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What next for 21 CFR Part 11?

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Synopsis

The FDA rule for electronic records and signatures is now six years old. As companies are working on implementing solutions for meeting the requirements stipulated by this rule, this article takes a look at how the interpretation and industry view has changed over this period of time, and tries to predict future trends and developments.

Introduction

For several years now it has been difficult to attend seminars and pharmaceutical gatherings without the topic of 21 CFR Part 11 cropping up, either in the formal session programme, or as a hot topic during conversations [1]. Frequently the rule, which deals with electronic records and signatures, is referred to as a "new" piece of law, when in fact it has been on the statute books for six years, and existed in draft form for another three years prior to that. As the rule matures, now seems an

opportune time to take a brief look back, and more importantly try to predict what the future developments might be. It should be pointed out that the Author does not possess privileged information from the FDA nor has he got a crystal ball, so the predictions are based on observed developments and personal experience in dealing with the rule and its implications. It is assumed that the reader is familiar with 21 CFR Part 11, but just in case, the main characteristics have been summarised in figure 1.

Figure 1: 21 CFR Part 11 Summary

- 21st July 1992: FDA publishes the advanced notice of proposed rulemaking (ANPRM).
- 31st August 1994: Proposed rule is published.
- 20th March 1997: Final rule is published.
- 20th August 1997: The rule becomes effective and enforceable.
- 1st July 1999: Enforcement policy for the rule is issued.
- The rule has two main areas of enforcements: electronic records and electronic signatures.
- Detailed procedural and technical requirements are given for both electronic records and signatures. Some of these include:
 - ability to discern invalid records
 - ability to generate electronic copies of records
 - automatically generated audit trail
 - access controls
 - securely link signature to record
 - use of unique secure signatures
- For the first time electronic signatures are given legal equivalence with traditional "wet ink" signatures on paper.
- The rule applies to all areas of volume 21 of Code of Federal Regulation (CFR) for US manufactured products and products distributed in the US.
- Electronic record keeping and electronic signature use are not mandatory, but if used must comply with the requirements of the rule.

Why did we end up with 21 CFR Part 11?

Whilst companies are often struggling to come to terms with the rule, it may be worthwhile to remind ourselves why this piece of law was put in place. By the 1980's technical solutions existed for generating fully electronic batch records utilising distributed control systems (DCS) with batch management capabilities. The batch management module would be either a separate software package or fully integrated with the DCS. This enabled a production plant to be operated in accordance with the S88 batch standard, generating working recipes, monitoring inventories, controlling plant equipment and collecting all salient data under a secure access control arrangement. The DCS had a configurable report package that enabled customised batch records and management reports to be generated. At the same time software was becoming available for the digital signing of records. The only item missing in the equation to make fully electronic batch records a possibility was the actual regulation. 21 CFR Part 211.188 states "...records checked for accuracy, dated and signed". Other clauses of Part 211 such as §186 refer explicitly to "full signature handwritten". These were seen as regulatory blocks on the pharmaceutical road to the digital world. Moving to fully electronic data handling promised huge cost savings from improved efficiency and reduced physical handling and storage compared to traditional paper records, as well as increased security, traceability and transferability of data.

It is not just in the manufacturing (GMP) area that electronic data handling offers noteworthy benefits. The amount of data generated in analytical laboratories operating under GLP is significant, and since this data requires review and approval signatures, 21 CFR Part 11 promises major improvements in workflows and data handling. The same could be said about clinical trials operating under GCP. The potential scope for efficiency savings with regard to regulatory submissions (IND, NDA, ANDA, ELA, etc.) is also substantial. For these reasons several pharmaceutical companies approached the FDA with the view of getting their approval for using electronic signatures in lieu of traditional handwritten ones.

The resulting legislation, which eventually became 21 CFR Part 11, had a long gestation

period, see figure 1. There were three principal reasons for this:

