, and providing the ability to support more customers/clients, more studies, more complex processes, etc. This brings us to 21 CFR Part 11.

This regulation identifies requirements to help ensure that information resulting from the use of technology is trustworthy and reliable. The Food and Drug Administration (FDA) will be able to grant approvals with minimal delays only if it believes that

the information it receives is trustworthy and reliable. So compliance to the regulation makes good business sense, because it will help minimize the chance of delays in the approval process, thus allowing the maximum return on investment.

This makes sense, right? So what's the problem here? The business premise of compliance to 21 CFR Part 11 is quite simple; adopt business processes to allow FDA to trust and rely upon your information. However, companies often do not see it as such, and unnecessarily complicate the issue. This shows up as the types of issues noted by FDA in the Scope and Application guidance: unnecessary restrictions on using technology, increased compliance costs, and lack of innovation and technical advances.[2] Yet in the Preamble to 21 CFR Part 11, back in August, 1997, the Agency pointed out that the regulation afforded "considerable flexibility" in adopting processes to permit use of technology. This flexibility, in my view, translates into common sense business solutions that could, and should be, employed when determining what is to be done to comply with the regulation. Let's take a closer look.

## A Common Sense Quiz

This section is a little pop "common sense" quiz. I will present selected "case studies," taken from the pages of my experiences, and ask you to select the approach that makes the most common sense. In the next section, I will describe what the client did (this, of course, will be one of the choices presented here) and discuss the consequences of the client's actions. Let's have some fun.

Scenario #1
What Do We Do With This Information?

Quite a while after a major development/integration effort of a global system began, the client undertakes an audit of the developer. The auditor's findings include the following:

- There is no independent review process to verify that the system being developed meets the developer's own quality requirements or pre-determined specifications
- The client's Quality Assurance (QA) unit is not actively involved, nor has plans to be involved, in reviewing the quality compliance of the system integration process
- Neither functionality associated with the base applications, nor those that have been added or modified, have not been adequately defined in existing specification documentation
- 21 CFR Part 11 requirements are not adequately integrated into applicable requirement/technical specification documentation to define how the completed system will comply with the regulation.

The approach that makes the most sense is for client management to:

A. Stop the process until all these items are resolved
B. Ensure that the developer defines and implements a remediation plan without delay, with the QA unit tasked with the responsibility to ensure that this is done
C. Continue as if the audit never took place

Scenario #2 – You Get What You Pay For

The company needs a data management system, so it evaluates three. The criteria for selection should focus on:

A. Cost only
B. Ability to meet every conceivable business need
C. Cost/benefit relationship between what the business needs, including functionality to support regulatory compliance, and the relative costs of each application

Scenario #3 – Don't Get SAS-sy

A company develops a Statistical Analysis System (SAS) programs to generate the company's specific statistical information (e.g., tables, listing, reports) to be included in information that is submitted to FDA. The validation of SAS should entail:

A. Qualification of the installation of SAS
B. Confirmation that the programs that generate the statistical information operate as intended
C. Both of the above
D. Neither of the above

Scenario #4 – To Deviate Or Not To Deviate?

A very complex system will require upwards of 300 test scripts to effectively perform user acceptance testing. The test script developers generate version number 1 of the scripts, in the process performing a dry run against the system to confirm that the scripts reflect the system. Based on comments by QA, the scripts are rewritten virtually in their entirety. The script developers rewrite the scripts against the original version of the system. The fly in the soup is that, somewhere between generating the test scripts and the QA feedback, the system changes to the next version. The initial user acceptance test plan calls for performing a dry run of 10% of those scripts that had to be revised per QA comments. It assumed no changes to the system and minimal test script revisions. In this scenario, it would make sense to:

A. Stick with the 10% dry run, because that is what the plan stipulates
B. Dry run the entire suite of revised scripts against the new version of the system
C. Dry run the revised scripts that test the portions of the system that have changed, with additional dry runs (minimal) against portions that should not have changed

Scenario #5 – Migration Migraine

For a number of years, a company has been using an unvalidated document management system to maintain and manage a large number of documents. The company validates a second document management system, at which time, it decides to migrate the documents from the unvalidated to the validated system. The company develops a system to perform this migration. Included in the migration system are utility programs to read the database in the validated system, to help confirm the complete and accurate migration of documents. These utility programs are for migration purposes only, and will not be used for ongoing operations. Should the last step in the migration process be to retrieve selected documents using the procedures designed for normal operational use?

