Discussion Topics

• Goals and Basics of 21 CFR 11
• Definitions
• Recent Updates
• Case Study
• Summary
21 CFR Part 11 Objectives

• Provide criteria for acceptance by the FDA
• Apply to all FDA program areas
• Permit the widest possible use of electronic technology
• Be compatible with the FDA’s responsibility to promote and protect public health

A Brief History of 21 CFR Part 11

• July 1992  • Advance Notice, Proposed Rule
• August 1994  • Proposed Rule
• March 1997  • Final Rule Published
• August 1997  • Final Rule Effective
• May 1999  • Agents Begin ER & ES Training
• June 1999  • Active Enforcement
• August 1999  • First Warning Letter Issued

Intent
To ensure the electronic record is:
• Trustworthy
• Reliable
• Equal to paper/handwritten signature
Recent Part 11 Survey

- The Majority of Participants Indicated They Are Familiar With Part 11 and Involved With Compliance
- 20% Belong to the 21cfrpart11.com Newsgroup
- More Than Half of the Poll Respondents Felt Their Organization Had Not Even Achieved 25% Compliance
- 20% Said Their Organization Had Completed a Part 11 Compliance Assessment
- 44% Responded That One Was in Process
- Over 40% Indicated That Electronic Signatures Would Be Used at Their Organization

Applicability

21 CFR Part 210,211
21 CFR Part 58
21 CFR Part 50,54, 312,314

21 CFR Part 11

GMP GLP GCP

*Drugs, cosmetics, food, medical devices, nutraceuticals*
Part 11 Applicability

- Manufacturing Execution Systems (MES)
- Maintenance Management Systems (MMS)
- Calibration Management Systems (CMS)
- Building Management Systems (BMS)
- Enterprise Resource Planning (ERP)
- Distributed Control Systems (DCS)
- SCADA Systems
- PLC Systems

- Stability Systems
- DM&PK Systems
- Toxicology Systems
- Laboratory Robotics Systems
- Environmental Monitoring Systems (EMS)
- Chromatography Data Acquisition Systems
- Laboratory Information Management Systems (LIMS)

GMP QA/QC GLP GCP

- Laboratory Information Management Systems (LIMS)
- Document Management Systems (DMS)
- GXP Training Tracking Systems
- SOP Systems

- Case Report Form Systems
- Clinical Data Management Systems
- Statistical Analysis Software (e.g., SAS)
- Adverse Event Reporting Systems (AERS)
- Remote Data Entry/Remote Data Capture (RDE/RDC)

Title 21 Retention Examples

- GCP Financial Disclosure (Title 21 CFR 54)
  - $$ arrangement between sponsor and clinic
  - Retained for two years after the date application approved

- GLP Laboratory Record (Title 21 CFR 58)
  - Records of training, experience, resume, job descriptions for people in non-clinical lab work
  - Retain for two years following approval of research or marketing application permit
What is an Electronic Record?

21 CFR Part 11 -- Subpart A, Section 11.3(6)

- Definition:
  "Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system."

• In practical terms this means …
  – any computer information …
  – starting its life as data written to durable media* …
  – either submitted to the FDA …
  – or required by the Agency to be maintained.

* Guidance for Industry, Computerized Systems Used in Clinical Trials

The Printed Hardcopy is a “Temporary Representation”

• Data in ‘metadata’
  – ie: calibration, integration, instrument method, etc.
  – ‘File Properties’ example in MS Word

• The printout cannot be guaranteed without e-records compliance

  • Agency will ask you to re-process report

“More about the record than what’s on paper; The Electronic Record is the Master”
**Typewriter Example**

**Part 11 Does Not Apply**
(No Storage - direct output to printer)

**Part 11 Applies**

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**You Cannot Just ‘Buy’ a Compliant System**

- **Technical Controls**: Hardware and s/w features designed into the system to provide functionality needed to address the requirement
- **Procedural Controls**: Direct conformance to a requirement by defining a process to be followed
- **Administrative Controls**: Policies Non-repudiation
Regulatory Requirements

• “…electronic records must be archived in electronic form. The electronic records must be protected to enable their accurate and ready retrieval throughout the relevant retention period…”

• Keep accurate transcriptions of data and “metadata” on durable media

• Keep links between signature and e-record

• Tighter controls required for “open” systems

How Do I Achieve Compliance?

21 CFR Part 11 -- Subpart B, §11.10
Controls for Closed Systems

– Validation
– Ability to generate accurate and complete copies of records
– Use of computer generated, time-stamped audit trails.
– Protection of records to enable accurate and ready retrieval
– Appropriate controls for system access and authority checks
Audit Trails

- Electronic audit trails should be:
  - Operator independent
  - Computer generated (automatically)
  - Time-stamped (clear date and time)
  - Secure

- Audit Trail Documentation:
  - Retain same period as electronic record
  - Available FDA review/copying

- ALL changes need to be documented
- Recorded changes must not obscure prior information

What Do You Do If You Have a Non-compliant System?

