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PhRMA

October 29, 2001

Mr. John Taylor
Director, Office of Enforcement
Office of Regulatory Affairs
Food and Drug Administration
(HFC-200)
5600 Fishers Lane
Rockville, MD 20858

Re: Proposed FDA Guidance on the Scope and Implementation of 21 CFR Part 11

Dear Mr. Taylor:

The following comments on the possible direction that FDA may be taking on the scope and implementation of 21 CFR Part 11 are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members are investing over $30 billion in 2001 for the discovery and development of new medicines.

PhRMA is pleased that you have established a series of dockets to receive comments in advance of the publication of various draft guidances on Part 11. Although there is not a docket established on this particular topic, PhRMA hopes that you will post it appropriately and distribute it to the FDA Part 11 work group.

Summary

The size and complexity of the task of implementing the requirements of 21 CFR Part 11 for electronic records and signatures, covering thousands of systems in a major company with an associated cost in excess of $100M, means that it will take significant time for companies to achieve compliance. Based on current experience, a risk/benefit approach, phased over a number of years is proposed, in which companies achieve compliance for high priority systems within 5 years. Medium and low risk systems would be addressed based on the availability of commercial software and the position of individual systems in their overall life cycle. Each company would generate its own remediation plan that would be made available to FDA and tracked during the course of inspections.

To clarify the requirements for 21 CFR Part 11, PhRMA proposes that electronic records be defined in accordance with the existing predicate rules together with those required by current agency rules or company standard operating procedures. PhRMA also proposes that a record is created when it is signed electronically, or completes the corresponding review process for those records that are not signed, in an analogous manner to the process used for paper records. Subsequent changes to these records would be tracked via an audit trail. Since the current environment in virtually all companies is based on a hybrid approach, using a mixture of paper and electronic records, PhRMA recommends that the current practice of printing and signing electronic records should be continued during the transition period. This reflects the fact that companies do not have the option of returning to a paper based approach.

Since companies rely heavily on commercially available software, remediation plans need to take account of the time required by vendors to develop new releases; typically 12-24 months after a clear set of requirements becomes available. Hence, the FDA needs to define new regulatory requirements in a manner that allows them to be incorporated into key software products. This is particularly important in the case where new technologies are required, since it can often be 3-5 years before they are incorporated into major software packages.

The rapid pace of obsolescence of technology (3-5 years), contrasted with the long retention cycles specified by the predicate rules (beyond the marketed life cycle for the product), makes if infeasible to preserve systems over this extended period. Hence, PhRMA recommends that long-term archiving focus on the storage of required records in a manner that ensures that they can be restored in human readable form.

Because of the high cost associated with implementing 21 CFR Part 11, PhRMA recommends that FDA conduct an economic impact analysis. This could then support the adoption of the proposed phased risk/benefit based approach.

Introduction

Experience gained by both FDA and the pharmaceutical industry (subsequently referred to as the industry) since the introduction of 21 CFR Part 11 in 1997 has shown that the cost and complexity of achieving compliance is significantly greater than was originally anticipated. The cost to a major pharmaceutical company is now understood to be in excess of $100M. A number of key factors have contributed to this, including:

1. Companies have large numbers of systems covered by the rule. In the case of major pharmaceutical companies, this can comprise several hundred systems.
2. The guidance provided by FDA has been ambiguous, leading to a variable approach to inspections and feedback.
3. Systems are strongly interconnected so that changes made to a given system have broad implications requiring extensive testing and validation.

4. Commercial software packages used in the industry often lack the functionality required by the regulation and it takes significant time for vendors to incorporate the required functionality into their products.
5. Some of the technologies required are new and immature and it can take several years for these to be incorporated into major commercial products.
6. The rapid pace of change of technology makes it difficult to provide secure long term archiving of data in electronic form.

Industry is, however, fully committed to the goals of 21 CFR Part 11 and the purpose of this document is to provide input to the FDA guidance process. In particular, it outlines a proposed approach to achieving compliance based on the experience gained to date together with the views of a broad range of technical experts within the industry.