A. Yes
B. No

Scenario #6 – I Don't Understand

A QA group hires a consultant to provide expertise regarding validation and 21 CFR Part 11. Over a 24-month period, the consultant has provided such expertise regarding a variety of major systems, has performed supplier/vendor audits, and has billed the company approximately $12,000 per month for services. The consultant currently uses the draft guidance on validation (withdrawn in August 2003) as a reference for document review ("I don't understand, I got it from the FDA website"), does not know of the existence of the Scope and Application Guidance ("really?"), and does not understand the nature of 21 CFR Part 11 ("what is a predicate rule?"). Is the consultant qualified to provide expertise regarding validation and 21 CFR Part 11?

A. Yes
B. No

## Common Sense – Quiz Results

Scenario #1 –
What Do We Do With This Information?

The correct answer is "B": ensure that the developer defines and implements a remediation plan without delay, with the QA unit tasked with the responsibility to ensure that this is done. System development was still taking place, so the audit findings could have been resolved with marginal impact on development time and costs. Additionally, the development of a remediation plan and the introduction of effective QA involvement would have addressed all issues before they resulted in significant problems. Stopping the process entirely until remediation was complete (choice "A") was not necessary, since remedies could have been applied to the system and to documentation while development was taking place, without affecting development time and costs, except in the most marginal of ways. Option "C", to continue as if the audit hadn't taken place, does not make sense, because the issues identified are symptomatic of larger issues that can cause major problems regarding project timelines, costs, effectiveness, etc.

The company chose "C." It chose not to upset the applecart by reopening efforts or revising documentation given political "realities." Additionally, the audit report did not address potential impacts of the issues identified, nor did company or QA management assess potential impacts. So the process continued on its way and problems, such as the following, appeared:

- The developer truncated developer testing to control costs and stay within established timelines
- The system proved unstable and had to undergo significant revision
- Local user requirements were defined after the system was developed
- Compliance to 21 CFR Part 11 was not effectively documented and had to be re-assessed
- The system users came to the realization that they didn't quite understand how the system would be used locally

And the impact of these problems? After three years of development and testing, and costs in the millions, company management put the project on hold until the system owners could figure out how it could be used.

Scenario #2 – You Get What You Pay For

"C" obviously makes the most sense. You need to evaluate the cost/benefit relationship to help ensure that you are getting what you need at a price you can afford. To do otherwise means that you stand a great chance of getting a system that doesn't meet your needs (for example, choice "B" could result in paying for functionality you don't need).

The company chose "A." Indeed, the application chosen was cheaper than the others, but it also lacked an audit trail and other functionality needed to comply with regulations. The company compounded the problem by relying on an in-house "expert" to "validate" the system, which resulted in inadequate validation processes and documentation. The impact of all this is that the company could not use the data collected and maintained by the system in forthcoming submissions. The system (a newer version with an audit trail) had to be re-validated in a new operating environment, and then the data had to be migrated to the new environment. This added tens of thousands of dollars of additional and unnecessary cost, and a delay of several months in being able to import the data into SAS to generate statistical information.

Scenario #3 – Don't Get SAS-sy

Trustworthy and reliable statistical information generated from SAS programs requires qualification of the installation of SAS, and confirmation that the programs that generate the statistical information operate as intended. "C", both of the above, is the correct choice. This is the essence of one of the great questions in industry: how do you validate SAS? Simply qualifying the installation of the server ("A") doesn't address functionality of the programs, and confirming validity of the programs without qualifying the server installation ("B") may result in improper/inefficient processing if the server is not installed correctly.

