Spreadsheet Data Integrity and Part 11 Compliance with Validation Center
eInfotree Excel Software for Part 11 Compliance with CIMCON Software
Spreadsheet Data Integrity and Part 11 Compliance

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- VP, Life Sciences QA
- 30+ years experience specializing in software quality assurance, validation and IT GxP regulatory compliance.
- Prior to joining Praxis, held management positions in the pharmaceutical industry in both Quality Assurance and Information Systems organizations

Praxis Life Sciences
- Life Sciences Consulting and Project Management since 1996
- Leader of regulatory compliance and process improvement initiatives in Pharmaceutical and Biotech companies, Medical Device companies, CROs, and associated software and service providers.
- Extensive expertise in IT GxP compliance in areas such as 21 CFR 11, Annex 11, GAMP 5
Your CIMCON Presenters

Sanjay Agrawal
- President and CEO
- 25+ years of experience in Part 11 compliance, computer systems validation and quality assurance. Experience in validating and implementing wide range of software systems such as ERP, MES, LIMS, HPLC, Stability, Control systems, and Equipment/Lab systems.
- Written facility wide Master Validation Plans and qualified campus area networks.

Doug Crane
- Sr. Manager
- 30+ years of experience helping customers with implementing document management and other business and compliance software
- 10 years of experience at CIMCON helping customers implement spreadsheet controls and compliance software

Webinar Outline

1. FDA Requirements for Spreadsheets
2. Spreadsheet Warning Letters
3. Overview of CIMCON and eInfotree Software
4. Demo of CIMCON’s eInfotree Excel Desktop Software for Part 11 Controls
5. Q&A
FDA Requirements for Spreadsheets

Section Overview

- FDA Regulation Examples
- FDA Guidance on Data Integrity and Compliance
- 21 CFR 11 *Electronic Records; Electronic Signatures*
Examples of FDA Regulations

**21 CFR 11**
Electronic Records; Electronic Signatures

... electronic records shall employ procedures and controls to designed to ensure the authenticity, integrity, and ... the confidentiality of electronic records, and ... that the signer cannot readily repudiate the signed record ...

Procedures and controls shall include validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

**21 CFR 211**
Current Good Manufacturing Practice for Finished Pharmaceuticals

Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Input to and output from the computer or related system or formulas .... shall be checked for accuracy.

A written record of the program shall be maintained along with validation data.

**21 CFR 820**
Quality System Regulation

When computers or automated data processing systems are used as part of the production or quality system, the manufacturer shall validate computer software for its intended use according to an established protocol.

All software changes shall be validated before approval and issuance.

These validation activities shall be documented.

Data Integrity ALCOA Principles

- **A** - ATTRIBUTABLE
  - Clear identification of who performed the task

- **L** - LEGIBLE
  - Human readable

- **C** - CONTEMPORANEOUSLY RECORDED
  - Recorded in real time

- **O** - ORIGINAL or TRUE COPY
  - Initial capture or complete copy, including metadata

- **A** - ACCURATE
  - Correct
### Access Controls:

When login credentials are shared, a unique individual cannot be identified through the login and the system would not conform to the CGMP requirements.

The system administrator role, including any rights to alter files and settings, should be assigned to personnel independent from those responsible for the record content.

### Audit Trails:

Audit trails include those that track creation, modification, or deletion of data and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file).

Audit trail review is similar to assessing cross-outs on paper when reviewing data.

Personnel responsible for record review under CGMP should review the audit trails that capture changes to data associated with the record as they review the rest of the record.
FDA Data Integrity Guidance

Electronic Signatures:
- Electronic signatures with the appropriate controls can be used instead of handwritten signatures or initials in any CGMP required record.
- Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically.
- See Part 11, which establishes criteria for when electronic signatures are considered the legally binding equivalent of handwritten signatures.

Part 11 Requirements

Record Protection
11.10(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

Copies
11.10(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the [FDA] agency.

Sequencing Functionality
11.10(f) Use of operational system checks to enforce permitted sequencing of steps and events.
Part 11 Requirements

Documentation

11.10(k) Use of appropriate controls over systems documentation including:
(1) Distribution of, access to, and use of documentation for system operation and maintenance.
(2) Change control procedures to maintain an audit trail that documents time-sequenced development and modification.

