

# Understanding and Implementing A Risk-Based Approach to 21 *CFR* Part 11 Compliance

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**FDA's risk-based approach to regulatory compliance has had a significant effect on 21 *CFR* Part 11 requirements and the processes that pharmaceutical companies are implementing in prioritizing activities.**

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**A**s the agency that oversees drug-product quality, FDA traditionally has taken a two-pronged approach: review submitted information such as new drug applications (NDAs) to determine safety and efficacy and proactively inspect key research and manufacturing facilities to ascertain compliance with regulatory requirements. Although this process has been reasonably effective for the past 25 years, several factors have led the agency to reconsider its approach. This article describes the dynamics that have affected FDA's thinking toward facility inspections and adherence to quality practices with a particular focus on how this is driving an industry transition toward a risk-based approach to regulatory compliance.

## **Toward a risk-based approach**

The number of pharmaceutical products has increased significantly during the past 25 years as a result of the advances in pharmaceutical research and manufacturing technologies as well as the application of new scientific techniques in biotechnology. However, applying the commensurate level of effort required to satisfy FDA regulations as it applies to these new technologies has proven to be a daunting task for the industry. At the same time, FDA's limited resources have made it difficult for the agency to perform intensive inspections of the growing number of pharmaceutical facilities in operation. To effectively address its commitment to product quality and patient safety, FDA launched a new initiative entitled "Pharmaceutical CGMPs for the 21st Century" and is encouraging the industry to implement a documented risk-based approach to regulatory compliance (1).

Similarly, FDA's Office of Pharmaceutical Science has begun an initiative to leverage the risk-based element related to changes in the chemistry, manufacturing, and control (CMC) area of submissions. Specifically, for resubmissions based on a change in CMC, FDA will now evaluate the change's effect on product quality and not automatically require an updated submission.

In line with this risk-based thinking, FDA has come to realize that some interpretations of 21 *CFR* Part 11 (Part 11) have begun to impede innovation and technological advances in the US pharmaceutical industry (2). Indeed, concerns have been raised that US pharmaceutical companies have not kept pace with their European counterparts in the adoption of new man-

ufacturing technologies, in particular manufacturing execution systems (MES) and process analytical technology (PAT).

This risk-based approach is not new among FDA-regulated industries. The medical device industry has used a risk-based approach in which experience, insight, and judgment are systematically applied to manage risk, which is defined as how often the harm may occur as well as how severe that harm might be. In fact, ISO 14971 (Application of Risk Management to Medical Devices)—which parallels the Quality System Regulation (QSR)—is now being integrated worldwide into every technical standard for medical devices.

The pharmaceutical industry and related organizations have been instrumental in adopting a risk-based approach. ISPE, a nonprofit group of technical experts in the life science industry, has recently published a white paper in support of this approach, stating,

Without careful interpretation, however, the requirements [of Part 11] can lead to over-engineered solutions that adversely impact the productivity of the industry without providing added benefit to patient health. The goal of this paper is to provide the philosophy necessary to apply risk management, and to encourage manufacturing innovation and technological advances. This philosophy is based on the ideas in the new FDA CGMP initiative. (3)

### Impact on Part 11

Given the increased emphasis on risk-based approaches, it is not surprising that in February 2003 FDA issued “Draft Guidance for Industry: Part 11, Electronic Records, Electronic Signatures—Scope and Application.” In the guidance, FDA cites the reasons for implementing this risk-based approach to Part 11 compliance, expressing concern that some interpretations of the Part 11 requirements would

(1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA’s stated intent in issuing the rule; (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted; and (3) discourage innovation and technological advances without providing a significant public health benefit.

In articulating its approach to specific Part 11 requirements (i.e., validation, audit trail, and records retention), FDA recommends approaching Part 11 compliance on the basis of “a justified and documented risk assessment and determination of the potential of the system to affect product quality and safety and record integrity.” This stance is clearly in line with FDA’s CGMP risk-based initiative. In addition, because FDA has clearly articulated in its draft guidance that it is important to look at predicate rule requirements when determining the scope of Part 11, now is the time for companies to correlate their Part 11 gaps with their corresponding predicate rule and determine its true importance given the risk-profile of a given regulated process.

### FDA’s overall approach to Part 11 requirements

In its “Guidance for Industry: Part 11, Electronic Records; Electronic Signatures—Scope and Application” draft document, FDA identifies three main elements for its approach to Part 11 requirements (2):

- Part 11 will be interpreted narrowly. The agency is currently clarifying that fewer records will be considered subject to the Part 11 rule.
- For records that have been clarified as subject to

Part 11, the agency intends to exercise “enforcement discretion” with regard to Part 11 requirements for validation, audit trails, record retention, and record copying in a manner described in the guidance and in “applying Part 11 to systems that were operational before the effective date of Part 11.”

- The agency will enforce predicate-rule requirements for records subject to Part 11.

### What the industry must do now

A risk-based approach, the methodical process of gauging risk and prioritizing the resulting actions, is not really a change in philosophy or thought process. Most organizations have been making decisions on the basis of a loose definition of *risk* that was never carefully analyzed. Now the approach to making informed decisions must be one that is more objective, better documented, and carefully quantified across both processes and systems.