Scope of 21 CFR Part 11

21 CFR Part 11 is the regulatory paradigm that covers the move from a paper-based to an electronic record. In addition to the GxP based record systems, the FDA has stated its commitment to move to electronic submissions and a paperless internal environment by 2002. This involves the shift from paper records and signatures, in which legal precedents have evolved over many years, to a new legal framework based on electronic documents and signatures requiring authorization, validation, authentication and non-repudiation. This environment will take time to evolve and, therefore, it is important that the initial steps, such as those required by 21 CFR Part 11, are scalable and extensible to meet these longer term needs.

Since it is clear that electronic records and signatures will form the basis for both FDA audits and electronic submissions, it is clear that the scope covers all GxP based systems, as stated in 21 CFR Part 11. However, given the size and complexity of the challenge, it PhRMA recommends that FDA adopt a risk-based, phased approach. This would enable industry to achieve compliance over a realistic period of time in a manner reflecting both the potential risks and benefits to public health together with the associated feasibility, cost and risks to the industry.

PhRMA has worked with the Industry Coalition on 21 CFR Part 11 that represents the range of FDA-regulated industries to provide input to FDA and endorses the Coalition recommendations on scope which are summarized below.

Scope of the Regulation (reference Section 11.1, taken from the proposal made by the Industry Coalition on 21 CFR Part 11)

1. Our understanding of the regulation is that 21 CFR Part 11, as stated in §11.1(b), applies:
    a. To those records defined in the predicate rule(s) that are created, maintained and/or submitted in electronic form. This includes records in electronic form called for by a company's Standard Operating Procedures

(SOPs) for the development, production and distribution of regulated product, but excludes electronic records not required for these processes but simply generated in the normal course of conducting business which may also be covered by company SOPs.

b. To those records set forth in agency regulations or those records submitted under the requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, when submitted in electronic form.

2. We also understand that the regulation applies only to required electronic records stored on durable media, such as magnetic disk or tape, and does not apply to electronic records created without human intervention, i.e., temporary records stored on non-durable media, such as flash memory in PDAs, or devices intended for short term data capture, such as programmable logic controllers and data loggers, which may have little or no ability to provide audit trails or to export data to other systems in electronic form. It is understood that temporary records, retained per a company's SOPs, may be inspected during inspection visits but are not subject to Part 11.

3. If and when there is an intent to substantively extend the scope of the regulation to cover electronic records other than those required by 1) and 2) above, then this should be accomplished via the standard rule making process of the FDA and not through the issuance of guidance documents.

4. Required records created, maintained and/or submitted in electronic form will be archived on durable media in a manner that enables the records to be made available in human readable form. In addition to the required records defined in 1) and 2) above, other records submitted to the agency electronically will also be archived in an analogous manner. Given the technical limitations and operational complexities of archiving very large volumes of electronic records for the period required by FDA regulations, the FDA and the Coalition should collaborate to achieve a workable approach through the development of an appropriate Guidance.

5. **Electronic Records:**
The term "electronic record" is very broad and may be interpreted differently depending on its context. For clarity in the discussion we suggest electronic records be split into two types: data records and documents.

a) Data Records:
Within these are two types dependent upon the method of creation, as follows:

- <u>Those records written directly to a permanent electronic media without a source document,</u> in accordance with a company's Standard Operating Procedures

(SOP). Part 11 would apply for these data records beginning when the record is stored to a durable medium and would then be subject to the requirements for an audit trail, archive, procedural controls, etc.

- Those records created from paper or a non-permanent electronic records. These are verified, in accordance with a company's Standard Operating Procedures (SOP), for example by dual key entry or a similar process. Interim changes to the electronic data record, until accepted as a genuine copy of the source (i.e., verified), are not audited. Auditing begins when the verified electronic data record is saved to durable media. It is then subject to the requirements for an audit trail, archive, procedural controls, etc. Corrections to the source data are recorded on the source document (required by SOP) and would have an audit trail.

b) Documents:

Documents are identified by Version Numbers. Changes to documents are reflected by issuing a new version with a new number. New versions supercede all older versions. Interim changes, released only in a controlled manner for comment during the drafting of a new version, are not covered by an audit trail.

