

**IT Compliance in the FDA
Regulated Industry**

IT & Automation Forum
November 13, 2007
Caribe Hilton, San Juan Puerto Rico
Speaker: Mr. Juan O. Pérez, Principal Consultant
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Food & Drug
Consulting Group

IT Responsibilities 10 Years Ago...



Compliance



IT Compliance is:
Achieving and Sustaining a Compliance State in IT Operations through the use of Good Practices

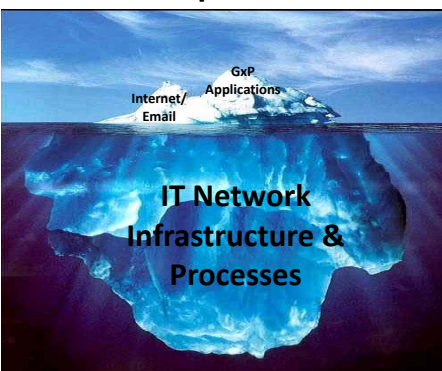


IT Compliance Scope

- 21 CFR 210, 211, 820,...
- August 1997 – 21 CFR Part 11
 - Electronic Records
 - Electronic Signatures
- July 2002 – Sarbanes-Oxley Act
- ITIL
- ISO 17799 (a.k.a. BS-17799)
- Other international regulations as applicable

IT is now one of the most heavily regulated operations

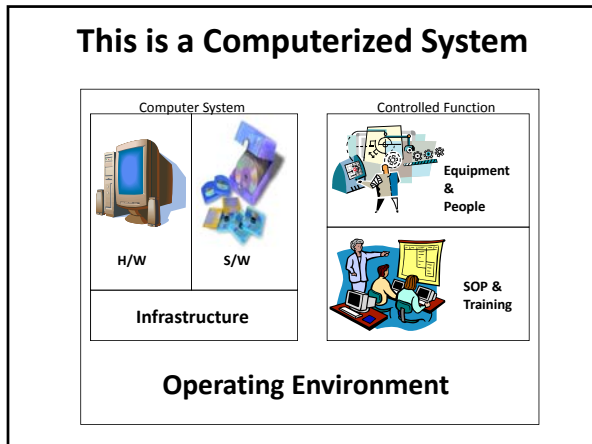
IT Operations



Internet/
Email

GxP
Applications

**IT Network
Infrastructure &
Processes**



Why is IT Compliance so important?

“The role of IT now plays helping to ensure compliance in a GxP environment is being acknowledge, and IT practices are being scrutinized during FDA inspections. This new role for IT requires establishment of a sound IT infrastructure...”

*Timothy Fields
President, Drumbeat Dimensions*

FDA Hiring Initiative

FDA U.S. Food and Drug Administration

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FDA News

FOR IMMEDIATE RELEASE
April 30, 2008

Media Inquiries:
Christopher Kelly, 301-627-6252
Consumer Inquiries:
888-INFO-FDA

FDA Embarks on Major Hiring Initiative for its Public Health Mission
Agency will fill more than 1,300 positions within the next several months

Biologists, chemists, medical officers, mathematical statisticians and investigators are among the experts in demand as the U.S. Food and Drug Administration begins a multi-year hiring initiative.

The FDA is hiring hundreds of individuals with science and medical backgrounds to help meet the agency's responsibilities to assure the safety and/or efficacy of human and veterinary drugs, biological products, medical devices, food, cosmetics and products that emit radiation.

"It takes a large pool of talented people for the FDA to protect and promote the public health," said John Dyer, FDA's Deputy Commissioner for Operations and Chief Operating Officer. "Each month there is a delay in bringing critical staff on board impairs the agency's ability to fulfill this mission."

In fiscal year 2008 alone, the FDA is looking to fill more than 600 new positions and to backfill over 700 others to implement the FDA Amendments Act of 2007, the Food Protection Plan and the Import Safety Action Plan. That's nearly triple the number of people hired from 2005-2007.