Training

11.10(l) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

Accountability

11.10(l) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

Access Controls

11.10(d) Limiting system access to authorized individuals.

11.10(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

11.300(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised.

11.300(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.
Part 11 Requirements

Electronic Signatures

11.200(a) Electronic signatures not based upon biometrics shall:

(1) Employ at least two distinct identification components such as an identification code and password.
(2) Be used only by their genuine owners;
(3) Be administered and executed to ensure that attempted use of an individual’s electronic signature by anyone other than its genuine owner requires collaboration.

11.100(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

11.300(a) Maintain the uniqueness of each combined identification code and password, such that no two individuals have the same combination.

11.70 Electronic signatures shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or transferred to falsify an electronic record by ordinary means.

Electronic Signatures, continued

11.50(1) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;
(2) The signature date and time
(3) The meaning of the signature

11.50(b) The items, above, shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).
Part 11 Requirements

Audit Trails

11.10(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

Validation

11.10(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

FDA Warning Letters for Spreadsheets
Section Overview

- Warning Letter Data
- Warning Letter Examples

Data Source
- FDA Warning Letters related to Software and Computer Systems
- 9 Year Range: 2010-2018

Software & Computer Warning Letters

9 Year Summary by System Type

- Device/product Software: 27%
- Laboratory Systems: 10%
- Manufacturing Control Software: 5%
- Complaint Systems: 4%
- SPREADSHEETS: 4%
- Inventory Control Systems: 3%
- Blood Management Systems: 2%
- Clinical Study Systems: 2%
- Document Management: 2%
- Others (< 2% each): 6%
Spreadsheet Warning Letters

9 Year Summary by Usage

Laboratory Calculations: 55%
Complaint Tracking: 4%
Annual Product Review Data: 14%
CAPA Tracking: 14%
Non-Conformance Tracking: 5%
Manufacturing Calculations: 4%
Qualification Tracking: 4%

Spreadsheet Warning Letters

9 Year Summary by Topic

Lack of Security: 31%
Failure to Validate: 4%
Not Suitable for Intended Use: 22%
Lack of Audit Trails: 9%
Data Integrity: 4%
CAPA for Spreadsheet Issue: 4%
Change Control: 4%
### FDA Warning Letter Examples

<table>
<thead>
<tr>
<th>Issuing FDA Office</th>
<th>CDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spreadsheet Usage</td>
<td>Annual Product Review</td>
</tr>
<tr>
<td>Warning Topic</td>
<td>Access Controls, Audit Trails</td>
</tr>
</tbody>
</table>

In your annual product reviews, you used unprotected Excel worksheets to perform calculations and statistical evaluations of production data, such as standard deviation and process capability.

These electronic files were **not secured to prevent unauthorized changes**, and have **no change history**.

Your firm’s lack of data control calls the reliability of your data into question.

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### FDA Warning Letter Examples

<table>
<thead>
<tr>
<th>Issuing FDA Office</th>
<th>Los Angeles District</th>
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<tbody>
<tr>
<td>Spreadsheet Usage</td>
<td>Laboratory</td>
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<tr>
<td>Warning Topic</td>
<td>Access Controls, Record Protection</td>
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</tbody>
</table>

Your firm enters data into [redacted] files to complete plate assay Calculations, but they are not locked from editing once the file has been reviewed.

Your response fails to include any corrective action to **ensure that there is no further access or ability to save over test results in [redacted] spreadsheets once reviewed and approved.**
### FDA Warning Letter Examples

<table>
<thead>
<tr>
<th>Issuing FDA Office</th>
<th>Baltimore District</th>
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<tbody>
<tr>
<td>Spreadsheet Usage</td>
<td>Laboratory Calculation</td>
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<tr>
<td>Warning Topic</td>
<td>Access Controls</td>
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</table>

Your firm failed to exercise appropriate controls over computer or related systems to ensure that changes are instituted only by authorized personnel.

