
CQS Innovation. Inc.

2003 FDA Guidance on 21 CFR Part 11: An Impact Analysis

Author: Steve R. Smith
Principal Engineer

In September 2003, the Food and Drug Administration published “Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application” in response to an avalanche of ‘suggestions’ from the pharmaceutical industry. This paper explores the potential of this guidance to lessen the regulatory burden related to the development, modification, compliance assessment, and remediation of computer systems involved in regulated manufacturing activities. This paper only reflects our opinions, and CQS Innovation, Inc. assumes no liability for adoption of any of the contents.

When the Food and Drug Administration (FDA) released 21 CFR Part 11 in March 1997, it could not have anticipated the firestorm of controversy and consternation it would invoke in the pharmaceutical industry. The simple intention of setting up rules for allowing electronic submissions to the agency spawned industry-wide efforts to investigate and remediate every computer-based system at every regulated site. Although both parties acted in good faith and with the best of intentions, the impact of 21 CFR Part 11 raged out of control until, in early 2003, the FDA announced that it would act to stem the tide of industry resources being diverted to address Part 11 issues. The action took the form of a publication entitled:

Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application.

This publication, referred to as *Final Guidance*, has the potential to lessen the regulatory burden related to the development, modification, compliance assessment, and remediation of computer systems involved in regulated manufacturing activities.

The goal of this paper is to describe the anticipated impact of the *Final Guidance* publication on pharmaceutical manufacturing automation. To accomplish this goal, we start with a review of the Electronic Records, Electronic Signatures (ERES) regulatory history and its impact on manufacturing automation. Next, the content of the *Final Guidance* is described in some detail. Finally, the anticipated impact is extrapolated from the current industry trajectory combined with the thrust of the *Final Guidance*.

Regulatory Background

21 CFR Part 11, Electronic Records; Electronic Signatures, hereafter referred to as “Part 11”, is a federal regulation issued on March 20, 1997. Its stated purpose is to:

“Provide criteria for acceptance by the FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper.”

In effect, however, it established a series of technical and procedural controls that must be in place before any computer system could be used for any regulated activity. In order to comply with this new regulation, virtually every pharmaceutical manufacturer embarked on a program to assess the compliance of all their computer systems and to eliminate deficiencies related to electronic records and electronic signatures.

As with many regulations, Part 11 is subject to interpretation. Industry attempts to establish practical policies for Part 11 compliance were often thwarted by the diversity of computer systems and applications. Compounding the problem were a growing, and ever more stringent, series of FDA statements and compliance guides, related to Part 11 scope and practical application, released between 1999 and 2002. Probably the most significant guidance, in terms of industry impact, was that the FDA expected any manufacturing data stored on durable media (i.e., disk drives) to be considered an electronic record.

The FDA was contacted early and often concerning interpretation and implementation of Part 11. Over time, the FDA received four (4) clear concerns with respect to Part 11 as it was initially issued:

1. It unnecessarily restricts the use of electronic technology,
2. It significantly increases the cost of regulatory compliance,
3. It discourages innovation and technological advances, and
4. It does not provide a significant public health benefit.

To address these concerns, in early 2003 the FDA announced its decision to re-examine Part 11, withdrew all previously released Part 11 guidance, and disavowed all previous Agency statements related to Part 11 interpretation. By early fall of 2003, the Agency was able to state that “we anticipate initiating rulemaking to revise the provisions of that regulation [Part 11]”. While Part 11 remains in effect, it is clear that a less burdensome approach to providing control over electronic records and electronic signatures is being sought. In early September 2003, the FDA published the *Final Guidance* to describe how the Agency intends to “exercise enforcement discretion with regard to certain Part 11 requirements during the re-examination of Part 11”.

Manufacturing Automation Systems and Part 11

Since it became law in 1997, Part 11 has had a chilling effect on the introduction of new manufacturing automation systems. The reasons for this are twofold:

1. Resources (people, time, and money) once dedicated to process improvement through the identification and implementation of new technologies have been redirected to evaluate and remediate existing computer systems, and

2. Regulatory uncertainty around computer systems, in an industry that has always been risk-averse, has resulted in a reluctance to authorize dependence on new systems or technologies.

Coupled with a sluggish economy, Part 11 gradually reduced industry outlays for new manufacturing automation systems to a trickle.

