Are you ready for Tag Along Inspections?

Electronic Data means Electronic Records
Gathering and sharing regulatory information

- Regulatory Bodies: FDA/WHO
- Industry groups: ISPE / GAMP
- Customers QA Dept
- Sales and Specialists
- Professional Services
- Product Functionality and Design
What Is Compliance?

- **Satisfying regulatory agencies** and certification organizations that a company's **processes** are being operated at a **level of control** that will ensure that their products will meet predetermined safety, efficacy, and quality specifications.
Electronic Record Regulations
Systems

- Quality - MANDATORY
  - SOPS and Policy Control
  - CAPA
- Facilities and Equipment
- Materials
- Production
- Packaging and Labeling
- Quality by Design Implementation
- Laboratory Control
- Risk Management
Purpose of Record Policies

- **Ensure Data Integrity**
  - Records should be created contemporaneously
  - Retained
  - Reliable
    - Changes should be noted, reasoned and non repudiated

- **Computer systems should be trustworthy**
  - Validated to intended use
  - “No resultant decrease in product quality, process control or quality assurance”

- **Evidence should be available to prove the above**
Fat Fingered, Falsification or Fraud

- Peer Review
- Disciplinary Action
- Regulatory Action

- Bob McDowall, Spectroscopy Dec 2010
**Responsibility**

<table>
<thead>
<tr>
<th>Lab Managers</th>
<th>Quality</th>
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<tr>
<td>Senior Managers</td>
<td>Regulatory Bodies</td>
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</table>
As with FDA regulations, EU regulations have rules overlaid with the electronic record rule (Annex 11)
As with FDA regulations, EU regulations have rules overlaid with the electronic record rule (Annex 11)
21 CFR Part 11 Controls

- **Administrative Controls:**
  - Set policies, assign roles and responsibilities, operator and administrator training, ITIL implementation, auditing

- **Procedural Controls:**
  - SOPs and Work Instructions for operation and administration, computer system validation, calibration, network qualification, awareness training

- **Technical Controls:**
  - Computerized features like audit trail, backup mechanism, user management and security, electronic signatures and/or digital signatures to assist or enforce administrative and procedural controls
Key Topics of Part 11

- Secure Records
  - Back up, archive, records retention policy of ALL data and meta data
  - Easy retrieval of e-records and Human Readable copies
  - controlled access with unique username and password
    - limit functionality
    - feeds audit trail
  - Secure computer generated audit trails for any changes to data
    - What changed, who, when why (and now where)

- Applications that work
  - Validation
  - Training

- Electronic Signatures
  - Non repudiation of signature (if using)
# Compliance Requirements: System Set Up and Policies

<table>
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<tr>
<th>Workstation</th>
<th>Client Server</th>
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<tr>
<td>Data stored on PC in the lab. PC hardware failures result in loss of data.</td>
<td>Data only stored on server in secured server room. RAID technology protects from failure.</td>
</tr>
<tr>
<td>Expensive to licence a username for every analyst on every workstation.</td>
<td>One user licence for every instrument in the lab.</td>
</tr>
<tr>
<td>Many user names and passwords to maintain.</td>
<td>Single set of passwords.</td>
</tr>
<tr>
<td>Time Stamps from unsecured PC time.</td>
<td>Time Stamps from the Server.</td>
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<tr>
<td>Access to OS (task manager/explorer) on PC compromises security of data.</td>
<td>Access to OS of PC does not compromise data security.</td>
</tr>
<tr>
<td>SOP’s’ need to synchronize naming conventions (files, methods, e-records).</td>
<td>Single data repository ensures uniqueness of ID’s.</td>
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If a firm is keeping electronic records or using electronic signatures, **determine if the** are in compliance with 21 CFR Part 11.

