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21 CFR Part 11 Electronic Records; Electronic Signatures

Guidance for Industry – Scope of Application

Position Paper: A Summary and Interpretation of the Guidance for Excel and Wimmer Systems DaCS™.

Note: This document has been prepared based on information released by FDA plus ABB's experience gained from working with a wide range of clients in the regulated industries. ABB cannot be held responsible for the accuracy of interpretation or implementation of the recommendations – this document is issued purely as help for the industry.

Background

This letter discusses the recent developments of the release of the 21 CFR Part 11 draft guidance for industry [1]. It will focus specifically on the implications for Excel spreadsheets and Wimmer Systems DaCS™.

Throughout this article specific reference will be made to the guidance document, quoting line numbers from the document in superscript.

Firstly it is important to say that 21 CFR Part 11 is still in effect. The rule itself has not been withdrawn and is still a federal regulation. It is noted however that the FDA may revise sections of Part 11^{33 & 104} and that a review of any changes is currently underway³⁴. During this review period the FDA have decided to narrow the scope of the interpretation and provide more leeway with enforcement³⁶. This is clearly good news for industry as a whole.

Is an Excel Spreadsheet within the scope of Part 11?

Part 11 will be focused on fewer electronic records than previously interpreted¹¹⁸. The question therefore is whether or not Excel spreadsheets are still covered by Part 11? This question is very dependent upon the spreadsheet in question, not all spreadsheets are subject to predicate rule requirements, and even some of those that are, may not be subject to Part 11.

The new guidance relies upon taking a risk-based approach to determining the scope of Part 11. We strongly recommend that this decision is based upon the following assessment factors.

- GxP Criticality
- Business Criticality
- Inspection Risk

The outcome of the criticality assessment will determine the way in which you deal with an individual spreadsheet. For spreadsheets that have high criticality, we recommend taking a significantly more serious approach to ensuring their compliance with predicate rules and Part 11.

For spreadsheets deemed to be high criticality, the FDA are stating that they will continue to fully enforce *'applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with predicate rules'*¹³⁶.

This raises three questions:

- Is the Excel spreadsheet a record that is required under predicate rules?
- Is the Excel spreadsheet going to be included in an electronic submission to the FDA, or maintained for FDA inspection in its original format?.
- Is the paper or electronic version the "official" copy?

The answers to these questions are not clear-cut for spreadsheets.

In the majority of cases we would expect a client to maintain or submit information to the FDA in paper printout form, not electronic form. The guidance states that *'when persons use computers to generate paper printouts of electronic records, those paper records meet all the requirements of the applicable predicate rule,the merely incidental use of computers would not trigger Part 11'*¹⁵¹.

We therefore need to decide whether the use of the computer is incidental?

In the situation of a MS Word document we would say that it is incidental. But can we take the same approach for spreadsheets? The spreadsheet is integral in processing the data, after which it is reported in paper format. Without the spreadsheet processing capability we would have to revert to manual calculations.

Our conclusion here would be that the use of spreadsheets is not merely incidental, it is an integral part of the generation of the submitted information.

There are some situations in which the interpretation is clear.

1. Part 11 will apply if you maintain a record (that is required by predicate rules) in electronic format only:
 - a. Therefore if we decide to use electronic submission of Excel files rather than paper printouts, Part 11 applies.
 - b. Or if we decide to use electronic signatures within a workbook (DaCS™ can allow this due to its ability to add electronic signatures), Part 11 applies.
2. Part 11 will not apply if a spreadsheet (or its output) does not need to be submitted or maintained (it does not fall under the predicate rules) ¹⁶⁷.

As mentioned, other situations are not as clear-cut as the examples above, in an effort to interpret those situations, line 168 in the guidance best describes the situation under which the majority of GxP critical spreadsheets fall.

'FDA considers Part 11 to be applicable to the following records.....Records that are required to be maintained by predicate rules, are maintained in electronic format in addition to paper format, and are relied on to perform regulated activities' ¹⁶⁸.

Many spreadsheets are maintained in electronic format AND in paper format (you may have "official" paper copies) and you use the output, whether it be the electronic version, or the paper version, to perform regulated activities.