The most appropriate response is for life sciences companies to take a holistic look at their systems and supporting processes to determine where and how they fit in the overall drug process and the effect on product quality and patient safety of a failure in any part of the chain. As such, a risk-based approach takes into consideration that systems are not equal and do not exist in a vacuum and encourages one to look at where the data are going and coming from. For example, even if a laboratory management system (LIMS) is secure, the instrument that sends data to the LIMS may not be, which ultimately results in unsecure data.

By making Part 11 investment decisions on the basis of the extent to which a given system and/or process will affect product quality and patient safety, a risk-based approach also may reduce a company’s overall compliance costs. By minimizing activities that add little or no value to regulatory risk reduction, additional energies can then be focused on technological and product innovation. This can be accomplished only if a company carefully incorporates and documents risk analysis activities.

### Implementing a risk-based approach

Risk exists in multiple dimensions and must be examined in context; i.e., risks must be evaluated in relation to each other. The following is a brief overview of five steps that one can take that will lead to a balanced approach to risk.

**Determine the scope.** What is the breadth and depth of the approach? In other words, how many areas of risk will need to be addressed (e.g., systems, functions, departments, or sites). How “deep” does the company want to go in each of those areas? An understanding of the end result will help drive scoping decisions. For example, remediation budgeting for an R&D site will have greater breadth and less depth, and the validation of tablet-coating equipment will have more depth but less breadth.

**Understand the risk environment.** An understanding of a company’s risk environment is driven by creating a risk profile. For

## Steps for incorporating a risk-based approach

The following activities may quickly produce a positive effect on a company's risk-based initiatives:

- Develop a methodology and tools for risk assessment, risk assessment reporting, and risk mitigation.
- Adjust validation and Part 11 methodologies to incorporate these risk assessment activities and deliverables.
- Revise Part 11 interpretation and tools to incorporate the revised, narrower scope.
- Conduct pilot risk assessments of systems to adjust validation and Part 11 strategies.
- Train key personnel in performing, analyzing, and documenting risk assessments.

example, application of a risk-based approach across all laboratory systems includes

- regulatory issues: Is the lab performing product quality testing or method development?
- business issues: If any of the systems failed, would clinical trial results be lost and a drug submission delayed?
- operational issues: Is the information coming into the laboratory from a compliant source? What happens to it when it leaves the laboratory? Is it verified at the next stage of the drug development process?

**Cataloging risks.** This is the opportunity to apply the work that has been done in assessing Part 11 compliance gaps by leveraging existing-system assessment documentation and reviewing the gaps that have been identified to translate them into defined business and regulatory risks. It is also important at this point to understand the gaps that may lie outside of each individual system (e.g., how the process of uploading data from one system to another by flat file may affect data integrity). Once these gaps are defined into risk categories, they can be rated in importance, which is a process that is driven by the probability of occurrence, the probability of detection, and the effect of a failure.

**Quantify and prioritize activities.** After risks have been categorized, the activities necessary to address these risks can be planned. These mitigation activities must be approached in two phases: First, the activities should be defined to specifically address a single given risk. Then, the related activities must be combined for greater efficiency. It is important that these activities be quantified both in terms of resource requirements and regulatory risk. At the same time, one should examine how much business value will be created, largely in terms of productivity gains, when these risk-mitigation activities are performed. This process will facilitate an understanding of the true benefit of the investment. The end result should be groups of activities, or projects and programs, rated by investment, risk reduction, and business value.

**Plan.** Review the projects, prioritize, and select them on the basis of business drivers such as regulatory and resource requirements. The result is a list of priori-

## Gaps in Part 11 compliance should be assessed, defined into risk categories, and rated according to importance and impact.

tized projects along with the associated timelines and resource requirements for a risk-based program plan that obviates the need for risk guessing and satisfies both FDA and the company's business needs.

### Putting the team together

As part of its initiative to update inspection practices while acknowledging the more closely integrated environment in which pharmaceutical companies are operating, FDA has committed to adding specialists in science, technology, and regulations to its plant inspection teams. This clearly indicates that one should match

these skill sets in deployment of risk-based initiatives. Because a formal risk-based approach to compliance requires guidance from several different functions, including quality assurance, regulatory, business, and information technology, many organizations have implemented

a compliance management office, a "big brother" of the more commonly known program management office. With this structure "owning" the risk-based approach to compliance and guiding the risk-rating process, one combines the understanding of the regulatory and business drivers that influence risk rating while enabling the forecasting, funding, and managing of regulatory compliance projects in a holistic, efficient manner.

### Conclusion

FDA and industry have a common objective: product safety and quality. To that

end, the goal of a risk-based approach is to create and document a mature, logic-driven process by which regulatory compliance activities can be prioritized while opportunities to add business value are evaluated. As life science companies review their functions holistically, a carefully thought-out risk-based methodology will yield the most benefit by helping these companies determine the most effective use of their compliance investment based on the quantified regulatory risks reduced and the identification of potential areas for improved efficiency.

### References

1. FDA, "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach: A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach" 21 August 2002.
2. FDA, "Draft Guidance for Industry: Part 11, Electronic Records, Electronic Signatures—Scope and Application," 20 February 2003.
3. ISPE, *A Risk-Based Approach to 21 CFR Part 11*, white paper. **PT**