At a minimum ensure that:

1. The firm has prepared a **corrective action plan** for achieving full compliance with part 11 requirements, and is making progress toward completing that plan in a timely manner;
2. **Accurate and complete electronic and human readable copies** of electronic records, suitable for review, are made available; and
3. Employees are **held accountable and responsible** for actions taken under their electronic signatures

- Personnel: who looks after, is responsible and are they trained?
- SOPs and suitable archived data as well as Back Up plans
- Validation Study and Plan, Change control. Test design
Objective 3 Data Integrity Audit

- Audit the raw data, hardcopy or electronic, to authenticate the data submitted..
- ..select key data sets or randomly select data filed in the application. Generally, data on finished product stability, dissolution, content uniformity, and API impurity are good candidates for this audit.
- ..compare **raw data, hardcopy or electronic**, such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory **with summary data** filed.
- ..should determine if data was not submitted to the application that should have been
  - Passing results substituted for failing ones
  - Improperly invalidate OOS and not include them
The following are some examples of data integrity problems that have been previously observed:

- Multiple analyses of assay with the same sample without adequate justification
- Exclusion of specific lots from the stability program to avoid submitting failed results
- Reworking or process modifications not adequately justified and appropriately reported
- Manipulation of a poorly defined analytical procedure and associated data analysis in order to obtain passing results
- Backdating stability test results to meet the required commitments
- Creating acceptable test results without performing the test
- Using test results from previous batches to substitute testing for another batch
Summary of Findings

- No Secure Access to only authorized personnel
  - No password
  - Shared user accounts
    - Set up that way
    - Shared in an emergency without documentation or justification
- No controls to limit access to the delete function (among others)
  - Either set up as administrators
  - Or with user type that permit deletion or data manipulation
- No audit trails
  - Software not equipped with audit trail
  - User not having unique log on prevents correct audit trails
  - No review of audit trails by managers or QA
- Trail injection data not kept or documented
  - Analyses being repeated without justification, then called trial injections
- Delaying, denying or limiting an inspection
  - Hiding data or records
Tag Along Inspections

- Thomas Arista and Robert Tollefson...
- CDER publicly announced in May 2010
  - “Evaluate the current pharmaceutical industry understanding of, and compliance with 21 CFR Part 11”
  - And “where industry may not be complying with, or understand the enforcement approach as stated in the guidance.”
- CDER says it will “take the pulse of the industry”
  - What actions to take next, which could include
    - Proposing changes to the requirements or
    - Honing enforcement efforts to target problem compliance areas
- “..take appropriate action to enforce Part 11 requirements for issues raised during the inspections”
European Rules: Annex 11
New Annex 11 - Data Integrity

- Data Storage, Migration and Archiving
  - Data integrity, accessibility, accuracy and readability
    - Validated and Periodically checked
- Audit trails reviewed
- Printouts should indicate if a result is changed
- E-Signatures
- Business Continuity

e-records?
Documentation may exist in a variety of forms, including paper based, electronic or photographic media.

The term ‘written’ means recorded, or documented on media from which data may be rendered in a human readable form.

Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.
Four new key areas in Annex 11

- Supplier Audits: including the requirement to share a summary of your assessment
  - Be sure this is agreed in your vendor NDA agreement
- Qualification of IT Infrastructure
  - And a formal agreement with IT departments
- Inclusion of Risk Management
  - In Regulation rather than in Guidance
- Review of Audit Trails
  - Specifically mentioned
  - Printouts should indicate a change
Accurate and Traceable Data Entry
- Audit Trails

- Annex 11§9
  - Based on Risk
    o Record of all GMP relevant changes and deletions
    o Reasons should be included
    o Convertible to human readable form and regularly reviewed.

- Additionally 11§8.2
  - ..ability to “generate printouts indicating if any data changed since original entry”
US FDA Audit Trail Review Warning Letters

- Gulf Pharmaceutical Industries Feb 2012
  - We also note that your SOP does not have provisions for any audit trail reviews to ensure that deletions and/or modifications do not occur.

- Banner Pharmacaps Sept 2006:
  - A second person must review these audit trails, particularly given the lack of controls for preventing data manipulation. Such an audit may well have detected the data manipulation which was occurring at your facility.

- Sunrise Jan 2010:
  - In addition, your firm's review of laboratory data does not include a review of an audit trail or revision history to determine if unapproved changes have been made.
Electronic Review and Approval

- **Electronic Signatures**
  - 21 CFR Part 11 was created to allow electronic signatures and has many detailed requirements for allowing e-sigs
  - Previous Annex 11 has nothing on e-sigs
  - Annex 11§14 is a new section on Signatures
    - Based on Part 11 but simpler
    - same impact as handwritten
    - Permanently linked to e record
    - Include TIME and DATE (no meaning)

- **Batch release should include identity and use e-signature**
Annex 11 is very much more prescriptive in this area