- A shift away from the fundamental use of handwritten signatures to verify all significant events of social-economical history for several centuries. On a government level handwritten signatures are still predominant, and in everyday life the default authorisation of transactions (legal, financial, administrative) is by handwritten signature. It is only fairly recently (thanks to the internet) that use of passwords and codes have begun to make inroads into financial transactions.
- The risk of loosening the link between signature and taking responsibility. This point is closely linked to the preceding one. The person applying a handwritten signature is normally fully aware of the significance of the act of signing, hence he or she is ready to accept the associated responsibility. As an individual it is expected that we would try to establish the circumstances for applying the signature (i.e. review, approve, release, etc.) before applying a signature. The actual act of signing is clearly identified, i.e. pick up the pen and apply the personal signature in a dedicated space. Compare this situation with typing in a password or code, perhaps in connection with several application log-ins and a lengthy computer terminal session. In this scenario the act of signing may not be as clear as before, and it is conceivable that the person typing the password may later try to repudiate his or her signature on the basis of not understanding the circumstances for signing.
- The risks imposed by cyber crime. Not only is cyber crime not uncommon and well publicised, but many surveys have shown that to the general public falsification of computer records are not seen as being as serious a crime as forgery of paper records. The computer tends to lend us anonymity, e.g. we may be happy to use different passwords to try to gain unauthorised access, but would not do so in a face-to-face situation. Cyber crime loosens the link between signature and taking responsibility. Typing on a standard computer is void of personal links whereas a handwritten signature is directly linked to the individual person.

In the end the commercial pressures were too large to be resisted, and any objections were overcome. There was a price to be paid, however, since the resulting legislation has two stings in the tail:

- The rule applies to existing systems put in before 20 August 1997.
- The rule applies to systems not employing electronic signatures and not being designed for these.

Whilst industry had expected that there would be rules and regulation for the use of electronic signatures, it was not easy to predict that Part 11 would apply retrospectively and to systems that had never been designed, planned or even required electronic signatures. So whilst industry was the instigator and main driving force behind the new rule, the FDA's interpretation of the demands took industry by surprise.

Interpretation, interpretation, interpretation ...

This unexpected turn of events, coupled with the demands imposed by the looming Y2K challenge, led to limited industry reaction once the rule was published. It was soon clear that many, if not most, legacy systems were non-compliant with several of the rule's requirements, and that for these there were no easy and inexpensive ways out. This left the industry in a quandary; it wanted to move to the paperless world (not least because of the economic drivers) and had asked for Part 11, but found the costs almost prohibitive, coupled with regulatory uncertainties around the interpretation and implementation of the rule. Generally it was not until early in 2000 that serious progress was being made in addressing Part 11.

Despite the lengthy review period resulting in numerous industry comments and responses from the agency, the interpretation of the law soon became the next stumbling block. To borrow a phrase from the British Prime Minister Tony Blair, the three most important subjects with regard to Part 11 were interpretation, interpretation and interpretation. It seemed that it was possible to read the law in many ways, and this affected even the most fundamental understanding of the rule, such as the exact meaning of a record (something which is still debated today!). Some of the advice given by the Agency appeared to be less than clear and sometimes even inconsistent. The latest example of this was the announcement on 28th January 2003 of the

withdrawal of the draft guidance on copies of electronic records, a guidance document that was released only five months earlier [2]. Some companies used this situation as an excuse for doing very little about achieving compliance, whilst others almost went the other way and interpreted the rule so strictly that it became nearly impossible to meet all requirements. In short, the industry was in turmoil. It didn't help that the FDA grew increasingly impatient, expecting to see some real results.

The reasons for these lengthy interpretations are a direct result of:

- The way the rule has been worded.
- Its enforcement on existing systems (retrospective law making).
- Its enforcement on systems initially thought outside of the rule (those without signature capability).

Part 11 is worded quite differently from say Part 211 (finished pharmaceuticals), which details mainly principles but says nothing about how those principles should be implemented. Part 11 on the other hand is much more specific, e.g. not only does it state that an audit trail must be present, but it also defines several of its attributes. It is the Author's view that this approach has led to many of the interpretation issues, i.e. one question soon leads to another, etc.

Did we gain the promised benefits? – The missed opportunities

Today six years after the rule came into being almost all attention is on making existing systems compliant. Almost without exception all life science companies have non-compliant systems, i.e. they are breaking the law. This is not a very comfortable situation to be in considering the increasingly vociferous and active approach taken by the FDA. Understandably all emphasis is on attaining compliance (or as near as this is possible to do). When fixing legacy systems rarely are the opportunities provided by Part 11 considered. For new systems the picture is more mixed; there are many fully electronic systems using electronic signatures such as retina scan or chip card or simply passwords, but it is equally true that there are probably even more new systems where the technology level has been kept fairly low, perhaps with an option of adding electronic signature capability sometime in the future. Whilst this situation is both undesirable and regrettable it is also understandable. The industry has a long

tradition of putting regulatory considerations ahead of technological advances. Whilst the uncertainties surrounding Part 11 and its interpretation and enforcement persist, it is expected that companies will tread carefully along the digital road. Part 11 should really be seen as an enabling law, making possible the comprehensive use of computer systems to record, secure and authenticate data. As we have already seen there are not only economical drivers for this, but also computer systems used intelligently will considerably reduce data handling risks and thus regulatory concerns.