Risk/Benefit Based Approach

Since it is clear that it will take the industry time to achieve compliance with 21 CFR Part 11, given its broad scope, PhRMA recommends that a phased risk/benefit approach be adopted based on the following key principles:

1. Perceived risk or benefit to public health – those systems perceived by FDA or industry to pose a significant risk to public health would be addressed as a priority.
2. Feasibility, cost and risk of the required transition – core systems, such as MRP and LIMS, would be the next highest priority, based on a consideration of the availability of proven commercially available solutions together with an assessment of the cost and risk of transition.
3. Risk and life cycle position of the corresponding systems in a given company – remediation of the remaining systems would be based on a consideration of potential risk and position in the system lifecycle, with those systems representing significant risk, or close to the end of their lifecycle being addressed first.

In terms of the perceived risk or benefit to public health, it is assumed that, based on current comments from both FDA and industry, the proposed order of priority is:

1. Manufacturing batch records
2. Manufacturing LIMS and QA systems
3. MRP and other key GMP systems
4. GLP Systems
5. GCP System

In terms of feasibility, cost and risk of the required transition, the proposed order of priority is:

1. Systems where compliant software is available from a leading industry vendor.
2. Systems where compliant software, based on stable technology, is expected to be available within 12 months from a leading industry vendor.
3. Systems where compliant software is likely to be available from a leading industry vendor in a period of more than 12 months or where the changes involve the use of new or immature technology.
4. Systems where compliant software is not available.

In terms of the risk and life cycle position of the corresponding systems in a given company, the proposed order of priority is:

1. Non-compliant systems with known deficiencies that provide a significant risk to product quality.
2. Non-compliant systems nearing the end of their life cycle with limited numbers of links to other systems.
3. Non-compliant systems nearing the end of their life cycle with extensive links to other systems
4. Non-compliant systems in the second half of their life cycle.

Phased Implementation

Given the large number of systems covered by 21 CFR Part 11, in the hundreds for major companies, even if the necessary commercial software was available, attempting to change a large number of highly interconnected systems in a short period of time poses a high level of risk to product quality and supply. Hence, as noted above, PhRMA recommends that FDA use a phased approach is recommended based on a consideration of the risks and benefits involved.

For many companies and systems, a five to ten year cycle would provide a reasonable balance between an aggressive upgrade program, the availability of key commercial software, and the ability to phase costs and link replacements to a combined risk/benefit assessment and system replacement life cycle. There may, however, be specific systems in particular industries for which a longer period is appropriate and these should be investigated on a case-by-case basis.

It is unrealistic to think that a large number of systems that were generating products of acceptable quality prior to the introduction of 21 CFR Part 11 could become inadequate overnight. A risk/benefit-based, phased approach enables systems with a high level of risk or expected benefit to be addressed in an initial phase. This can be followed by a phase covering systems for which commercial software is available, with a final phase in which vendors would have had time to develop the required systems and validate

any new technologies required. Hence, based on the risk/benefit recommendations above, the priorities would be:

1. Systems that pose a significant risk to product quality or public health would be remediated during an initial phase covering a period of 1-2 years. This could include the use of interim procedures to address specific defects.
2. Systems for which appropriate commercial software was available and which represented medium risk would be upgraded over a period of 2-5 years.
3. Systems for which commercial software was not yet available, and represented medium risk, would be upgraded within 3 years of the required software being available.
4. Medium and low risk systems with long remaining system life cycles would be upgraded on a planned cycle based on the level of risk, availability of commercial software, and position in the system life cycle. If necessary, interim plans could be developed to address specific shortcomings prior to replacement.
5. Companies would implement a generic system assessment process as part of the commitment to a "good faith" approach. This would include identifying the systems that are affected, providing a "gap analysis" defining the remediation activities required and providing expected dates for the upgrading or replacement of each system.