FDA's answer

Greetings,

Thanks for your message. If your client intends to apply electronic signatures to fill FDA requirements for signatures, then, the answer is yes. The certification is only an affirmation that the signer's organization considers electronic signatures as the same as legally binding handwritten signatures.

Regards,

P. Motise

Blind leading the Blind 2

"I can warn Engineering or IT they are in violation of a regulation, but I can't force them to fix the issue, they do it if they want."

QA Manager at a Medical Device Company

CSV <> IT Compliance

"CSV, typically, concentrates on the application; however, the emphasis is changing and network infrastructure and the IT departments that operate them on behalf of the users are now under regulatory scrutiny and this can open a black hole in many organizations."

Dr. Bob McDowall – McDowall Consulting



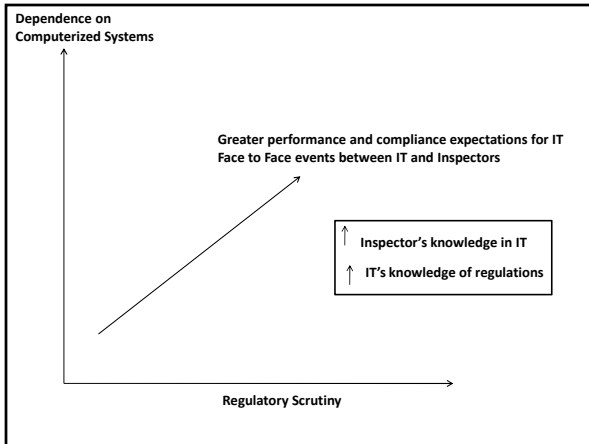
Common IT Compliance Issues

- 21 CFR 820.22
- 21 CFR Part 11
- CPG 425.100 (a.k.a. CPG 7132a.11) Hardware = Equipment = PM
- Weak procedures / policies / understanding
- Risk Based / Risk Averse
- Vendor Management (820.50a, CPG 425.200 a.k.a. 7132a.12)
- Spreadsheets management
- Resources / Training (820.25)
- Change Control <> Configuration Management

Compliance is not a cost

“FDA maintains that costs of implementing compliance and the regulatory systems will be offset by reductions in the time required to get new drugs approved and launched to market.”

Laura Bush, Biopharm International






“There will be fewer warning letters but they speak louder.”
David Horowitz, FDA

- All WL's have to be approved by FDA Management, no single opinion, but FDA Opinion
- Inspectors are out with most recent interpretations of the regulations.
- Inspections to computer systems will aim for compliance with GMPs as per Part 11 most recent interpretations.



“Failure to see the writing on the wall is likely to end in a close and unpleasant encounter with regulatory inspectors.”
Juan O. Pérez
IT and Compliance in the Regulated Life-Science Industry
Pharma IT Journal – January 2007

IT Compliance



Compliance <-> System

Compliance <-> Cost

Compliance = Good Practices

Recommendations

- High Level System Documentation
 - Comprehensive Documentation for H/W, S/W
 - Risk Rating, System Owner
- Environmental Conditions (Data Center)
- Network Qualification – Pharmacia WL 2001
 - Change Control / Configuration Management
- Segregate regulated / non regulated applications
- Audit Management Training
- Documented DRP/BCP Dry Run
- Audit (IT, Audit Trail (otherwise meaningless),...)

IT Compliance Audit

- Absence of Evidence <> Evidence of Absence
- Procedures and evidence of activities that are followed in the IT Department
 - Trained in GXP regulations and procedures
 - Network qualified and maintained
 - Support activities documented and Regulations are followed
- IT Operations are in Control
- Action Plan documented

Internal QA Audit Reports

- Internal QA Reports are confidential – do not show to an inspector (CPG 7151.02 1983, reaffirmed 2007)
- Unless:
 - For cause inspection
 - Judicial investigation

Warning!!

- Audits only sample: you can miss non-compliances
- Internal audits only good if people are honest and open
 - Is it preferable that you rather than the FDA find a problem with the system?
 - External Audits are sometimes needed to see the organization from the outside.