Missing Tools

Part 11 requires users to employ procedures and controls designed to ensure the authenticity and integrity of records and signatures created, modified, maintained, or transmitted in electronic form. Many of these controls must, or at least should, be provided by computer system features (for example, electronic and human-readable record copying, audit trails, authority checks, and inextricable linking electronic signatures to electronic records).

Unfortunately, at the time Part 11 became law, no commercially available process control hardware or software products provided these controls “out-of-the-box”. In fact, most products were incapable of meeting Part 11 requirements regardless of how they were configured and/or programmed.

Most process control software vendors that serve FDA-regulated industries have begun to upgrade their products to allow better compliance with Part 11. However, since most integrated systems are dependent on more than one vendor’s product line (e.g., any PC-based products), usable reforms have been painfully slow in coming. While core applications may include important Part 11 compliance features, integrated solutions inevitably exhibit weaknesses that are not easily overcome.

Climbing the Learning Curve

The cost of Part 11 compliance manifests itself in the need for new policies and procedures, new technology selection paradigms and constraints, and increased lifecycle burden (including additional system development documentation, additional qualification testing, more rigorous system administration practices, etc.). However, arguably the most significant impact of the regulation has been to expose insufficient validation documentation for existing manufacturing computer systems. Many manufacturers have discovered that important quality control information is being generated by computer-based systems that have not been adequately validated. The new Part 11 burdens, combined with the “catch-up” activities for compliance assessment and existing system remediation, have effectively overwhelmed most pharmaceutical manufacturers’ resources.

By 2003, most major pharmaceutical manufacturer’s at least had a handle on Part 11 planning and strategies. Most had their compliance assessment and remediation program(s) well underway. Into this state of affairs comes the new Part 11 *Final Guidance* for industry. It has been met with cautious enthusiasm. The good news is that the regulations impeding investment in automation may be easing somewhat. The bad news is that it forces another industry re-calibration to an even more ambiguous regulatory environment.

Part 11 Final Guidance

The “Guidance for Industry” on Part 11’s scope and application, published September 3, 2003, provides “Part 11 relief” in three (3) forms:

1. It narrows the scope by defining a limited set of records that are subject to Part 11,

2. It allows, based on documented risk analysis, less stringent application of four (4) specific Part 11 requirements (Validation, Audit Trail, Copies of Records, and Record Retention), and
3. It provides exemptions for some legacy systems (i.e., some systems operational prior to August 20, 1997, the effective date of Part 11).

Records Subject to Part 11

Narrowing the interpretation of scope is probably the most significant aspect of the Part 11 *Final Guidance*. Verbiage changes between the draft and final versions of the guidance suggest that this narrowing of scope is intended to be permanent. In effect, Part 11 no longer applies to all electronic manufacturing data. It will now be interpreted to apply only to those records and signatures needed to comply with FDA regulations. Further, “the use of computer systems in the generation of paper records would not trigger Part 11”.

The *Final Guidance* states that Part 11 only applies to four (4) categories of electronic data:

1. FDA-required records that the manufacturer opts to maintain in electronic format *in place of paper format*,
2. FDA-required records that are maintain in both electronic and paper formats where *the electronic records are relied on to perform regulated activities*,
3. Any records *submitted* to the FDA in electronic format, and
4. Any electronic signature intended to be the equivalent of a handwritten signature required by the FDA.

The key to identifying Part 11 records is now identifying actual business practices related to the use of electronic data. Automation system project planning (e.g., the system validation plan) should clearly identify the intended use of any electronic data and identify it as subject to Part 11 or not subject to Part 11. This intention should be formalized in SOPs that describe quality control practices related to the automated system.

Risk-Based Compliance Measures

While the *Final Guidance* describes specific approaches to reducing the stringency of Validation, Audit Trail, Copies of Records, and Record Retention requirements, the theme is the same: “good faith” measures to comply with Part 11 requirements can now be justified. The basis for this justification, in all cases except Copies of Records, is a documented risk assessment. Though unspoken in the *Final Guidance*, the FDA’s view of “risk” should be interpreted as risk to public health and safety. The inability to prove (e.g., in court) the quality of every prevailing product lot (e.g., through equipment, ingredient, and operational quality control documentation) is construed by the FDA as placing the public at risk.

Agency leniency in applying Part 11 relief based on risk-assessment is limited in time by the *Final Guidance*. What the FDA euphemistically calls “exercising enforcement discretion” is limited to “while the re-examination of Part 11 is underway”. However, the focus on risk-based compliance strategies is a comprehensive initiative for the FDA. It is likely that much of the *Final Guidance*’s “approach to specific Part 11 requirements” will be codified in the anticipated revision to Part 11.