As long as there is a considerable backlog of non-compliant legacy systems that are being pursued by the FDA, this situation is not likely to change in the near future. It will take a change of heart by the FDA, where the advantages of fully electronic systems will be allowed to outweigh concerns regarding legacy systems.

The 'Risk Based' approach

The technical demands imposed by Part 11 can all be construed as being reasonable, but only for critical computer systems that have recently been designed for the life science industry. As we know the majority of employed systems do not fall into this category, hence Part 11 is imposing a considerable load on companies to comply. The key question is therefore "Is the imposition of Part 11 on legacy systems in proportion to the risk these systems represent to public health". It is of course impossible to answer such an open question with any certainty and general applicability, but from the Author's limited view the answer is probably "No". Too often it appears that the sole objective is to comply with some technical and procedural demands without an assessment of what this will actually achieve. In short, companies are expending efforts that could have been better deployed elsewhere to reduce the overall risk. Frequently the interpretations by the agency of the rule do not seem to be based on the perceived risk to public health.

Interestingly the FDA appears to have taken this criticism to heart and last year issued a statement that a 'risk based approach to GMP' would be adopted for their regulatory inspections [3]. It is expected that this philosophy will be extended to Part 11 as well, which is specifically referenced in the

announcement. Perhaps it was no coincidence that this major development was announced a day after the fifth anniversary of the effective date of 21 CFR Part 11. Most parties would welcome such a 'Risk Based' approach as it enables a more focused way in dealing with the implications of the rule.

A classic example is the requirement for the computer system to have an automatic electronic audit trail. Whilst this is generally a good idea and a valuable tool in assessing changes to critical data, it is hard to see its applicability to a system where critical records cannot easily be changed. For a start how could such an audit trail be verified when the data it is supposed to trail is static? In this case it seems that it is more appropriate to ascertain that records are maintained safely and that adequate access controls are in place. Unfortunately the wording of the rule doesn't allow for this interpretation.

As yet it is not known how this 'Risk Based' approach will be implemented by the Agency. In the meantime there is no reason why companies should not develop a model for handling Part 11 based on well-identified risk criteria such as:

- Criticality of the computer system to the drug product and product related data. A direct impact system will carry a higher risk since it directly affects GxP functions or data as opposed to an indirect system.
- Standardisation, size, complexity and age of the computer system. A well-proven and understood system will naturally represent a lesser degree of risk in contrast with a new highly complex bespoke system.

This is in line with the 1999 enforcement policy for Part 11 [4], which takes into account some of the above factors, such as:

- The degree of deviation from the rule.
- Closeness of the computer system to the drug and drug related data.
- How appropriate and timely any corrective actions are.
- The regulatory compliance history of the company concerned.

Please refer to figure 2 for an example of a 'Risk Based' model that has been developed by ABB [5].

Figure 2: A 'Risk Based' approach

ABB has developed a pragmatic and risk based approach to dealing with 21 CFR Part 11. The main characteristics of this model are:

- Assessments are brief and directed towards where the highest risk is.
- No assessment is done in isolation from identifying the remediation.
- All corrective actions are justified with a rationale, both those that are to be implemented and those that are not.
- Regulatory, inspection and business criticality are determined.
- Prioritisation is based on criticality, cost and economical life cycle.
- Corrective actions are globally optimised for maximum risk reduction, rather than system based sub-optimisation.

Underlying this approach are three keywords: consistency, rationales and risk reduction. Please visit 'Consulting Services' at www.abb.com/services for further details.

One major consideration is how to make a beneficial transition from a traditional approach to Part 11 to the risk based one. Such transition must be both possible and practical by means of maximising the use of already generated assessment and remediation data whilst minimising any rework. The ABB approach sets out to do just that.

One way of applying a practical approach to Part 11 is to look beyond the wording of the

rule, i.e. remove the interpretation issues, and concentrate on using the rule to reduce any risks posed by non-compliances. Far too often Part 11 related work is concerned with assessing systems in great detail against every clause and paragraph of the rule, whilst not aggressively addressing the real risk factors. Figure 3 shows how such a pragmatic approach can be applied to MS Excel spreadsheets [6].