Since the key issues arise not from specific systems but from the fact that companies must upgrade a complex set of highly interconnected systems, the industry proposes that each company generate its own phased implementation plan based on the risk/benefit factors outlined above. These would be available to FDA, which could both comment on the priorities and track the overall implementation of the plan and any associated interim measures.

Interim Hybrid Approach

Within the industry, electronic systems have been introduced into the existing paper-based environment over a period of many years. Hence, by definition, the industry operates in a hybrid environment in which some records are paper-based and others electronic. Since paper-based records were the norm, it has been common practice to print out and sign records from electronic systems to provide permanent paper records.

This approach has worked well over many years and PhRMA proposes that such a hybrid approach remain acceptable during the period of transition. Once a paper record has been generated, it would subject to the audit trail requirements for equivalent paper records.

Since the current generation of systems was designed to operate in this hybrid manner, it requires the phased upgrading of virtually all of the major systems before a manufacturer is able to move to a fully electronic approach. The option of returning to a paper-based approach is not viable, since the industry relies heavily on the current

generation of hybrid electronic systems. It is also clear that moving back to paper-based records from the current position would compromise, rather than improve, product quality and supply. Hence, PhRMA's specific recommendations in this area are:

1. Generating paper records by printing and signing records from electronic systems should remain an acceptable approach during the transition to an electronic record environment.
2. As systems are upgraded they will support the requirements for electronic records and signatures. Hybrid records may, however, still be required for data exchanged between upgraded and non-upgraded systems.
3. Audit trail requirements for hybrid records that have been printed and signed would be the same as those for the equivalent paper records.

Limitations of Commercially Available Software

Most companies rely heavily on commercially available software from leading vendors. Many companies, particularly the smaller ones, lack the facilities for custom software development and support. This is a general trend across all major industries. PhRMA asserts that it is neither a viable or desirable option for the regulated industries to return to custom development.

The use of standard commercial software is in the combined interest of industry, FDA and the public. It allows the use of proven software products that can be implemented in a consistent manner across companies promoting standardization and the use of best practice approaches from both within and outside the regulated industries.

The consequence of this is that FDA needs to provide sufficient clarity on its requirements to enable vendors to incorporate them into their products. Similarly, if changes are to be implemented rapidly, then they need to be based on viable approaches using proven technologies. Hence, PhRMA recommends that:

1. FDA guidance needs to be sufficient to enable commercial software vendors to develop compliant products.
2. The time cycle for major new product releases, based on current best practice and the use of mature technologies, is 12-24 months. This does not include the time required by industry to implement the new software releases, which, typically, expands the time scale to 24-36 months.
3. Historically, vendors are reluctant to develop major new releases of software that are not based on current best practice or that incorporate new or unproven technologies. New technologies, in particular, often take 3-5 years to be incorporated into mainstream commercial software products.

Long Term Electronic Archiving

The speed of change of information technology means that systems become obsolete within a period of around 3-5 years. This means that, although it is easy to record

information electronically, it is difficult to guarantee that such information can be restored for more than approximately 5 years. Given the long required life of Predicate Rule records, there is no guarantee that such records can be restored towards the end of their life.

The goal of being able to restore not only the data but also the system that processed it is an even greater challenge that is probably not achievable in the current technical environment. Hence, the focus must be on preserving the electronic records, plus associated descriptive information, in a format that is likely to have a significant life and can be restored in human readable form. Hence, although the scope of 21 CFR Part 11 needs to include the long term archiving of electronic records, PhRMA asserts the requirements in this area need to reflect the capabilities of the technology.

Economic Impact Analysis

The FDA's initial assumption that 21 CFR Part 11 could be implemented without significant cost to the regulated industry has turned out to be invalid. Given the current understanding of the cost to the industry of well in excess of $1B, PhRMA asserts that FDA should conduct a formal economic impact analysis to identify the true potential costs. This would then support the adoption of a phased risk/benefit approach to the implementation of 21 CFR Part 11 as recommended in this proposal.

PhRMA trusts that these comments are useful to the FDA as the Agency procedes with implementing this critical regulation.

Sincerely,