Conclusion



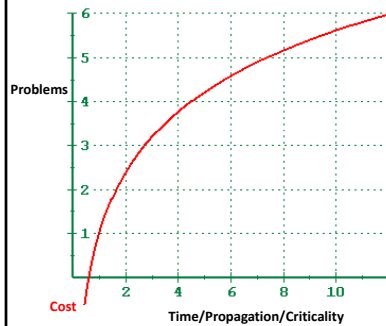
Decision Making / ROI

When IT Operations are in Compliance, Control is ensured and Computerized Systems are properly implemented...

Processes

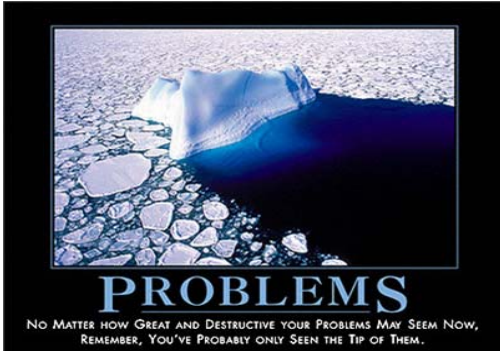


Conclusion



When not

Terrible Truth



**Thank you very
much for your
attention**

**A Deeper Review of
IT Regulatory Requirements
applicable to the FDA Regulated Industry**

IT & Automation Forum
November 13, 2008
Caribe Hilton, San Juan Puerto Rico
Speaker: Nidia Acevedo, Esq.
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The Legal Basis

- Federal Agencies are delegated their authorities from Congress
- FDA authority comes from the FD&C Act, however, the process by which the agency enforces the Act is governed by:
 - The Federal Administrative Procedures Act (FAPA)
 - An act designed to give uniformity to the rule-making and adjudicative proceedings of federal administrative agencies.
- In most instances, administrative remedies must have been exhausted before a Court can take jurisdiction.

What are the Predicate Rules?

- Any requirements set forth in the Food, Drug and Cosmetic Act (the Act), the PHS Act (Public Health Service Act), or FDA regulations.
- The predicate rules prescribe:
 - What records must be maintained
 - The content of records
 - Whether signatures are required
 - » The 'Predicate Rules' (GxP) regulations determine what records must be signed, not Part 11.
 - Record Retention

What is a Computerized System?

*Any programmable device including its software, hardware, peripherals, **procedures, users,** interconnections and inputs for the electronic processing and output of information used for reporting or control.*

Changes in Regulatory Perspective

- | | |
|---|---|
| <ul style="list-style-type: none">• Early Years (1983-1996)<ul style="list-style-type: none">– Relatively little computer system oversight from the FDA.– Small number of FDA Investigators• 1997-The Shift Point<ul style="list-style-type: none">– Electronic Record Requirements | <ul style="list-style-type: none">• 2000-2002<ul style="list-style-type: none">– Computer System 483 observations more than tripled– Audit Trails / E-Sig– Security• 2003<ul style="list-style-type: none">– Part 11 Turning Point– Compliance Guidance Docs were withdrawn |
|---|---|

What does the shift in the Regulatory Perspective Mean?

- Industry must have a deeper understanding of the predicate rules.
- Risk Management must become the driver of decisions:
 - Data Driven decisions
 - Clear understanding of product quality, safety and record integrity
 - Know the risks and manage them based on impact

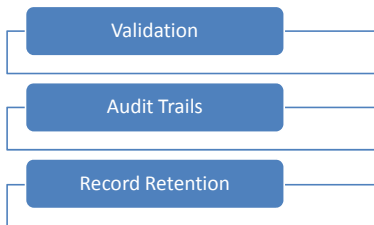
When Does Part 11 Apply?

Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any record requirements set by the FDA.