- Put administrative & procedural controls in place immediately!
  - Follow the predicate rules
  - Make sure system validation is current and complete
  - Develop SOP’s to cover short term deficiencies
  - Institute Part 11 training and awareness
  - Define responsibility and accountability

- Develop a plan for instituting technical controls now!
  - Plan for legacy upgrade … be prepared to spend money
  - Clearly document your intentions in detail
  - Set adequate timelines
  - Secure operating systems and operating environments
  - Implement complete audit trails
  - Validate!
“We’ll take enforcement discretion if you have a process in place.”

Jennifer Thomas, CBER And Part 11 Compliance Committee

Definitions 11.3

• **Electronic Signature** means
  – “a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.”
What about Electronic Signatures?

21 CFR Part 11 -- Subpart B, Section 11.50
- Requirements for signature manifestations on electronic records:
  - Printed name of signer.
  - Date/Time signature is executed.
  - Meaning associated with the signature.

21 CFR Part 11 -- Subpart C, Section 11.200
- Employ at least two distinct identification components, such as an identification code and a password if not biometric.
- Series of signings during a single period of controlled access requires use of both components for first signing and at least one component during subsequent signings.
- One or more signings not performed during a single, continuous period requires both components.
- Non-biometric e-signatures must be administered to prevent forgery.

Definitions 11.3

- Biometrics means
  - “A method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.”
    - voice prints
    - finger prints
    - retinal scans
  - Designed to ensure use only by genuine owner
Electronic Signature Security

21 CFR Part 11 -- Subpart C, § 11.300
E-sigs based on ID codes & passwords must employ controls to ensure security and integrity
- No two people can have the same combination of ID code/password
- ID codes/passwords must be periodically checked, recalled, revised
- Transaction safeguards to prevent unauthorized use and to detect and report any attempts at unauthorized use

And Signature/Record Linking?

21 CFR Part 11 -- Subpart B, §11.70
- Electronic signatures and handwritten signatures executed to electronic records must be linked to their respective electronic records.
- Signatures cannot be excised, copied or otherwise transferred to falsify an electronic record by ordinary means.
Certification

• Prior to use of electronic signatures must:
  – Certify with FDA that intent is for
    • Electronic Signature = Handwritten Signature
    • Provide one-time, global written statement of intent
      – In paper form with traditional handwritten signature
  – When
    • Before or at time of use
    • Once submitted the statement is legally binding
      – Any signatures made electronically have the same legal ramifications as handwritten ones

Part 11 Isn’t Going Anywhere

• The “Biggest thing since GxP”
• Perceived to be a bigger task than Y2K with less management commitment
• Agency is expecting the big, profitable companies to be further along
• Increase in warnings are result of more awareness of Part 11 requirements by inspectors
• FDA anticipates number of GMP inspections will rise by >50 percent by 2003
  – (FDA acting Senior Associate Commissioner for Management and Systems Jeff Weber, Feb. 5)
**Controversies**

- Scope & how much work is involved
- Interpretation of rule & applicability
- Still thinking signed hardcopy is the original record
- Estimated company Part 11 costs at more than $100 million*
- Impossible to return to paper-based systems to avoid Part 11 compliance
- Legacy systems

* Reg. Affairs Focus, May 2001

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**Compliance Impact**

What impact has occurred or do you expect to occur in your organisation as a result of complying with 21 CFR Part 11:

- We have had to train staff for compliance: 85%
- We have had to install new software to manage compliance: 75%
- Data access controls for those accessing the data have been increased: 69%
- The number of people having access to data has been restricted: 69%
- We have had to buy new computer hardware to manage compliance: 56%
- Knowledge transfer has speeded up: 22%
- Knowledge transfer has slowed down: 14%
Compliance Benefits

Have you perceived any collateral benefits of 21 CFR Part 11 compliance?

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better security</td>
<td>2.97</td>
</tr>
<tr>
<td>Better data management</td>
<td>2.68</td>
</tr>
<tr>
<td>Easier/faster data exchange between partners and operating units</td>
<td>1.73</td>
</tr>
<tr>
<td>Easier/faster data access</td>
<td>1.72</td>
</tr>
<tr>
<td>Reduced data management costs</td>
<td>1.35</td>
</tr>
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</table>

Interpretation:
1. No perceived benefit.
2. A minor benefit.
3. A benefit.
4. A major benefit.

Enforcement

- Nature and extent of Part 11 deviations considered **significant** if:
  - More numerous
  - Deviations make it difficult for agency to audit or interpret data
  - Deviations undermine integrity of data or electronic system
  - Effect on product quality or safety

FDA CPG 1999
Warning Letter & 483 Statistics

- 42 Part 11 related issues (not traditional computer issues) identified in:
  - 15 Warning letters
  - 2 FDA 483s
- Oldest observation: November 1997
- Newest observation: Jan 2002

Source: SEC Associates, GERM 2001

Part 11 Issues in Recent Warning Letters & 483s

- Drug product manufacturing: 18%
- Sterile drug manufacturing: 17%
- Parenteral manufacturing: 7%
- Contract laboratory testing: 7%
- Clinical study sponsor: 51%
- e-sig controls: 7%
- other: 7%
- security/integrity: 7%
- audit trail: 7%
- record retention: 7%

Source: SEC Associates, GERM 2001
Take the Warnings Seriously!