N.B. We interpret "perform regulated activities" ¹⁶⁹ to include performing data processing, or making decisions in the manufacture or analysis of a product. If the spreadsheet is not performing data processing (collection, manipulation or

calculations) then we would argue that the spreadsheet is merely incidental and would not fall under the rule.

The process of maintaining spreadsheets in electronic format AND in paper format is likely to remain common practice, as paper versions fit easily into the signature process, and electronic formats are generally required to be saved for business and compliance purposes.

Why does the spreadsheet need to be maintained in electronic format?

There has always been a discussion around whether you can rely solely upon the paper version (the paper output) of the spreadsheet. In our experience the majority of spreadsheets need to be maintained in electronic form to '*perform the regulated activity*' ¹⁶⁹. As a result that spreadsheet (commonly a spreadsheet template) would be securely maintained, and be validated to ensure that the calculation process can be performed. In these cases the spreadsheet is required to be maintained in electronic form to satisfy its intended use.

N.B if the spreadsheet (and associated data processing) is not saved in electronic form, and was generated each time, it could be argued that it does not fall under the rule. However this approach would raise serious concerns over the validation and reliability of the outcome from the spreadsheet, and would not be recommended in any circumstances other than extremely simple data reporting.

These conclusions match up with the FDA comments in their following two paragraphs ^{171 & 179}, where they explain that the business practices dictate whether you are using electronic records instead of paper records. The following statement is taken directly from the text, but we have included the word spreadsheet rather than record to clarify the Excel example.

'If the results from a spreadsheet are required to be maintained by a predicate rule and you use a computer to generate a paper printout of the electronic spreadsheet, but you nonetheless rely on the electronic spreadsheet to perform regulated activities, the Agency may consider you to be using the electronic spreadsheet instead of the paper record.' ¹⁷²

The guidance then goes on to say that you should decide whether you want to rely on the electronic record, or the paper record to perform the activities. Note carefully the wording used, to perform the activity, and not report the activity. This implies that we either decide to perform the calculation by electronic means (use a spreadsheet), or we decide to perform the

reporting activity using paper form (which could be from the spreadsheet output or a manual calculation).

Implications of specific Part 11 requirements

Validation.

Although we think that many GxP critical spreadsheets do constitute an electronic record, it is worth further reinforcing the need for control of spreadsheets by considering validation.

There is a requirement to validate the calculation process within a GxP critical spreadsheet to ensure correct data processing and therefore comply with predicate rules.

The guidance states the need for a risk-based approach to validation.

Commonly the following risks are associated with Excel spreadsheets:

- Spreadsheets are often not validated and therefore there is no confidence in the generated results.
- Spreadsheet calculations are not secure from modification and can be altered from their validated state, therefore invalidating their output.
- Spreadsheet usage is not restricted to authorized individuals, resulting in potentially fraudulent or uncontrolled output.
- Stored spreadsheet results (in electronic form) are not secure from modification and can be modified from their saved and reported state.

From the predicate rules it should be clear that GxP critical spreadsheets need to be validated, and that validation must cover the key risk areas, these are the access security and the ability to modify the spreadsheet from its initial validated state or saved state.

Standard Excel **does not** allow you to validate a critical spreadsheet to the standards expected by industry guidance such as the General Principles of Software Validation [2] or GAMP 4 [3].

DaCS™ **does** allow you to validate a spreadsheet to the standards expected. It provides the access security, and the traceability of modified results.

The biggest regulatory benefit that DaCS™ provides is the ability to adequately validate Excel spreadsheets. We consider this to be more important than the fact that

it provides an audit trail, or that it allows you to execute electronic signatures.

Audit Trail

The guidance advises that an audit trail is not now going to be specifically enforced²¹⁸ on all systems, and recognizes that the benefits or purpose of an audit trail can be provided in other ways (such as adequate security which would prevent record modification). The message is that the need for audit trails should be determined on a case-by-case basis²²⁹, considering criticality assessment.

Excel spreadsheets are an example of where audit trails are very useful for ensuring compliance, and also provide the most efficient business controls around your operation.