- From 4 paragraphs to 8
  - Risk Based validation effort
  - Should include change control docs
  - Full listing of GMP systems
  - User Requirement Spec required and traceable though validation
  - Supplier assessment
  - Special considerations for bespoke software
  - Evidence of testing and approval of automated test tools
  - Data transfer or conversion checks
11§3 Suppliers and Service Providers
- Formal agreements, including your own IT dept
- Supplier audit based on risk
- Documentation supplied should be reviewed
  - to ensure User Requirements are met
- Quality System and Audit Information should be made available to inspectors

11§4.5 Validation
- ...the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.
Quality Mission Statements and policies available online
Regulatory Position FAQ’s available online
Software Testing summaries available on request
Supplier Assessment / Postal Audit answers supplied
Other Quality documents available during On site audits
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Annex 11 to Influence Part 11?
Electronic Data and Raw Data in the Laboratory

Does this apply in my lab?
FDA Raw Data Motto

- “If it isn’t written down, it never happened”

- “In God we trust, all others bring data”
A day in the life of Raw Data

Raw Data

Quantification

Change control

Qualification and Maintenance

Reporting

Prepare Standards & Samples

CDS
For computerized lab systems e-records ARE defined as raw data for both US and EU

FDA Scope and Application Guidance
- Where e-records are used for regulatory activity

FDA FAQs on GMP
- Printout of chromatograms do not comply...

EU Chapter 4
- Raw data used to create other (critical) records

Warning Letters...
Major Changes in the 2003 Guidance Document:

- Scope of application narrower
  - SOP to define which are e-records
  - Risk based
  - Paper for regulated activities

- Definition of Part 11 Electronic Records
  - Records required under *predicate rules* that are maintained in electronic format **in place of paper**.
  - Records *submitted* to FDA under *predicate rules* in electronic format.(i.e. even if not required by predicate rule)
  - *Electronic signatures* that are intended to be the equivalent of handwritten signatures.
  - Records required under *predicate rules* and are kept in paper and electronic format and the **electronic format is relied on to perform regulated activities**.
Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports

1. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?

2. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

3. How do the Part 11 regulations and "predicate rule requirements" (in 21 CFR Part 211) apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?

"the printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in 21 CFR Part 211.

The electronic record must be maintained and readily available for review by, for example, QC/QA personnel or the FDA investigator"
The printed paper copy of the chromatogram would not be considered a “true copy” of the entire electronic raw data used to create that chromatogram, as required by 21 CFR 211.180(d). The printed chromatogram would also not be considered an “exact and complete” copy of the electronic raw data used to create the chromatogram, as required by 21 CFR 211.68. The chromatogram does not generally include, for example, the injection sequence, instrument method, integration method, or the audit trail, of which all were used to create the chromatogram or are associated with its validity.
Laboratory source e-records

From presentation of Robert D Tollesen National Expert-Computers at FDA’s ORA
ISPE GAMP Nov 2011 Brussels

e-data files from complex analytical systems (i.e.; Chromatography systems)

- Must be retained as per 21CFR211.194(a)
- Must be reviewed for completeness and accuracy and compliance with established standards as per 21CFR211.194(a)(8)
- Must be available for inspection as per 21CFR211.180(c)
Printouts of Electronic Records

- The printed hardcopy is a “temporary representation”.
- It cannot be guaranteed without e-records compliance.
- This includes a print to paper or a print to PDF
  - You must record the meta data
  - Where are the audit trails in a paper record or in a PDF?
- Agency may ask you to re-create report from the electronic record.
- .....even if your “final” data is in paper format with a handwritten signature.

“More about the record than what’s on paper; The Electronic Record is the Master”
E-Record Decision Flow Chart

- **E-Record**
  - Yes: Part 11 Annex 11 Records
  - No: NOT Part 11 Annex 11 Records

- **Part 11 Annex 11 Records**
  - Yes: Yes
  - No: No

- **Predicate Rules Apply?**
  - Yes: High Risk?
  - No: NOT Part 11 Annex 11 Records

- **High Risk?**
  - Yes: Audit
  - No: Remediation Plan

Audit

Remediation Plan
FDA Predicate Rules for Records Management

- **21 CFR 211.194 Laboratory Records**
- 21 CFR 58.185, 58.190, 58.195 Records and Reports
- 40 CFR 160.185, 160.190, 160.195 Records and Reports
- 21 CFR 113.100 & 114.100 Records and Reports
- 21 CFR 820.180-198 Records
- 21 CFR 312.57 and 312.62 Record Keeping and Retention
- 21 CFR 11.10 (b,c,e,k) Electronic Records
21 CFR Part 211: What records need to be kept?