“Sitting at a computer, we are one step away from games”

Part 11 Work Products

- Part 1: "Good Electronic Records Management: GERM" Was Just Published
  - Architects
- Part 2: “Complying With 21 CFR Part 11, Electronic Records and Electronic Signatures" Was Published Last Fall
  - Project managers
  - Carpenters
Guidance Documents

- Non-binding on Industry and FDA
- Can’t countermand regulation
- Presents FDA’s “Current Thinking”
- Series of Short FDA Guidance Documents Due:
  - Glossary
  - Validation
  - Time Stamps
  - E-Record Maintenance (Archiving)
  - E-copies
  - Audit Trails

Now What…?

- Bush Appoints Marc McClellan As New FDA Commissioner
- Consolidation of FDA's Responsibility for Reviewing New Pharma Products Into CDER
  - Center for Drug Evaluation and Research
- Formerly Performed in Part by CBER
  - Center for Biologics Evaluation and Research
- CDER Will Take the Lead on Part 11 Implementation
- Part of Agency’s Overall Revision of Inspection Program to Enforce GMP Regulations
CDERs Lead on Part 11 Means…?

• More Inspection Policies
• More Aggressive and Frequent Inspections
• Major Overhaul of GMP Program
• Increase ‘Risk Management’ Enforcement
• Firms Need to Develop an Understanding of Risk Analysis When Developing Part 11 Compliance Plans

There’s More…?

• Part 11 and Guidances “On the Table” and May Be Revised or Re-written???
• CDER Actively Seeking Input From Industry on How Would Like to See Part 11 Changed

Bill Bradley, Chairman, Steering Committee
Industry Coalition on 21 CFR Part 11
cGMP: Integrated Quality Systems Approach

- Citing Part 11 As One Justification, FDA Will Issue a Revised cGMP
  - 25 years since the last revision of GMP
- GMP Purpose
  - Help ensure that drugs meet the statutory requirements for safety
  - Establish accountability in the manufacturing process
  - Risk Management and Integrated Quality Systems Approach

“We Were Out of Compliance Before Employing our Scientific Data Management System”

--- Associate Scientist, Big Pharmaceutical Company in Illinois
Pharma Case Study

Account Metrics:

- Development - GXP, Part 11
- 220 Users
- 105 - 110 Instruments (HPLC, GC, LC-MS, IR, AA, UV/VIS, TOC, etc.)
- Scattered labs, multiple sites
- Autosamplers run overnight
Pharma Case Study

• **The Problem:** No long term archiving solution for raw and report data
  – Nobody believed that the FDA could possibly mean the RAW DATA had to be archived long term!
  – Y2K received initial attention
  – Began to hear more about Part 11 at conferences

• Need one approach, not 30-40 vendor’s approaches to audit trails and e-sigs

• Scanning in human-readable data for e-reports

Pharma Case Study

• **Retrieval Issues:**
  – “This is where most people get into trouble”
  – Can’t find the raw data that supports the paper data
  – Can’t find archived paper reports
    • Have to cross reference notebooks
    • Have to find the physical notebook
    • 2-3 ft. of files to look through
    • Keep local for 1 year, then move down the street to corporate records
    • Access is at someone else’s mercy
    • Takes hours to days to retrieve report data
Pharma Case Study

• **The Solution**: NuGenesis ARCHIVE
  • Now they feel that they are 90 - 95% in compliance!
    – Archive raw data side to durable media
    – Can show the raw data to a reviewer to support the notebook data

• **The Solution**: NuGenesis VISION
  • Easy to create electronic reports from disparate sources
  • Can search and retrieve reports easily
    – With NuGenesis, it only takes a minute or two!
    – “You can actually find the stuff!”
    – “No more high blood pressure due to lost sheets of paper”

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Pharma Case Study

• **The Meta Data Story**:  
  – Collecting the right meta data pays the largest dividends
  – Can find the data 20 years from now
  – Can capture what is important and unique to your system
  
  – For CDS that use the same sets of names within a sample sequence over and over
    • If you have 50-60 instruments collecting data at the same time - the date and time stamps MAY BE identical
    • BUT… the meta data will be different (instrument, user, lot #, etc.)
Make The Regulation Work For You

• How do you comply with the regulations and still get your job done?
  – Need for a Lab/Enterprise Wide Scientific Data Management Solution
  – Non Invasive
  – Automatic
  – Electronic

• Capture, Find, Reuse!

What Can You Do Now?

Create System Inventory ➔ Identify Critical Systems ➔ Critical System Ranking

Gap Analysis ➔ Remediation Plan ➔ Revalidation

Compliant? ➔ No ➔ Detailed Part 11 Assessment ➔ Yes ➔ End?
Thank You For Your Attention!

Questions........................?