Figure 3: MS Excel Spreadsheets

MS Excel spreadsheets do not comply with 21 CFR Part 11 mainly due to two aspects:

- There is no secure audit trail
- There is only one level of logical password security, which is restricted to spreadsheet development rather than routine use

MS Excel is a powerful yet easy to use tool that has a role to play particularly in GLP areas. ABB has therefore developed a pragmatic 'risk based' approach to dealing with this situation. Each application is assessed and the spreadsheet is categorised into one of three main types:

- Simple spreadsheets that are used in lieu of calculators. These ought not to raise any serious security issues and are best dealt with outside Part 11.
- Spreadsheet templates that are manually populated and the results are printed out. The template must be securely controlled so no unauthorised changes can be made. Depending on the criticality of the application, a decision needs to be made as to whether the generated results need to be saved in electronic form. Under normal circumstances the electronic results should be saved, and therefore technical remediation is required (see next bullet point). However if criticality and risk are low, a justification could be made that no electronic copy is kept as long as the 'raw data' is retained elsewhere, and the result file could be reconstructed should it be required.
- Spreadsheets where the data must be saved, or that are populated over a period of time and are electronically kept. This type of spreadsheet represents the greatest risk to data integrity, and an audit trail and enhanced password controls are essential. ABB has developed a package based on Wimmer Systems DaCS software to fully overcome the inherent deficiencies of MS Excel.

Please visit 'Consulting Services' at www.abb.com/services for details of the Excel solution incorporating DaCS.

Future developments

The 'risk based' approach mentioned above is almost certain to be adopted by the FDA and industry, although in what form remains very much to be seen. It is an integral part of modern computer validation philosophy and naturally fits in with the ethos of CFR volume 21. But what else can we expect from the future? One sure guess is that there will be increased moves to eliminate the regulatory uncertainties surrounding Part 11. We can anticipate supplementary guidance documents from the FDA in addition to those that have been issued in draft so far [7]. Industry groups will also be active in this area. The ISPE/GAMP and PDA have issued guidance on various aspects of Part 11, and several GAMP Special Interest Groups (SIG) are working on addressing specific aspects of the rule such as electronic archiving [8]. This, coupled with an increased level of experience in dealing with legacy systems as well as new technology, should lead to a more consistent, enforceable and generally acceptable interpretation of Part 11. Hopefully we will move on from spending time and energy discussing the rule interpretations to actually drawing the advantages that are available to us.

Although this article is dealing exclusively with 21 CFR Part 11, let it be noted that an EU directive legalising electronic signatures has been in place since 1999 [9]. Perhaps because this directive is universal, so far it has had negligible impact on the life science industry. The EU regulation is in many aspects different to the US one, although there are also similarities. It is a likely prediction that in years to come we will see some impact from the directive, but any harmonisation between EU and US law is probably a long time off judging by the slow development of bringing other aspects of regulations into line. In this context it is worth noting the work being performed under the Pharmaceutical

Inspection Co-operation Scheme [10].

As new compliant systems and system upgrades become more prevalent and legacy systems come to the end of their economical life cycle, many issues will be resolved by means of system replacement. This in itself, however, will focus attention on an often neglected and frequently unsatisfactorily resolved area, namely electronic archiving. Presently it is still often the case that the cost of storage media has kept pace inversely with the required volume of storage, i.e. a simple 'solution' to the archiving issue has been to simply buy bigger disks! As the volume of data increases and computer systems become obsolete, this approach will not work. Solutions to the storage of data from obsolete systems, indexing and search facilities as well as capture and storage of complex databases with dynamic interlinked data will need to be developed in a practical yet safe manner.

In due course it is expected that Part 11 becomes an integrated part within modern computer validation. Much of what Part 11 contains is both reasonable and desirable and consistent with validation techniques and thinking. There is therefore no specific reason to keep the validation and enforcement of Part 11 discrete from other regulatory issues. But we are not there yet; it is still advisable to keep separate test scripts to demonstrate compliance with Part 11. The Author hopes that this will not be needed in the future, but rather that the principles of Part 11 become an integral part of computer systems design and validation. Although we cannot predict the future, we can be fairly sure that Part 11 will remain in one form or another, and that the principles the rule enshrines are likely to be extended to those beyond the life science industry. 21 CFR Part 11 is not a 'problem' that is going to go away; far from it, the rule's influence is instead likely to extend beyond the current areas.

References

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