**Specifically**

Your firm’s laboratory analysts have the ability to access and modify the formulas in the Excel spreadsheets used to calculate assay results for drug products. Due to the unrestrictive access, there is no assurance that the formulas in the Excel spreadsheets are accurate and valid.

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<table>
<thead>
<tr>
<th>Issuing FDA Office</th>
<th>Kansas City District</th>
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<tbody>
<tr>
<td>Spreadsheet Usage</td>
<td>Product Complaints</td>
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<tr>
<td>Warning Topic</td>
<td>Data Integrity, Audit Trails</td>
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</tbody>
</table>

Your Complaint SOP states that QA shall maintain the customer complaint report files. Your firm’s QA unit maintains a separate Excel spreadsheet for those complaints that come directly into the QA unit.

The use of Excel requires many management controls to prevent data alteration, and Excel does not have an audit trail to identify data changes.
FDA Warning Letter Examples

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<td>Spreadsheet Usage</td>
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<tr>
<td>Warning Topics</td>
<td>Security, Validation, Change Control</td>
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</tbody>
</table>

At the drug facility, the investigator noticed that the use of the Excel spreadsheets in analytical calculations are **neither controlled nor protected from modifications or deletion**.

The investigator noticed that the calculation for residual solvent uses an Excel spreadsheet that has not been qualified.

We are **concerned about the data** generated by your QC laboratory from non-qualified and uncontrolled Excel spreadsheets.

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Overview of CIMCON and eInfotree Software
Company Overview

- Global company, headquartered in Boston, Massachusetts
- Pioneered Part 11 compliance for Spreadsheets and Access databases 20 years ago
- Largest installed base of over 500 clients in 30 countries, including most of the top Life Science companies
- Proven and Mature Software based on client feedback and domain experience
- Strong development team with hundreds of years of total experience
- 24/7 Support Available

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Excel Software for Part 11 Compliance

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Part 11 Compliance Requirements

3 main pillars:
• Security
• Audit trails &
• E-signatures

"... data integrity refers to the completeness, consistency and accuracy of data."

Data Integrity and Compliance With Drug CGMP - Questions & Answers Guidance for Industry, December 2018

Security

• Control Access to File (Read, Write, None).
• Lock calculations and/or cells
• Lock Macros/VBA
• Restrict Print / Save As

"FDA recommends that you restrict the ability to alter specifications, process parameters, data, or manufacturing or testing methods by technical means where possible."

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Audit Trail

- One of the key requirements of Part 11.
- Audit trail records all system entries with date, timestamp, User ID, cell address, type of entry, old value and new value as applicable.

“Audit trails include those that track creation, modification, or deletion of data... Electronic record-keeping systems, which include audit trails, can support these CGMP requirements”.

Data Integrity and Compliance With Drug CGMP - Questions & Answers: Guidance for Industry, December 2018

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Audit Trail

eInfotree tracks changes to Excel with an irrevocable audit trail that includes:
- A timestamp of change
- User who made the change
- Type of change (Add, Modify, Delete)
- Cell address, old and new values
- Reason field and e-signature details.
Go Paperless using Electronic Signatures

No more printing and signing spreadsheets! Also, can implement e-signatures using compliant spreadsheets. Upon signoff, an email alert can be sent to all stakeholders.

“Electronic signatures with the appropriate controls can be used instead of handwritten signatures or initials in any CGMP required record.”

Compare Workbooks

Reduce Review/Approval times by 50% by comparing the current copy against the last approved version.
Advanced Features

- Supports Office 2019/365/SharePoint
- Work Offline
- Create Remote Copies
- Multiple Site Support

Benefits

- Make your existing spreadsheets fully Part 11 compliant, avoiding the need to move to expensive enterprise systems.
- Eliminate repetitive tasks of re-calculating all formulas.
- No need to print the spreadsheet for wet signatures.
- Unchanged user experience - simply double-click and open files as before.
- Integration with Emails and Active Directory
Demo of CIMCON’s eInfotree Excel Desktop Software for Part 11 Controls

Q&A
Thank You!

Thanks for your interest in Spreadsheet Compliance

Any questions about what we have discussed today?
Please, feel free to contact us:

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