Part 11 Compliance Requirements

- On September 4, 2003 the FDA issued to Industry the prevailing Part 11 Compliance Guidance Document.
- Agency expressed its intention to exercise discretionary enforcement on some segments of the regulations.
 - This applies to legacy systems.
- FDA expects industry to take a risk based approach to compliance.

Part 11 Discretionary Enforcement



Enforcement is Based on the Predicate Rules



Can a Supplier Certify a Software to be Fully Compliant with Part 11 Regulations ?

?

Can a Supplier Certify a Software to be fully Compliant with Part 11?

- A vendor that makes such a claim is incorrect.
- Part 11 requires both procedural controls to be put in place by the user in addition to the technical controls that the vendor can offer.
- At best, the vendor can offer an application containing the technical requirements of a compliant system.

Answer

When do Audit Trail Requirements Begin?

?

When Do Audit Trail Requirements Begin?

- For Data:
 - Begins the instant moment the data hits the durable (or recording) media.
- For Text-Documents:
 - Upon approval and release of the document.

Answer

Computer System Validation

A Significant Quality Element

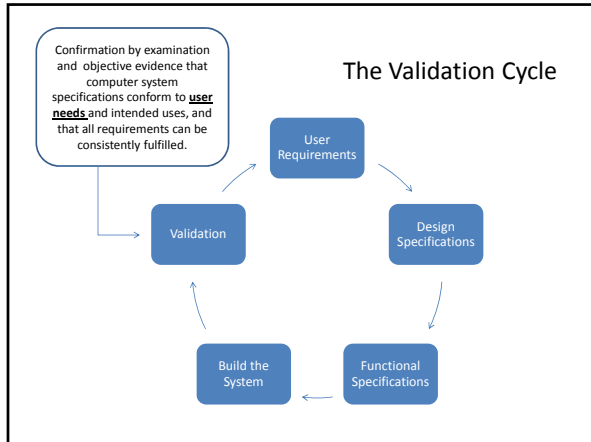
System Validation Considerations

You need to:

- Set up the Validation Committee
- Identify systems that require validation

Important Steps in identifying systems that require validation:

- Creating an Inventory
- Identifying the Systems
- Assessing Each System for Validation
- Determining Validation Priority to be revealed on a Master Plan



Maintaining the System Validation Status

- When a system has been validated, the control procedures should ensure that it continues to operate as validated.
 - Small changes over time can cumulatively affect the performance of a system and the validation status. (Change Control <-> Configuration Management)
- The system should therefore be reviewed periodically to provide additional assurance of validation.
 - The interval will depend on the level of risk of the system and its criticality based on company policies.
- It is the responsibility of system owner to ensure that the periodic reviews are performed.

The System Periodic Review should include:

- Hardware and software to identify recurring problems or unresolved major problems
- Verification of Fulfillment and Reconciliation with approved user requirements
- Change control log
- Audit the Audit Trail
- Maintenance logs
- Work practices
 - To ensure SOPs still reflect usage
- System security
 - To ensure user access rights are appropriate

Are emails Regulated Documents?

?

Are e-mails FDA regulated documents?

- If the text in an email supports such activities as change control approvals or failure investigations, then the e-mails have to be managed in a compliant way.
 - E.g. delegation emails

Answer

FDA Definition

U.S. Food and Drug Administration
 CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Manual of Standard Operating Procedures and Policies
 Regulatory - Communication
 Handling of Regulatory Electronic Communications

SOPP #119 Version #1 September 16, 2008

- Purpose**
 The purpose of this SOPP is to describe the policies and procedures for the Center for Biologics Evaluation and Research (CBER) staff on the handling of regulatory electronic messages (emails). Regulatory emails may be either internal communications or messages received from or sent to sponsors/applicants.
 Outgoing emails can be used in place of telephone communication to relay regulatory issues and requests for information. Internal emails may document a decision reached by a review committee or a decision regarding a regulatory submission.
- Definitions**
Regulatory Email
 A regulatory email is an electronic message received or sent by CBER as part of an investigational or marketing application or pre-application. A regulatory email may be a stand-alone message or a message with an attached file.
Secure Email
 A secure email is an electronic message received or sent from a sponsor/applicant that has exchanged secure email certificates with FDA. Secure email certificates may include the entire corporate or organization structure of a sponsor/applicant or a subset of users.