Legacy Systems

In response to industry complaints about the cost of replacing older systems that cannot be made compliant with Part 11, the *Final Guidance* attempts to “grandfather” the use of such systems. The *Final Guidance* is clear that grandfathering only applies to systems (referred to as “Legacy Systems”) that were operational prior to August 20, 1997, the effective date of Part 11. Unfortunately, the legacy systems provision in the draft guidance was sufficiently vague (especially with regard to older systems that have been modified since 1997) that it could only be strictly interpreted to exempt very few systems.

In the *Final Guidance*, the FDA attempted to expand the number of exempted systems by identifying the difference between significant modifications (i.e., ones that make the system subject to Part 11) and insignificant modifications. Unfortunately, the resulting verbiage is too vague to be understood:

“If a system has been changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, Part 11 controls should be applied”.

In any case, the legacy systems provision in the *Final Guidance* specifies that all systems must comply with all predicate rules (other than Part 11) and must have documented evidence and justification that it is fit for its intended use (i.e., it must be validated). This standard, combined with the limited number of systems still in operation since 1997, will severely limit the benefit to manufacturers of the legacy systems provision.

Impact on Manufacturing Automation

Records Subject to Part 11

The narrow interpretation of scope allows for manufacturing automation without undue Part 11 concerns. As long as a computer system prints or plots “official” records in real time, a strong argument can be made that Part 11 does not apply to that system. This is reminiscent of early attempts to avoid computer system validation by providing ancillary “official” trend chart recorders and/or paper logs.

While this type of “rule dodging” is clearly not optimal, it does provide a path for process improvement, using automation, without the regulatory hurdles. Instead of deferring automation projects indefinitely, hybrid systems can now be implemented with a vision of closing the electronic data collection gaps once Part 11 compliance technology matures. The result should be a renewed impetus for improving manufacturing through the application of automation.

Risk-Based Compliance Measures

The risk-based approach to justifying compliance measures permeates not only the Part 11 *Final Guidance*, but also many other recent FDA initiatives (e.g., “systems approach” to inspections and “Process Analytical Technology” guidance). The perspective of the FDA is that pharmaceutical manufacturers should understand the specific risks associated with what they do, and take appropriate steps to reduce that risk to an acceptable level. In the manufacturing automation arena, this means a well-designed system should have at least one documented risk assessment.

Adding one or more risk-assessment activities and documents to a system development project will not be inexpensive. However, the documented analysis can help reduce other compliance costs and technology constraints. It is likely that understanding of, and experience with, efficient risk assessment techniques will be a highly valued capability going forward.

Also valued, at least by the astute manufacturers, will be to ability balance the amount of project effort devoted to risk assessment against the potential for cost avoidance. To this end, detailed familiarity with the current compliance limitations of automation products will be increasingly important. Also, standard verbiage for justifying less than “letter-of-the-law” compliance with specific Part 11 requirements will be a valuable asset.

Legacy Systems

While the new legacy system grandfathering provision will be very important to some situations, it must be remembered that all systems that fall under this exclusion are already more than six (6) years old. Much of the technology available before August 1997 is already approaching obsolescence and the inevitable corresponding spike in ongoing maintenance costs. The good news about the legacy system provision is that it provides manufacturers with the ability to act strategically, as opposed to reactively, to replace these aging systems.

Summary

Part 11 has had a chilling effect on the pharmaceutical manufacturing systems integration business for the past few years. Released in September 2003, the “Guidance for Industry: Part 11... Scope and Application” (a.k.a. *Final Guidance*) is intended to counter unintended consequences of Part 11 by:

- Facilitating the use of electronic technology in pharmaceutical manufacturing,
- Reducing the cost of Part 11 compliance, and
- Encouraging innovation and technological advances.

The *Final Guidance* describes the FDA's intention to: 1) narrow their interpretation of the scope of Part 11, 2) show leniency where strict Part 11 compliance is not justified by risk, and 3) exempt certain legacy systems from Part 11 compliance.

The impact of the *Final Guidance* on manufacturing automation is expected to manifest itself as follows:

- Investment in pharmaceutical manufacturing automation will increase in the long term, though added regulatory uncertainty will delay this increase,
- Manufacturers will be able to employ a more reasonable and strategic approach to technology selection, and
- Manufacturers will place increased value on risk assessment capabilities and understanding of product capabilities and constraints relative to Part 11.