So "C" is the obvious choice, right? Not to the company, which chose to do neither of the above ("D"). This was not a conscious choice. It resulted from a lack of understanding, on the part of management and staff, of the need to help ensure the validity of information resulting from computerized systems. The impact here is that the SAS programs have to be "validated" (i.e., can we confirm that the programs do what they are supposed to do?) before they can be used to generate data that can be submitted. In the case at hand, there were hundreds of SAS programs in the scope, and each had to be assessed as to whether it would be used to generate data to be submitted. Then, the selected programs required validation, and the data had to be processed again, this time using the validated programs. As you would expect, this added many thousands of dollars of additional and unnecessary cost, not to mention huge delays, to the submission process.

Scenario #4 – To Deviate Or Not To Deviate?

Choice "C", dry running the revised scripts that test the modified portions of the system, with additional dry runs against unchanged portions, makes the most sense. The company can devote resources to address areas of risk (i.e., system changes). Dry running the entire suite of scripts against the new

version of the system ("B") may be too robust, since it would apply resources to areas that may not require it (i.e., unchanged aspects of the scripts or system). Option "A," sticking with the existing plan irrespective of changed conditions, is the riskiest option, but the easiest to do, because it requires no effort or immediate commitment of resources.

The company chose the easiest option ("A"), which is to stick with the plan irrespective of changed conditions (systems changes and re-written scripts). The project is in process. Management is banking on the fact that the 10% dry run of modified scripts will not uncover issues, either with the scripts or with the system (the initial dry run uncovered some system issues). The risk here is that it is likely that a significant number of test script errors, and possibly system errors, will be encountered when the user acceptance testing is performed.

Scenario #5 – Migration Migraine

It makes good business sense to retrieve selected documents using the procedures that are designed for retrieving documents ("A"); in this case it would be trying to retrieve documents from the validated system, rather than by using the utility programs (which were not validated, by the way). The risk of not confirming functionality of the system is the potential inability to access and retrieve documents. The impact of this is that the system is out of compliance with 21 CFR Part 11, because the user may not be able to generate records suitable for inspection – a clear violation of section 11.10(b).

Scenario #6 – I Don't Understand

Did anyone choose "A" ("yes")? I hope not. By relying on, and continuing to rely on, this "expertise," the company risks overlooking regulatory compliance problems in the existing systems. And, to the extent that such regulatory compliance problems may exist and may be uncovered by FDA, the costs incurred for services rendered will have been for naught.

## Conclusions

Complying with 21 CFR Part 11 is not a technical or even a regulatory issue. It is a business issue, and a matter of using good business sense to meet regulatory obligations, while still being profitable. It can be done, and starts at the top.

The common denominator of the scenarios presented above is poor judgment and lack of common sense – not following up on audit findings, overlooking business requirements in selecting a system, using untested software, sticking with an obsolete plan, overlooking crucial activities, relying on inexpert "expertise." Other examples abound out there. What causes such poor judgment is that the people making these decisions lack an understanding of business principles, practical experience, and/or an understanding of integrating regulatory requirements and expectations into the company's business needs. It is company management's responsibility to manage the business and to rectify, or at least mitigate, this problem as follows:

- *Hiring*
  Company management must ensure that all personnel who are responsible for scientific, technical, regulatory, QA, and financial decisions have a solid understanding of business principles and practices, and "real world" experiences they can draw upon.

- *Training*
  Company management must ensure that all personnel are trained in and understand the current regulatory environment. This training must be continuous to keep current with developments.

- *Accountability*
  Company management must hold personnel accountable for poor judgment, such as that described above. Poor decisions have a financial impact to the company – increased cost, delays in the ability to realize revenue because of delays in receiving approvals, inefficiencies due to ineffective utilization of technology, etc. In none of the scenarios described above was anyone held accountable. The people responsible for these decisions will make the same poor decisions again, and enough of these poor decisions can result in serious business risks to the company.

## Final Words

My final words take the form of one more question - the key ingredient to effective compliance with 21 CFR Part 11 is:

A. A computer science degree?
B. Decades of regulatory experience?
C. Pure luck?
D. A healthy dose of common sense? ❑

## About the Author

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## References

1. Code of Federal Regulations, 21CFR Part 11, Electronic Records; Electronic Signatures, Final Rule, March, 1997.
2. Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application; August, 2003, pg. 6.

### Article Acronym Listing

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| FDA: | Food and Drug Administration |
| QA: | Quality Assurance |
| SAS: | Statistical Analysis System |