Record Retention Requirements

- If predicate rule requirements are met and the content and meaning of the records are preserved and archived
 - You can delete the electronic version of the records.
- In addition, paper and electronic record and signature components can co-exist
 - Predicate rule requirements must be met and the content and meaning of those records are preserved.

A Review of Significant Observations
WARNING LETTERS

You failed to exercise appropriate controls over computer or related systems to assure that changes in master production are instituted and input and output from the computer or related system of formulas are checked for accuracy and maintained [21 CFR 211.68(b)], in that

- there is no documentation to support software manufacturing change performed to the [redacted] used in the manufacture of XYZ Products...

OEWL-08-02
Multinational Pharmaceutical Company
April 28, 2008

Warning Letters

Failure to establish test procedures or other laboratory control mechanisms designed to assure that drug products conform to appropriate standards to assure that any deviation from the written test procedures or laboratory control mechanisms be recorded and justified [21 CFR 211.160(a) and (b)]. For example:

- During review of atypical process reports, QA release personnel may edit the number of occurrences calculated by the software. This practice is not addressed in the product release SOP.

Warning Letters

OEWL-08-02
Multinational Pharmaceutical Company
April 28, 2008

Failure to establish and maintain adequate procedures for validating the device to include software validation and risk analysis, as required by 21 CFR 820.30(g). For example:

- Your validation protocol failed to document how you validated the software upgrade (added additional user language) or how you validated the pediatric capability transfer.

Warning Letters

European Facility Medical Device Company
Defibrillator Manufacturer
July, 2006

The company uses ABC system and network computer software program. ABC performs functions typical of a laboratory information management system. The quality unit uses this program for disposition of materials, stability testing and others.

- Once material is dispositioned, the ABC system communicates to the network program used by warehouse. These system are deficient in that:
 - The network program lacked adequate validation and/or documentation controls. For example:
 - The program was not controlled by the revision numbers

Warning Letters

US Company – European Facility
January, 2001

- Inadequate SOPs to ensure that records are included with validation documentation, maintained and updated when changes were made
- There was no assurance that complete functional testing had been performed. For example:
 - Failed to assess all historical testing and compare functionality to ensure that all system functionality has been adequately evaluated.

Warning Letters

European Facility Medical Device Company
Defibrillator Manufacturer
July, 2006

The computer system lacked adequate validation documentation controls. For example:

The equipment's computer used for filling operations which retains equipment errors that occur during filling operations, lacked the capacity to retain electronic data. After every 15th filling operation, the information was overwritten due to the storage capacity of the equipment's hard drive.

Warning Letters

WL 320-01-8
US Company – European Facility
January, 2001

- Inadequate oversight by the Quality Control Unit (QCU) to ensure that controls which impact the quality of sterile products are implemented for manufacturing operations. For example:
 - The QCU failed to ensure that adequate procedures were put into place to define and control computerized production operations, equipment qualifications, documentation review and laboratory operations.

Warning Letters

WL 320-01-7
US Company – European Facility
January, 2001

The deeper view of things

Lessons Learned

- Information Technology (IT) is more than hardware and software. The users, system uses and operational processes are fundamental components.
- IT is cornerstone to quality and compliance. It requires to be proven that it does what it is intended to.
 - This must be documented.

- The validation is not a one time exercise, it is a dynamic process that requires continued evaluation via change management procedure.
- The decision in terms of the extent of your controls must be based on Risk Analysis.

Keep in mind that it is only apparent that regulatory enforcement has been driven away from specific regulatory guidelines.

Enforcement of regulatory & legal requirements is based on the ability to demonstrate that manufactured products that are safe and fulfill their intended use.

**Thank you very
much for your
attention**

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