- 211.182 Equipment cleaning and use log.
- 211.184 Component, drug product container, closure, and labeling records.
- 211.186 Master production and control records.
- 211.188 Batch production and control records.
- 211.192 Production record review.
- 211.194 Laboratory records.
- 211.196 Distribution records.
- 211.198 Complaint files.
21 CFR Part 211.194: Laboratory Records

All records required to be kept

Lab Book or forms

Various PCs in Lab

Analytical Applications or Excel

Lab Book or forms
Part 58 Definition

(k) Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.
Data that supports batches records

- Xian Libang, Feb 2010:
  The laboratory control records should include complete documentation of all raw data generated during each test, including graphs, charts and spectra from laboratory instrumentation.

Data that supports method validation

- Cambrex, August 2009:
  a. Raw data (e.g., chromatograms, standard and sample weights,..., for the method validation were not available

Data that support instrument qualification or calibration

- Yunnan Hande Bio-Tech, October 2010:
  Your firm also fails to maintain raw data associated with the re-qualification and calibration of your laboratory instruments.
August 2009

- a. **Raw data** (e.g., chromatograms, standard and sample weights, calculations, standards, reagents, and instrument information) for .... And related substances, method validation were not available during the inspection.
February 2009

- no **raw data** used to support the **verification of the software** used in ... device.
- Failure to store and retain all **raw data, documentation, protocols, final reports** ...generated as a result of nonclinical laboratory studies. (21 CFR §§ 58.190(a) and 58.195(b)].
- d. The study director for studies TOX [[(b)(4)]] and [[(b)(4)]] failed to assure that **all raw data**, documentation, protocols, specimens, and final reports were **transferred to the archives** during or at the close of the studies.
October 2010

- Your firm also **fails to maintain raw data** associated with the re-qualification and calibration of your laboratory instruments. However, you were unable to provide raw data or documentation regarding the qualification and calibration of your instruments and data to demonstrate that your quality unit reviewed and approved the work performed by your contractor.

September 2010

- The gas chromatographic analysis performed and the **data** provided to the application sponsor is **not traceable to raw data**. The **original chromatograms could not be located** during the inspection.
4. Your firm has not established appropriate controls over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Your firm also fails to maintain a backup file of data entered into the computer or related system [21 CFR § 211.68(b)].

- For example,
  
  o a) There is no system in place to ensure that all electronic raw data from the laboratory is backed up and/or retained.
Raw Data

- Failure to have laboratory records that include **complete data derived from all tests**..
  - In your response, include your remediation plans to ensure all raw data is recorded and maintained, including the written procedure describing the retention policy for all laboratory control records.
2. Your firm does not have laboratory control records which include complete data derived from all tests conducted to ensure compliance with established specifications and standards [21 C.F.R. § 211.194(a)].

For example, your laboratory notebooks are incomplete. Missing data included, but was not limited to lot numbers of reagents used, documentation of weights and volumes, and dates and signatures of second-person review for accuracy, completeness, and compliance.

Your firm should include in its response a list of the specific SOPs and laboratory records that you plan to revise to ensure all test data is complete.
During the inspection, you informed our investigators that electronic raw data would not exist for most HPLC assays over two years old because data is not backed up and storage space is limited.

- Data is deleted to make space for the most recent test results. You also informed our investigators that printed copies of HPLC test results are treated as raw data.
Printed copies of HPLC test results from your firm’s systems do not contain all of the analytical metadata (for example: instrument conditions, integration parameters) that is considered part of the raw data.... Also describe your firm’s policy for retaining HPLC raw electronic data associated with pending applications.
Your firm does not have laboratory control records which include complete data derived from all tests necessary to ensure compliance with established specifications and standards [21 C.F.R. § 211.194(a)].

Your firm failed to include the required raw data, including the sample dilution, mobile phase preparation, equipment used, conditions of the chromatographic system, and the signature and date of the analyst who performed the tests.

You failed to maintain important raw data, such as sample and standard preparation.

Please review all of your analytical records and calculations to ensure that your laboratory results are accurate and support
1. Your firm has not established appropriate controls designed to assure that laboratory records include all data secured in the course of each test,

- including graphs, charts, and spectra from laboratory instrumentation,

properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested [21 CFR 211.194 (a)(4)].
Missing Raw Data

- For example, your firm could not provide complete raw data derived from the endotoxin tests performed on purified water samples, including a complete description of the sample, test method used, record of all raw data generated during the test, and signatures of the person who performed the task and the person who reviewed it.