- The nature of operating most spreadsheets involves repeated data input and processing. This provides a significant risk of *'testing into compliance'*. An audit trail would record and monitor this practice (whilst still allowing for approved amendments to be made to a result or process).
- The audit trail not only covers data input, but also the content of 'calculation cells', which are part of the validated spreadsheet. Any changes of this type should go through change control, and the audit trail provides a method of detecting and monitoring any changes to the validated system.
- The audit trail monitors who is opening and using the spreadsheet. This may be important particularly in a busy laboratory environment, or across a network, when physical access and logical network access to a spreadsheet is difficult to control.

The guidance states that 'audit trails are particularly important when users are expected to create, modify, or delete regulated records during normal operation'²³¹. This is clearly the case with spreadsheets were you are repeatedly creating new sets of processed data.

Some individuals may argue that if a spreadsheet is developed as a **secure** template, and that data is not saved electronically (printed out to paper) that there is no need for an audit trail. We would agree with that conclusion given controlled operating practices. In this situation the justification for not having an audit trail would be that one is not needed because the system is adequately secure and that changes cannot be made to the template. To accept this justification we would however have to ensure that the security and validation of the template is adequate. In the previous section we stated that standard Excel is not secure, and cannot be adequately validated. Many people feel that the use of

Visual Basic will adequately secure each spreadsheet. We believe this goes against the principles of GAMP and unnecessarily introduces customised code for each and every spreadsheet, each occurrence would require GAMP category 5 validation commitment.

DaCS™ provides the best of both worlds. It provides the security and the ability to validate sufficiently, but it then also goes on to provide an audit trail capability that detects data manipulation. DaCS™ inherently solves all requirements in a standard software package (GAMP category 3) and removes concerns over traceability.

Legacy Systems

The section on Legacy system is not likely to be applicable to spreadsheets, as it is probable that all current spreadsheets will be in a format developed after Aug 20 1997. This is reinforced by the fact that any old spreadsheets that have been converted to newer versions of Excel should have been validated during the conversion process.

Copies of Records

Excel can be considered as being a common format, but at present the problem is that they are not portable (they can be modified on route without detection). The following points promote the use of DaCS™ and assist compliance with this section of Part 11.

- DaCS™ allows Excel spreadsheets to be fully portable. The DaCS™ controlled spreadsheet can be read by any user that has Excel, but cannot be modified outside of the DaCS™ environment.
- Many current systems use Excel as a reporting method, and the use of DaCS™ now provides a secure and portable reporting format from a range of instruments.
- Excel is a very compatible and widely used reporting tool, and DaCS™ allows secure reporting in Excel format.

Record retention

Record retention for Excel format is straightforward and easy to manage. It requires no specific software other than standard office applications, which allows display

of Excel files. The significant concern is that modification of these files is also possible at any point in the future, and it would occur undetected. DaCS™ solves this problem. For retention and retrieval it requires no specific software other than standard office applications, which allows secure display of DaCS™ controlled files. These files would still be viewable should the user decide to stop using DaCS™ in the company. They would remain as secure read-only Excel files.

Conclusions

The following conclusions have been made throughout this paper.

Risk based criticality assessment needs to be performed as an integral part of your spreadsheet process. There is a need to determine exactly which spreadsheets are required by predicate rules and which ones are required by Part 11. The majority of your critical spreadsheet will still fall under the requirements of Part 11.

In many cases the use of spreadsheets is not merely incidental, it is an integral part of the generation of the submitted (or maintained) information and are relied upon to perform regulated activities.

The majority of spreadsheets need to be maintained in electronic format to satisfy their intended use.

Standard Excel does not allow you to validate a spreadsheet to the standards expected. DaCS™ removes this validation concern. It provides the security features and the ability to validate sufficiently, coupled with audit trail capability to solve concerns over traceability of data.

Standard Excel presents significant compliance concerns for record retention and reproduction. DaCS™ allows Excel spreadsheets to be fully portable and allows simple retention and retrieval whilst retaining strict security and integrity.

References

1. *Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application.* (US FDA, 20th Feb 2003).
2. *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (FDA, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, 2002).
3. *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated, GAMP 4* (ISPE/GAMP Forum, 2001).

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