Unsuitable related substances HPLC tests

- ..during the inspection your firm could not provide forced degradation data to support suitability of the HPLC test method for stability testing ..Review of the chromatograms from the release testing of related substances ..show peaks that do not separate, suggesting the method is not capable of detecting all related substances present.
Deleting Raw Data from trial analyses

- your QC manager stated during the inspection that the initial injections were trial runs, and that performing trial standard and sample analysis prior to official analysis is a standard practice in your QC laboratory.

Repeating analyses due to accidental deletion of data

- you analyzed API lot at 2:55 a.m., and then retested it at 2:05 p.m. using a new sample solution. You did not maintain any raw data associated with the initial test.
- the retest was performed due to data deletion of the original analysis. the analyst misused the administrator password to delete and overwrite the actual data logged in the audit trail.

Only Printed Raw Data

- our investigator requested to review the electronic analytical raw data to compare the values for (b)(4) assay and degradation products. However, your firm provided only the printed copies of the raw data because your firm did not have the software program available to view the electronic raw data.
Electronic files for trial injections and retests not kept or not reported
- kept some samples, data and results outside of the local systems for assessing quality
- your firm was testing samples unofficially, and not reporting all results obtained
- were retested without a record of the reason for the retest
- multiple raw data chromatograms in digital files labeled “test” and “demo”

Investigate all electronic data generated
- **identify any data found in your electronic record repositories** (or other locations) ..not also described in your product release files
- a review of the audit trail from the software that describes surrounding events for each piece of extra data identified that represents a finished API batch
Records do not include data derived from all of the tests

- The management of electronic data permitted unauthorized changes, as digital computer folders and files could be easily altered or deleted
- The FDA was informed during the inspection that all electronic raw data files are automatically stored on a central server.
  - Later in the inspection, FDA found that raw data was being stored in several folders on PCs.
- Recently informed us that High Pressure Liquid Chromatography units and PCs were removed from the facility for the duration of the inspection to conceal data manipulations
- An employee was observed attempting to hide manufacturing related records in his pocket from the FDA Investigator.
Failed documentation
- unofficial batch records for approximately 75 batches of injectable finished drug products torn in half in a waste area

No complete data (211.104(a))
- performing "trial" sample analysis for HPLC analyses prior to collecting the "official" analytical data for stability testing
- your quality control HPLC raw data files can be deleted from the hard drive using the common PC login used by all ..analysts

Failed to record or justify deviations
- "the loss of instrument activity logs (audit trails)" following a computer crash on the back up PC
- several of the HPLCs had the audit trail functions disabled
- at least one QC officer had the ability to delete data on the affected system
- failed to provide a risk assessment for the products tested using the HPLC instruments that had the audit trail functions disabled
January 2010

- 3. Failure to have adequate controls to prevent manipulation of raw data during routine analytical testing.
  - For example, your firm's laboratory analyst had modified printed raw data related to the IR Spectra. We are concerned that the lack of security or system controls allows for this practice.
  - For example, your quality control unit failed to detect that IR spectra were being substituted by a laboratory employee and therefore, misrepresenting the actual results of the tested incoming material. Your response is inadequate in that it does not address the ability of your quality unit to control and detect the manipulation or alteration of laboratory documents.
The requirements of 21 CFR Part 11 can be summarized as:

- **Know and understand the business process** in the laboratory, coupled with the applicable predicate rule requirements

- **Define and document the electronic records** and signatures that are generated during the course of regulated activities

- **Identify and manage risks to regulated records** and signatures

Similarly, EU GMP Chapter 4 requirements can be summarized as:

- Among the regulated documents are **records that are required as evidence of actions** from instructions such as analytical procedures, protocols, and standard operating procedures.

- For hybrid and homogeneous systems, regulated **users need to define the raw data used to make quality decisions**.
FDA GLP and cGMP: raw data is the machine readable bits and bytes
- New Annex 11: true for EU too
- Paper/reports are not the raw data

Training on data integrity to increase confidence of investigators:
- by Green Mountain
- By vendors,
- By industrial organisations

NuGenesis SDMS takes care of raw scientific data, reported data and converted data for long term archiving.